RESPIRATORY TRACT TUMORS
(Conceptos / Keywords: NSCLC; SCLC, Mesotheliomas; Tracheal tumors; Bronchial tumors; etc).
Agosto - Septiembre 2013 / August - September 2013

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[1]

TÍTULO / TITLE: - Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Bradley A; Marshall A; Stonehewer L; Reaper L; Parker K; Bevan-Smith E; Jordan C; Gillies J; Agostini P; Bishay E; Kalkat M; Steyn R; Rajesh P; Dunn J; Naidu B
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Heart of England NHS Foundation Trust (HEFT), Birmingham, UK.
RESUMEN / SUMMARY: - OBJECTIVES: The aim of the study was to develop a multistranded pragmatic rehabilitation programme for operable lung cancer patients, that looks into feasibility, process indicators, outcome measures, local adaptability, compliance and potential cost benefit. METHODS: An outpatient-based complex intervention, rehabilitation for operated lung cancer (ROC) programme, was developed to optimize physical status, prepare for the inpatient journey and support through
recovery after surgery. It includes exercise classes, smoking cessation, dietary advice and patient education and was tested in an enriched cohort study within a regional thoracic unit over 18 months. RESULTS: A multistranded pragmatic rehabilitation programme pre- and post-surgery is feasible. Fifty-eight patients received the intervention and 305 received standard care. Both groups were matched for age, lung function comorbidity and type of surgery. Patients in the intervention group attended exercise classes twice a week until surgery, which was not delayed. Patients attended four sessions presurgery (range 1-15), resulting in an improvement of 20 m (range -73-195, P = 0.001) in a 6-min walk test and 0.66 l in forced expiratory volume in 1 s (range -1.85 from 1.11, P = 0.009) from baseline to presurgery. Fifty-four percentage of smokers in the intervention group stopped smoking. Sixteen percentage of patients were identified as being at risk of malnourishment and received nutritional intervention. There was a trend in patients in the intervention group towards experiencing fewer postoperative pulmonary complications than those in the non-intervention group (9 vs 16%, respectively, P = 0.21) and fewer readmissions to hospital because of complications (5 vs 14% respectively, P = 0.12). CONCLUSION: Chronic obstructive pulmonary disease-type pulmonary rehabilitation before and after lung cancer surgery is viable, and preliminary results suggest improvement in physical measures. A multicentre, randomized controlled trial is warranted to confirm clinical efficacy. ISRCTN REGISTRATION NUMBER: ISRCTN00061628.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1002/ijc.28448
AUTORES / AUTHORS: - Dabir S; Kluge A; McColl K; Liu Y; Lam M; Halmos B; Wildey G; Dowlati A
INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Case Western Reserve University, Cleveland, Ohio 44106.
RESUMEN / SUMMARY: - Protein inhibitor of activated STAT3 (PIAS3) is an endogenous inhibitor of STAT3 that negatively regulates STAT3 transcriptional activity and cell growth and demonstrates limited expression in the majority of human squamous cell carcinomas of the lung. In the present study we sought to determine if PIAS3 inhibits cell growth in non-small cell lung cancer (NSCLC) cell lines by inducing apoptosis. Our results demonstrate that over-expression of PIAS3 promotes mitochondrial depolarization, leading to cytochrome c release, caspase 9 and 3 activation and PARP cleavage. This intrinsic pathway activation was associated with decreased Bcl-xL expression and increased Noxa expression and was independent of p53 status. Furthermore, PIAS3 inhibition of STAT3 activity was also p53 independent. Microarray
experiments were performed to discover STAT3-independent mediators of PIAS3-induced apoptosis by comparing the apoptotic gene expression signature induced by PIAS3 over-expression with that induced by STAT3 siRNA. The results showed that a subset of apoptotic genes was uniquely expressed only after PIAS3 expression. Thus, PIAS3 may represent a promising lung cancer therapeutic target because of its p53-independent efficacy as well as its potential to synergize with Bcl-2 targeted inhibitors.

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[2]
TÍTULO / TITLE: - EGFR, KRAS, BRAF and ALK Gene alterations in lung adenocarcinomas: patient outcome, interplay with morphology and immunophenotype.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Warth A; Penzel R; Lindenmaier H; Brandt R; Stenzinger A; Herpel E; Goeppert B; Thomas M; Herth FJ; Dienemann H; Schnabel PA; Schirmacher P; Hoffmann H; Muley T; Weichert W
INSTITUCIÓN / INSTITUTION: - University Hospital Heidelberg, Germany.
RESUMEN / SUMMARY: - Numerous studies have been published on single aspects of pulmonary adenocarcinoma (ADC). To comprehensively link clinically relevant ADC characteristics, we evaluated established morphologic, diagnostic, and predictive biomarkers in 425 resected ADC. Morphology was reclassified. CK7, TTF1, napsin A, thymidylate synthase (TS), and ERCC1 expression, ALK rearrangements as well as EGFR, KRAS and BRAF mutations were analysed. All characteristics were correlated with clinical and survival parameters. Morphologic ADC subtypes were significantly associated with smoking history and distinct patterns of diagnostic biomarkers. KRAS mutations were prevalent in male smokers while EGFR mutations were associated with female sex, non-smoking and lepidic as well as micropapillary growth patterns. TTF1 expression (HR for OS=0.61, p=0.021) and BRAF mutations (HR for DFS=2.0, p=.046) were found as morphology- and stage-independent predictors of survival in multivariate analysis. Adjuvant radio-/chemotherapy in some instances strongly impacted on the prognostic effect of both diagnostic and predictive biomarkers. Our data draw a comprehensive picture of the prevalence and interplay of yet established histological and molecular ADC characteristics. This data will help to develop time and cost effective diagnostic and treatment algorithms for ADC.

TÍTULO / TITLE: - Down-Regulation of MiR-30c Promotes the Invasion of Non-Small Cell Lung Cancer by Targeting MTA1.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Randomized, Double-Blind, Placebo-Controlled, Phase III Chemoprevention Trial of Selenium Supplementation in Patients With Resected Stage I Non-Small-Cell Lung Cancer: ECOG 5597.

Background: The connection between microRNA expression and lung cancer development has been identified in recent literature. However, the mechanism of microRNA has been poorly elucidated in non-small-cell lung cancer (NSCLC).

Methods and Results: Comparing with adjacent tissues (n=75), miR-30c has a lower expression in lung cancer specimens (n=75). The knockdown of miR-30c enhanced the invasion of A549 cells; meanwhile, the overexpression of miR-30c could reverse the effect of the knockdown of miR-30c in vitro. A luciferase assay revealed that miR-30c was directly bound to the 3'-untranslated regions (3'-UTR) of MTA1. QRT-PCR and western blot shows MTA1 was up-regulated in mRNA and protein levels. The effect taken on the invasion of NSCLC by overexpression of MTA1 works the same as down-regulated miR-30c. Conclusion: miR-30c may play a pivotal role in controlling lung cancer invasion through regulating MTA1 in NSCLC.

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[3]
RESUMEN / SUMMARY: - PURPOSE: Selenium has been reported to have chemopreventive benefits in lung cancer. We conducted a double-blind, placebo-controlled trial to evaluate the incidence of second primary tumors (SPTs) in patients with resected non-small-cell lung cancer (NSCLC) receiving selenium supplementation.

PATIENTS AND METHODS: Patients with completely resected stage I NSCLC were randomly assigned to take selenized yeast 200 µg versus placebo daily for 48 months. Participation was 6 to 36 months postoperatively and required a negative mediastinal node biopsy, no excessive vitamin intake, normal liver function, negative chest x-ray, and no other evidence of recurrence. RESULTS: The first interim analysis in October 2009, with 46% of the projected end points accumulated, showed a trend in favor of the placebo group with a low likelihood that the trial would become positive; thus, the study was stopped. One thousand seven hundred seventy-two participants were enrolled, with 1,561 patients randomly assigned. Analysis was updated in June 2011 with the maturation of 54% of the planned end points. Two hundred fifty-two SPTs (from 224 patients) developed, of which 98 (from 97 patients) were lung cancer (38.9%). Lung and overall SPT incidence were 1.62 and 3.54 per 100 person-years, respectively, for selenium versus 1.30 and 3.39 per 100 person-years, respectively, for placebo (P = .294). Five-year disease-free survival was 74.4% for selenium recipients versus 79.6% for placebo recipients. Grade 1 to 2 toxicity occurred in 31% of selenium recipients and 26% of placebo recipients, and grade >/= 3 toxicity occurred in less than 2% of selenium recipients versus 3% of placebo recipients. Compliance was excellent. No increase in diabetes mellitus or skin cancer was detected. CONCLUSION: Selenium was safe but conferred no benefit over placebo in the prevention of SPT in patients with resected NSCLC.

[4]

REFERENCES / REFERENCES:

**TÍTULO / TITLE:** Results of the two incidence screenings in the National Lung Screening Trial.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Aberle DR; DeMello S; Berg CD; Black WC; Brewer B; Church TR; Clingan KL; Duan F; Fagerstrom RM; Gareen IF; Gatsonis CA; Gierada DS; Jain A; Jones GC; Mahon I; Marcus PM; Rathmell JM; Sicks J
INSTITUCIÓN / INSTITUTION: - Department of Radiological Sciences, David Geffen School of Medicine at the University of California at Los Angeles (UCLA), Los Angeles, CA 90024, USA. daberle@mednet.ucla.edu

RESUMEN / SUMMARY: - BACKGROUND: The National Lung Screening Trial was conducted to determine whether three annual screenings (rounds T0, T1, and T2) with low-dose helical computed tomography (CT), as compared with chest radiography, could reduce mortality from lung cancer. We present detailed findings from the first two incidence screenings (rounds T1 and T2). METHODS: We evaluated the rate of adherence of the participants to the screening protocol, the results of screening and downstream diagnostic tests, features of the lung-cancer cases, and first-line treatments, and we estimated the performance characteristics of both screening methods. RESULTS: At the T1 and T2 rounds, positive screening results were observed in 27.9% and 16.8% of participants in the low-dose CT group and in 6.2% and 5.0% of participants in the radiography group, respectively. In the low-dose CT group, the sensitivity was 94.4%, the specificity was 72.6%, the positive predictive value was 2.4%, and the negative predictive value was 99.9% at T1; at T2, the positive predictive value increased to 5.2%. In the radiography group, the sensitivity was 59.6%, the specificity was 94.1%, the positive predictive value was 4.4%, and the negative predictive value was 99.8% at T1; both the sensitivity and the positive predictive value increased at T2. Among lung cancers of known stage, 87 (47.5%) were stage IA and 57 (31.1%) were stage III or IV in the low-dose CT group at T1; in the radiography group, 31 (23.5%) were stage IA and 78 (59.1%) were stage III or IV at T1. These differences in stage distribution between groups persisted at T2. CONCLUSIONS: Low-dose CT was more sensitive in detecting early-stage lung cancers, but its measured positive predictive value was lower than that of radiography. As compared with radiography, the two annual incidence screenings with low-dose CT resulted in a decrease in the number of advanced-stage cancers diagnosed and an increase in the number of early-stage lung cancers diagnosed. (Funded by the National Cancer Institute; NLST ClinicalTrials.gov number, NCT00047385.).

[5]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

REVISTA / JOURNAL: - Enlace al texto completo (gratuito o de pago) 1200/JCO.2012.47.5947
RESUMEN / SUMMARY: - PURPOSE: In this prospective National Cancer Institute-funded American College of Radiology Imaging Network/Radiation Therapy Oncology Group cooperative group trial, we hypothesized that standardized uptake value (SUV) on post-treatment $[18F]$fluorodeoxyglucose positron emission tomography (FDG-PET) correlates with survival in stage III non-small-cell lung cancer (NSCLC). PATIENTS AND METHODS: Patients received conventional concurrent platinum-based chemoradiotherapy without surgery; postradiotherapy consolidation chemotherapy was allowed. Post-treatment FDG-PET was performed at approximately 14 weeks after radiotherapy. SUVs were analyzed both as peak SUV (SUVpeak) and maximum SUV (SUVmax; both institutional and central review readings), with institutional SUVpeak as the primary end point. Relationships between the continuous and categorical (cutoff) SUVs and survival were analyzed using Cox proportional hazards multivariate models. RESULTS: Of 250 enrolled patients (226 were evaluable for pretreatment SUV), 173 patients were evaluable for post-treatment SUV analyses. The 2-year survival rate for the entire population was 42.5%. Pretreatment SUVpeak and SUVmax (mean, 10.3 and 13.1, respectively) were not associated with survival. Mean post-treatment SUVpeak and SUVmax were 3.2 and 4.0, respectively. Post-treatment SUVpeak was associated with survival in a continuous variable model (hazard ratio, 1.087; 95% CI, 1.014 to 1.166; $P = .020$). When analyzed as a prespecified binary value ($\leq v > 3.5$), there was no association with survival. However, in exploratory analyses, significant results for survival were found using an SUVpeak cutoff of 5.0 ($P = .041$) or 7.0 ($P < .001$). All results were similar when SUVmax was used in univariate and multivariate models in place of SUVpeak. CONCLUSION: Higher post-treatment tumor SUV (SUVpeak or SUVmax) is associated with worse survival in stage III NSCLC, although a clear cutoff value for routine clinical use as a prognostic factor is uncertain at this time.

Enlace al Resumen / Link to its Summary


AIDS Program, Yale-New Haven Hospital, and Department of Medicine, Yale University School of Medicine, New Haven, CT, USA.

Probability of cancer in pulmonary nodules detected on first screening CT.

Enlace al Resumen / Link to its Summary


Vancouver General Hospital, Vancouver, BC, Canada.

BACKGROUND: Major issues in the implementation of screening for lung cancer by means of low-dose computed tomography (CT) are the definition of a positive result and the management of lung nodules detected on the scans. We conducted a population-based prospective study to determine factors predicting the probability that lung nodules detected on the first screening low-dose CT scans are malignant or will be found to be malignant on follow-up. METHODS: We analyzed data from two cohorts of participants undergoing low-dose CT screening. The development data set included participants in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan). The validation data set included participants involved in chemoprevention trials at the British Columbia Cancer Agency (BCCA), sponsored by the U.S. National Cancer Institute. The final outcomes of all nodules of any size that were detected on baseline low-dose CT scans were tracked. Parsimonious and fuller multivariable logistic-regression models were prepared to estimate the probability of
lung cancer. RESULTS: In the PanCan data set, 1871 persons had 7008 nodules, of which 102 were malignant, and in the BCCA data set, 1090 persons had 5021 nodules, of which 42 were malignant. Among persons with nodules, the rates of cancer in the two data sets were 5.5% and 3.7%, respectively. Predictors of cancer in the model included older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and spiculation. Our final parsimonious and full models showed excellent discrimination and calibration, with areas under the receiver-operating-characteristic curve of more than 0.90, even for nodules that were 10 mm or smaller in the validation set. CONCLUSIONS: Predictive tools based on patient and nodule characteristics can be used to accurately estimate the probability that lung nodules detected on baseline screening low-dose CT scans are malignant. (Funded by the Terry Fox Research Institute and others; ClinicalTrials.gov number, NCT00751660.).

[8]
TÍTULO / TITLE: - Clinical problem-solving. Weak in the knees.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1056/NEJMcps1210293
AUTORES / AUTHORS: - Conwell WD; Josephson SA; Li H; Saint S; Janssen WJ
INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Denver, USA.

[9]
TÍTULO / TITLE: - Economic analysis of a randomized phase III trial of gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer (Italian GEMVIN3/NCIC CTG BR14 trial).
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.07.012
AUTORES / AUTHORS: - Reaume MN; Leighl NB; Mittmann N; Coyle D; Hirsh V; Seymour L; Tu D; Shepherd FA; Graham B; Gridelli C; Perrone F; Di Maio M; Bradbury PA; Evans WK
INSTITUCIÓN / INSTITUTION: - NCIC Clinical Trials Group, 10 Stuart Street, Kingston, Ontario, K7L 3N6, Canada. Electronic address: nreaume@ottawahospital.on.ca.
RESUMEN / SUMMARY: - BACKGROUND/OBJECTIVE: Non-platinum-based chemotherapy is a potential alternative to platinum doublet therapy for advanced non-small cell lung
cancer in selected patients. We determined the cost-effectiveness of gemcitabine/vinorelbine (GEMVIN), versus cisplatin/gemcitabine (PG) or cisplatin/vinorelbine (PV), from a government payer perspective. METHODS: Results from a randomized trial of GEMVIN versus PG or PV demonstrated no significant difference in global quality of life (primary endpoint) or overall survival between regimens, but superior progression-free survival for platinum-based regimens. A cost analysis was conducted using direct medical costs of treatment, grade 3 or 4 toxicity management, and investigations for the mean number of cycles per study arm. Costs were calculated using Canadian dollars in 2005, and then in 2013 after drug patent expiry. RESULTS: In 2005, GEMVIN was the most expensive regimen ($6868), and PV the least expensive ($4650), with an incremental cost of GEMVIN over PV of $2218. Diagnostic and administration costs did not differ significantly among regimens; GEMVIN had the lowest toxicity costs. The principal cost driver in 2005 was the cost of chemotherapy. In 2013, toxicity and administration costs emerged as major drivers; GEMVIN was less costly than PV and PG, (cost savings of $413 over PV). CONCLUSION: Despite similar outcomes, GEMVIN was more expensive than PV or PG in 2005 because of higher chemotherapy costs. By 2013, after chemotherapy drug patent expiry, GEMVIN became the least costly regimen. Economic considerations in oncology change over time, and should be revisited in policy decisions based on cost.

[10]

TÍTULO / TITLE: - Contribution of multidrug resistance-associated proteins (MRPs) to the release of prostanoids from A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago)
1016/j.prostaglandins.2013.08.002
AUTORES / AUTHORS: - Furugen A; Yamaguchi H; Tanaka N; Shiida N; Ogura J; Kobayashi M; Iseki K
INSTITUCIÓN / INSTITUTION: - Laboratory of Clinical Pharmaceutics & Therapeutics, Division of Pharmasciences, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan.
RESUMEN / SUMMARY: - Previous studies indicated that several members of the multidrug resistance-associated protein (MRP) family mediate the transport of prostanoids. However, the importance of MRPs in the release process of prostanoids has not been fully elucidated. In this study, we investigated the contribution of MRPs, including MRP1, MRP2, and MRP4, to the release process of the prostanoids from human lung adenocarcinoma epithelial A549 cells. The extracellular levels of PGE2, PGF2alpha, and TXB2 (a metabolite of TXA2) were decreased by treatment with MRP
inhibitors (dipyridamole, MK571, and probenecid). The studies using membrane vesicle suggest that the effects of the inhibitors were in part by inhibiting MRP4 function. The effects of knockdown of each MRP (MRP1, MRP2, and MRP4) were also investigated. The extracellular levels of PGE2 and PGF2alpha were significantly decreased after MRP4 knockdown. Our results suggest that MRPs including MRP4 contribute the release process of prostanoids in A549 cells.

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**TÍTULO / TITLE:** - Cisplatin-induced downregulation of SOX1 increases drug resistance by activating autophagy in non-small cell lung cancer cell.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


- Enlace al texto completo (gratuito o de pago) 1016/j.bbrc.2013.08.065

**AUTORES / AUTHORS:** - Li N; Li X; Li S; Zhou S; Zhou Q

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450000, China.

**RESUMEN / SUMMARY:** - SOX1 was aberrant methylated in hepatocellular cancer and non-small cell lung cancer (NSCLC). Long-term cisplatin exposure promotes methylation of SOX1 in ovarian cancer cell, suggesting that SOX1 may be involved in cisplatin resistance. Our aim was to test the hypothesis that cisplatin resistance is associated with alteration of SOX1 expression in NSCLC. Expression of levels of SOX1 was examined using RT-PCR in cisplatin resistance cells and parental cells. The level of SOX1 mRNA in cisplatin resistance cells was markedly reduced when compared to parental cells. Promoter methylation of SOX1 was induced in cisplatin resistance cells. We also found that SOX1 silencing enhanced the cisplatin-mediated autophagy in NSCLC. This study shows that inactivation of SOX1 by promoter hypermethylation, at least in part, is responsible for cisplatin resistance in human NSCLC.

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[11]

**TÍTULO / TITLE:** - Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


- Enlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.08.016

**AUTORES / AUTHORS:** - Iuchi T; Shingyoji M; Sakaida T; Hatano K; Nagano O; Itakura M; Kageyama H; Yokoi S; Hasegawa Y; Kawasaki K; Iizasa T
RESUMEN / SUMMARY: - BACKGROUND: Brain metastases (BM) are a common in patients with lung cancer. Although whole-brain radiation therapy (WBRT) is the standard therapy, it may have a risk of decline in cognitive function of patients. In this study, we evaluated the efficacy of gefitinib alone without radiation therapy for the treatment of patients with BM from lung adenocarcinoma. MATERIALS AND METHODS: Eligible patients had BM from lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations. Gefitinib was given at 250mg orally once a day until tumor progression or unacceptable toxicity. RESULTS: Forty-one patients were enrolled. The response rate was 87.8%. No patient experienced grade >/=4 toxicity. The median progression-free survival time was 14.5 months (95% CI, 10.2-18.3 months), and the median overall survival time was 21.9 months (95% CI, 18.5-30.3 months). In compared with L858R, exon 19 deletion was associated with better outcome of patients after treatment with gefitinib in both progression-free (p=0.003) and overall survival (p=0.025). CONCLUSION: Favorable response of BM to gefitinib even without irradiation was demonstrated. Exon 19 deletion was both a predictive and prognostic marker of patients with BM treated by gefitinib.

[12] TÍTULO / TITLE: - Impact of Weight Change During the Course of Concurrent Chemoradiation Therapy on Outcomes in Stage IIIB Non-Small Cell Lung Cancer Patients: Retrospective Analysis of 425 Patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Topkan E; Parlak C; Selek U

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Baskent University Adana Medical Faculty, Adana, Turkey. Electronic address: docdretopkan@gmail.com.

RESUMEN / SUMMARY: - PURPOSE: We retrospectively investigated the impact of weight change (WC) during concurrent chemoradiation therapy (C-CRT) on clinical outcomes of stage 3B non-small cell lung cancer (NSCLC) patients. METHODS AND MATERIALS: A total of 425 patients treated with C-CRT were included. All patients received 60 to 66 Gy of thoracic radiation therapy concurrently with 1 to 3 cycles of platinum-based chemotherapy. Pre- and posttreatment weight measurements on first and last days of C-CRT were used for WC. Patients were divided into 2 groups: group 1 = weight loss (WL); group 2 = weight preservation/gain (WP) for comparative analyses. RESULTS: Following C-CRT, 252 patients (59.3%) experienced WL, while 89 patients (20.9%) and 84 patients (19.8%) showed WP or WG. At median 24.2 months of follow-up, 142
patients (33.4%) were alive (84 WP [48.6%] and 58 WL [23.0%]), and 58 (13.6%) of them were free of disease progression (41 [23.7%] for WP and 17 [6.7%] for WL). Median overall survival (OS), locoregional progression-free survival (LRPFS), progression-free survival (PFS), and distant metastases-free survival (DMFS) for the entire population were 22.8, 14.4, 10.6, and 11.7 months, respectively. Intergroup comparisons between WP and WL cohorts revealed significantly superior OS, LRPFS, PFS, and DMFS in WP patients (P<.05 for each). On multivariate analyses, only WL and advanced T stage were associated with poor prognosis (P<.05). CONCLUSIONS: Present results in 425 stage 3B NSCLC patients demonstrated that WL during C-CRT is strongly associated with inferior survival outcomes compared to WP. This emerging finding might be useful by forming an encouraging basis for future investigations in facilitating a way to improve the outcomes of these patients experiencing WL during C-CRT.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gelsomino F; Agustoni F; Niger M; Valota M; Haspinger ER
INSTITUCIÓN / INSTITUTION: - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lee SY; Yoo SS; Kang YR; Choi YY; Lee WK; Choi JE; Jeon HS; Shin KM; Oh Ij; Kim KS; Lee J; Cha SI; Kim CH; Kim YC; Park JY
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea.
RESUMEN / SUMMARY: - This study was conducted to analyze a comprehensive panel of single nucleotide polymorphisms (SNPs) in genes in DNA repair and apoptosis
pathways and determine the relationship between polymorphisms and treatment outcomes of patients with non-small cell lung cancer (NSCLC) treated with first-line paclitaxel-cisplatin chemotherapy. Three hundred eighty two patients with NSCLC were enrolled. Seventy-four SNPs in 48 genes (42 SNPs in 27 DNA repair pathway genes and 32 SNPs in 21 apoptotic pathway genes) were genotyped and their associations with chemotherapy response and overall survival (OS) were analyzed. Among SNPs in DNA repair genes, BRCA1 rs799917 was significantly associated with both chemotherapy response and OS. XRCC1 rs25487 exhibited a significant association with chemotherapy response and ERCC2 rs1052555 with OS. Four SNPs in apoptotic genes (TNFRSF1B rs1061624, BCL2 rs2279115, BIRC5 rs9904341, and CASP8 rs3769818) were significantly associated with OS, but not with response to chemotherapy. When the six SNPs which were associated with OS in individual analysis were combined, OS decreased as the number of bad genotypes increased (Ptrend=2x10^{-6}). Patients with 3, and 4-6 bad genotypes had significantly worse OS compared with those carrying 0-2 bad genotypes (adjusted hazard ratio [aHR]=1.54, 95% CI=1.14-2.08, P=0.005; aHR=2.10, 95% CI=1.55-2.85, P=2x10^{-6}, respectively). In conclusion, these findings suggest that the six SNPs identified, particularly their combined genotypes, could be used as biomarkers predicting chemotherapy response and survival of NSCLC patients treated with first-line paclitaxel-cisplatin chemotherapy.

[15] TÍTULO / TITLE: - Phase II trial of customized first line chemotherapy according to ERCC1 and RRM1 SNPs in patients with advanced non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mazzoni F; Cecere FL; Meoni G; Giuliani C; Boni L; Camerini A; Lucchesi S; Martella F; Amoroso D; Lucherini E; Torricelli F; Di Costanzo F
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, Firenze, Italy. Electronic address: francescamazzoni@hotmail.com.
RESUMEN / SUMMARY: - OBJECTIVES: Customized chemotherapy has several advantages: patients are more likely to be treated with the most effective agents and can be spared the toxicity of ineffective drugs. Based on the literature, excision repair cross complementation group 1 (ERCC1) and ribonucleotide reductase M1 (RRM1) genes represent predictive biomarkers of response to platinum compound and gemcitabine, in NSCLC. MATERIALS AND METHODS: We had planned a phase II trial (Simon design) to evaluate combination chemotherapy according to single nucleotide polymorphisms (SNPs) of ERCC1 (118T/C and 8092C/A) and RRM1 (-37C/A and -524T/C) in naive
patients affected by advanced NSCLC. ERCC1 and RRM1 SNPs assessment was performed in peripheral blood lymphocytes (PBLs). Combination chemotherapy was selected based on ERCC1 and RRM1 SNPs: we assume that patients with one or two C alleles at position 118 and with one or two A alleles at position 8092 in ERCC1 gene would correspond to Cisplatin non-responder and than with two A alleles at -37 and two C alleles at -524 in RRM1 gene to gemcitabine non-responder. Four schedules were provided: cisplatin+gemcitabine, cisplatin+docetaxel, gemcitabine+docetaxel; docetaxel+vinorelbine. Primary endpoint was overall response (ORR) in the intention-to-treat population. RESULTS: 42 patients were enrolled from January 2010 to November 2011; 40 patients received at least 1 cycle of chemotherapy; median age was 66 years (range: 47-72); 36(90%) had stage IV, 4(10%) IIIB; 23(58%) had adenocarcinoma, 14(35%) squamous carcinoma. Twenty-five (62%) patients received treatment A, 3(8%) treatment B, 11(28%) treatment C, 1(23%) treatment D. ORR was 55%, analysis in squamous patients subgroups showed 71.4% ORR. The median follow-up was 19.7 months, PFS was 23 weeks (95% CI=15-26) and OS was 40.4 weeks (95% CI=32-55). Treatment was well tolerated. CONCLUSION: We observed an increase of ORR in NSCLC patients when they were treated with chemotherapy according to ERCC1 and RRM1 SNPs status.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Satoh Y; Onishi H; Nambu A; Araki T
INSTITUCIÓN / INSTITUTION: PET Center, Kofu Neurosurgical Hospital, Sakaori 1-16-18, Kofu, Yamanashi, Japan 400-0805; Department of Radiology, Yamanashi University, Chuo, Yamanashi, Japan.
RESUMEN / SUMMARY: Purpose: To evaluate the prognostic importance and predictive performance of volume-based parameters of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in patients with stage I non-small cell lung cancer (NSCLC) after stereotactic body radiation therapy (SBRT). Materials and Methods: This study had institutional review board approval. All patients gave written informed consent for SBRT as well as for future anonymous use of clinical data. Data in 88 patients with stage I NSCLC (68 patients with T1N0M0 disease and 20 with T2aN0M0 disease) who had undergone FDG PET/CT and then SBRT were retrospectively evaluated. Seventy-seven tumors were histopathologically proved (48 adenocarcinomas, 24 squamous cell carcinomas, and five unspecified non-small
cell carcinomas), and the remaining 11 tumors were diagnosed clinically without histopathologic diagnosis. Maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were analyzed. The MTV of the primary tumor was calculated as all voxels with an SUV of 2.5 or greater within the isocontour line, while TLG was calculated as MTV multiplied by the average SUV, by using fixed thresholds of either 50% (TLG_{50}) or 60% (TLG_{60}) of the maximum intratumoral FDG activity. The prognostic importance of PET parameters and other clinicopathologic variables (age, sex, tumor size, tumor location [peripheral or central], and biologically effective dose) was assessed by using Cox proportional hazards regression analysis of overall survival (OS) and disease-free survival (DFS) for both univariate and multiple-variable analyses.

Results: The median follow-up period was 33 months. At 3 years, OS and DFS were 70.0% and 49.7%, respectively. In the univariate analyses, SUV_{max} (P = .001), MTV (P = .002), TLG_{50} (P = .001), and TLG_{60} (P < .001) were found to be significantly associated with DFS. In multiple variable analysis, these parameters were also significantly associated with DFS (P = .011 for SUV_{max}, P = .010 for MTV, P = .004 for TLG_{50}, and P = .005 for TLG_{60}). Only volumetric parameters (MTV, TLG_{50}, and TLG_{60}) were significant indicators of DFS in patients with tumors larger than 3 cm. Conclusion: SUV_{max}, MTV, and TLG at FDG PET/CT have a prognostic role for patients with NSCLC treated with SBRT. When tumors are larger than 3 cm, only MTV and TLG are predictive of DFS. © RSNA, 2013 Supplemental material: http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13130652/-/DC1.

[17] - CASTELLANO -
TÍTULO / TITLE: Radiochemotherapie mit Temozolomid für Patienten mit Hirnmetastasen bei nicht kleinzelligem Lungenkarzinom.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1007/s00508-013-0402-7

AUTORES / AUTHORS: - Hassler MR; Pfeifer W; Knocke-Abulesz TH; Geissler K; Altorjai G; Dieckmann K; Marosi C

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine I, Clinical Division of Oncology, Medical University of Vienna, Wahringer Gurtel 18-20, 1090, Vienna, Austria.

RESUMEN / SUMMARY: - BACKGROUND: This multicentric randomized phase II study investigated the feasibility and toxicity of temozolomide (TMZ) added to whole brain
radiotherapy (WBRT) followed by adjuvant TMZ in patients with multiple brain metastases of non-small-cell lung cancer (NSCLC). METHODS: Patients with multiple brain metastases from NSCLC aged ≥ 18 years, classified according to recursive partitioning analysis class I or II and with adequate organ functions were eligible. Treatment consisted of WBRT + TMZ 75 mg/m² for 2 weeks followed at day 28 by TMZ 100 mg/m²/day 2 weeks on/2 weeks off for up to 6 months (radiochemotherapy, RCT) or WBRT alone (radiotherapy, RT). RESULTS: The study enrolled only 35 patients (22 patients in RCT and 13 in RT) and had to be closed prematurely due to poor accrual. The toxicity was mainly due to TMZ with WHO grade 3 and 4 thrombocytopenia in 3/22 versus 0/13, leucocytopenia in 1/22 versus 0/13 and lymphocytopenia in 7/22 versus 12/13 patients in RCT and RT respectively. Thirteen patients in RCT and six in RT progressed systemically and dropped out before first restaging of the response in brain. Median time to progression (TTP) was 2.4 months (95 % CI: 2-2.6 months) and 2.0 months (95 % CI: 0.5-3.5 months), median overall survival (OAS) was 3 months (95 % CI: 1.7-3.1 months) and 6.3 months (95 % CI: 0.2-7.6 months) in RCT and RT, respectively. CONCLUSIONS: Like other studies before on patients with brain metastases, insufficient number of recruited patients does not allow conclusions on efficacy and toxicity as the study closed prematurely.

[18]


RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Ramalingam S; Crawford J; Chang A; Manegold C; Perez-Soler R; Douillard JY; Thatcher N; Barlesi F; Owonikoko T; Wang Y; Pultar P; Zhu J; Malik R; Giaccone G

INSTITUCIÓN / INSTITUTION: Department of Oncology, Robert W. Woodruff Health Sciences Center of Emory University, Atlanta.

RESUMEN / SUMMARY: BACKGROUND: Talactoferrin alfa is an oral dendritic cell (DC)-mediated immunotherapy (DCMI). We tested whether talactoferrin was superior to placebo in advanced non-small-cell lung cancer (NSCLC). PATIENTS AND METHODS: An FORTIS-M trial was an international, multicenter, randomized, double-blind comparison of talactoferrin (1.5 g p.o. BID) versus placebo BID, in patients with stage IIIB/IV NSCLC whose disease had failed two or more prior regimens. Treatment was administered for a maximum of five 14-week cycles. The primary efficacy end point was overall survival (OS); secondary end points included 6- and 12-month survival, progression-free survival (PFS), and disease control rate (DCR). RESULTS: Seven hundred and forty-two patients were randomly assigned (2:1) to talactoferrin (497) or
placebo (245). The median OS in the intent-to-treat (ITT) population was 7.66 months in the placebo arm and 7.49 months in the talactoferrin arm [hazard ratio (HR), 1.04; 95% CI, 0.873-1.24; P = 0.6602]. The 6-month survival rates were 59.9% (95% CI, 53.4% to 65.8%) and 55.7% (95% CI, 51.1% to 59.9%), respectively. The 12-month survival rates were 32.2% (95% CI, 26.3% to 38.2%) and 30.9% (95% CI, 26.8% to 35%), respectively. The median PFS rates were 1.64 months and 1.68 months, respectively (HR, 0.99; 95% CI, 0.835-1.16; P = 0.8073). The DCRs were 38.4 and 37.6%, respectively [stratified odds ratio (OR), 0.96; 95% CI, 0.698-1.33; P = 0.8336]. The safety profiles were comparable between arms. CONCLUSIONS: There was no improvement in efficacy with talactoferrin alfa in patients with advanced NSCLC whose disease had failed two or more previous regimens.

[19]

TÍTULO / TITLE: - 10-year long-term survival (LTS) of induction chemotherapy with three cycles cisplatin/paclitaxel followed by concurrent chemoradiation cisplatin/etoposide/45Gy (1.5Gy bid) plus surgery in locally advanced non-small-cell lung cancer (NSCLC)-A multicenter phase-II trial (CISTAXOL).

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Eberhardt WE; Gauler TC; Lepechoux C; Stamatis G; Bildat S; Krbek T; Welter S; Grunenwald D; Fischer B; Rodrigo Hde L; Theegarten D; Le Chevalier T; Seeber S; Stuschke M; Poettgen C

INSTITUCIÓN / INSTITUTION: - West German Cancer Centre, Department of Medical Oncology, 45122 Essen, Germany. Electronic address: wilfried.eberhardt@uni-essen.de.

RESUMEN / SUMMARY: - BACKGROUND: Induction chemoradiotherapy plus surgery remains an option to study in IIIA(N2) and selected IIIB NSCLC. Here we report ten-year long-term survival of a prospective multicenter German-French phase-II trial with trimodality. PATIENTS AND METHODS: Mediastinoscopically proven IIIA(N2)/selected IIIB NSCLC received three cycles cisplatin (50mg/m(2) day 1+8) and paclitaxel (175mg/m(2)d1) qd 22. Concurrent CTx/RTx followed: 45Gy (1.5Gy bid) with cisplatin 50mg/m(2) day 2+9 and etoposide 100mg/m(2) d 4-6. Surgery was planned three to five weeks after RTx. If evaluated inoperable/irresectable at the end of RTx, definitive RTx-boost (20Gy; 2Gy qd) followed. Here we report 10-year-LTS for this cohort.

RESULTS: All 64 patients were accrued 3/99 to 2/02. Patients characteristics: IIIA(N2)/IIIB 25/39; m/f 48/16; adeno/squamous/large-cell/adenosquamous/NOS 15/26/18/3/2; age: median 52.5 (range 33-69). 36 operated: R0 32/36 (89%); pCR 16/36 (44%). 10-year-LTS%; all 26.0; IIIA(N2) 37.1; IIIB 17.9; relevant prognostic factors
PRETREATMENT - HISTOPATHOLOGY (SQUAMOUS/ADENO) - AGE (<50/\geq50) - CHARLSON-CI: 1/\geq1 - BMI (>25/\leq25) - PACK YEARS SMOKING (>10/\leq10); TREATMENT-DEPENDENT - R0/NO-R0. CONCLUSIONS: This regimen achieves substantial LTS.

Interestingly, adenocarcinomas, older patients, unfavorable comorbidity scores, higher BMI and light smokers demonstrate poor long-term outcome even with aggressive trimodality. This dataset defines the rationale for our ongoing randomized trial with surgery after induction therapy in IIIA(N2)/SELECTED IIIB (ESPATU).

[20]

TÍTULO / TITLE: Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group.

RESUMEN / SUMMARY: Background: The palliative role of chemoradiation in the treatment of patients with locally advanced, inoperable non-small-cell lung cancer stage III and negative prognostic factors remains unresolved. Methods: Patients not eligible for curative radiotherapy were randomised to receive either chemoradiation or chemotherapy alone. Four courses of intravenous carboplatin on day 1 and oral vinorelbine on days 1 and 8 were given with 3-week intervals. Patients in the chemoradiation arm also received radiotherapy with fractionation 42 Gy/15, starting at the second chemotherapy course. The primary end point was overall survival; secondary end points were health-related quality of life (HRQOL) and toxicity. Results: Enrolment was terminated due to slow accrual after 191 patients from 25 Norwegian hospitals were randomised. Median age was 67 years and 21% had PS 2. In the chemotherapy versus the chemoradiation arm, the median overall survival was 9.7 and 12.6 months, respectively (P<0.01). One-year survival was 34.0% and 53.2% (P<0.01). Following a minor decline during treatment, HRQOL remained unchanged in the chemoradiation arm. The patients in the chemotherapy arm reported gradual deterioration during the subsequent months. In the chemoradiation arm, there were more hospital admissions related to side effects (P<0.05). Conclusion: Chemoradiation was superior to chemotherapy alone with respect to survival and HRQoL at the expense of more hospital admissions due to toxicity.
Gene expression profile of A549 cells from tissue of 4D model predicts poor prognosis in lung cancer patients.

RESUMEN / SUMMARY: The tumor microenvironment plays an important role in regulating cell growth and metastasis. Recently, we developed an ex vivo lung cancer model (four dimensional, 4D) that forms perfusable tumor nodules on a lung matrix that mimics human lung cancer histopathology and protease secretion pattern. We compared the gene expression profile (Human OneArray v5 chip) of A549 cells, a human lung cancer cell line, grown in a petri dish (two-dimensional, 2D), and of the same cells grown in the matrix of our ex vivo model (4D). Furthermore, we obtained gene expression data of A549 cells grown in a petri dish (2D) and matrigel (three-dimensional, 3D) from a previous study and compared the 3D expression profile with that of 4D. Expression array analysis showed 2,954 genes differentially expressed between 2D and 4D. Gene ontology (GO) analysis showed upregulation of several genes associated with extracellular matrix, polarity and cell fate and development. Moreover, expression array analysis of 2D vs. 3D showed 1,006 genes that were most differentially expressed, with only 36 genes (4%) having similar expression patterns as observed between 2D and 4D. Finally, the differential gene expression signature of 4D cells (vs. 2D) correlated significantly with poor survival in patients with lung cancer (n = 1,492), while the expression signature of 3D vs. 2D correlated with better survival in lung cancer patients with lung cancer. As patients with larger tumors have a worse rate of survival, the ex vivo 4D model may be a good mimic of natural progression of tumor growth in lung cancer patients.

Volumetric tumor growth in advanced non-small cell lung cancer patients with EGFR mutations during EGFR-tyrosine kinase inhibitor therapy: Developing criteria to continue therapy beyond RECIST progression.

RESUMEN / SUMMARY: The tumor microenvironment plays an important role in regulating cell growth and metastasis. Recently, we developed an ex vivo lung cancer model (four dimensional, 4D) that forms perfusable tumor nodules on a lung matrix that mimics human lung cancer histopathology and protease secretion pattern. We compared the gene expression profile (Human OneArray v5 chip) of A549 cells, a human lung cancer cell line, grown in a petri dish (two-dimensional, 2D), and of the same cells grown in the matrix of our ex vivo model (4D). Furthermore, we obtained gene expression data of A549 cells grown in a petri dish (2D) and matrigel (three-dimensional, 3D) from a previous study and compared the 3D expression profile with that of 4D. Expression array analysis showed 2,954 genes differentially expressed between 2D and 4D. Gene ontology (GO) analysis showed upregulation of several genes associated with extracellular matrix, polarity and cell fate and development. Moreover, expression array analysis of 2D vs. 3D showed 1,006 genes that were most differentially expressed, with only 36 genes (4%) having similar expression patterns as observed between 2D and 4D. Finally, the differential gene expression signature of 4D cells (vs. 2D) correlated significantly with poor survival in patients with lung cancer (n = 1,492), while the expression signature of 3D vs. 2D correlated with better survival in lung cancer patients with lung cancer. As patients with larger tumors have a worse rate of survival, the ex vivo 4D model may be a good mimic of natural progression of tumor growth in lung cancer patients.
BACKGROUND: The objective of this study was to define the volumetric tumor growth rate in patients who had advanced nonsmall cell lung cancer (NSCLC) with sensitizing epidermal growth factor receptor (EGFR) mutations and had initially received treatment with EGFR-tyrosine kinase inhibitor (TKI) therapy beyond progression. METHODS: The study included 58 patients with advanced NSCLC who had sensitizing EGFR mutations treated with first-line gefitinib or erlotinib, had baseline computed tomography (CT) scans available that revealed a measurable lung lesion, had at least 2 follow-up CT scans during TKI therapy, and had experienced volumetric tumor growth. The tumor volume (in mm³) of the dominant lung lesion was measured on baseline and follow-up CT scans during therapy. In total, 405 volume measurements were analyzed in a linear mixed-effects model, fitting time as a random effect, to define the growth rate of the logarithm of tumor volume (loge V). RESULTS: A linear mixed-effects model was fitted to predict the growth of loge V, adjusting for time in months from baseline. Loge V was estimated as a function of time in months among patients whose tumors started growing after the nadir: loge V = 0.12*time + 7.68. In this formula, the regression coefficient for time, 0.12/month, represents the growth rate of loge V (standard error, 0.015/month; P < .001). When adjusted for baseline volume, loge V₀, the growth rate was also 0.12/month (standard error, 0.015/month; P < .001; loge V = 0.12*months + 0.72 loge V₀ + 0.61). CONCLUSIONS: Tumor volume models defined volumetric tumor growth after the nadir in patients with EGFR-mutant, advanced NSCLC who were receiving TKI, providing a reference value for the tumor growth rate in patients who progress after the nadir on TKI therapy. The results can be studied further in additional cohorts to develop practical criteria to help identify patients who are slowly progressing and can safely remain on EGFR-TKIs. Cancer 2013. © 2013 American Cancer Society.

[23]

TÍTULO / TITLE: - Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: An updated retrospective study on local failure and survival rates.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 3109/0284186X.2013.813635

AUTORES / AUTHORS: - Jeppesen SS; Schytte T; Jensen HR; Brink C; Hansen O
INTRODUCCIÓN / SUMMARY: - Abstract Introduction. Stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC) is now an accepted and patient friendly treatment, but still controversy exists about its comparability to conventional radiation therapy (RT). The purpose of this single-institutional report is to describe survival outcome for medically inoperable patients with early stage NSCLC treated with SBRT compared with high dose conventional RT. Material and methods. From August 2005 to June 2012, 100 medically inoperable patients were treated with SBRT at Odense University Hospital. The thoracic RT consisted of 3 fractions (F) of 15-22 Gy delivered in nine days. For comparison a group of 32 medically inoperable patients treated with conventional RT with 80 Gy/35-40 F (5 F/week) in the period of July 1998 to August 2011 were analyzed. All tumors had histological or cytological proven NSCLC T1-2N0M0. Results. The median overall survival was 36.1 months versus 24.4 months for SBRT and conventional RT, respectively (p = 0.015). Local failure-free survival rates at one year were in SBRT group 93% versus 89% in the conventional RT group and at five years 69% versus 66%, SBRT and conventional RT respectively (p = 0.99). On multivariate analysis, female gender and performance status of 0-1 and SBRT predicted improved prognosis. Conclusion. In a cohort of patients with NSCLC there was a significant difference in overall survival favoring SBRT. Performance status of 0-1, female gender and SBRT predicted improved prognosis. However, staging procedure, confirmation procedure of recurrence and technical improvements of radiation treatment is likely to influence outcomes. However, SBRT seems to be as efficient as conventional RT and is a more convenient treatment for the patients.

[24]
TÍTULO / TITLE: - Patterns of disease progression on 18F-fluorodeoxyglucose positron emission tomography-computed tomography in patients with malignant pleural mesothelioma undergoing multimodality therapy with pleurectomy/decortication.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1097/MNM.0b013e3283653862
AUTORES / AUTHORS: - Bille A; Chicklore S; Okior L; Cook GJ; Spicer J; Landau D; Lang-Lazdunski L
INSTITUCIÓN / INSTITUTION: - aDepartment of Thoracic Surgery bPET Imaging Centre cDepartment of Oncology and Haematology, Guy’s & St Thomas’ Hospital NHS Foundation Trust dDivision of Cancer Studies and Division of Imaging Sciences and Biomedical Engineering King’s College, London, UK.
INTRODUCTION: The aim of this study was to evaluate the patterns of disease progression in patients treated with pleurectomy/decortication (P/D), hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy and adjuvant chemotherapy, using F-fluorodeoxyglucose (F-FDG) PET/computed tomography (PET/CT). 

MATERIALS AND METHODS: This was a retrospective study of 65 patients treated with a multimodality therapy including P/D between October 2004 and March 2012. Thirty-two patients underwent F-FDG PET/CT within 6 weeks of completion of adjuvant chemotherapy and 6-monthly thereafter at our institution. The first site of relapse on F-FDG PET/CT was recorded, and all scans were reviewed by an independent observer. 

RESULTS: Thirty-two patients (27 male, median age 61 years, range 45-73) underwent their F-FDG PET/CT scans at our institution. Eighteen of the 32 patients were alive at last follow-up (median follow-up 42 months, range 16-76). Nine patients were alive with disease recurrence. Fourteen patients died of disease progression (median survival 24.7 months, range 15-38). The median maximum standardized uptake value (SUVmax) in relapsing mesothelioma was 10.9 (range 4.9-27.3). There was a statistically significant correlation between the SUVmax and tumour lesion glycolysis of recurrent mesothelioma and overall survival (P=0.05). The site of disease recurrence was the pleura in the majority of the alive patients and was extrapleural in the dead patients. There was a statistically significant correlation between disease-free survival and complete macroscopic resection (P=0.02). 

CONCLUSION: After P/D with hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy and adjuvant chemotherapy, the most frequent site of recurrence is the pleural cavity. Peritoneal seeding is rare. The tumour SUVmax and tumour lesion glycolysis correlate significantly with overall survival.

[25]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Yamaguchi S; Ohguri T; Ide S; Aoki T; Imada H; Yahara K; Narisada H; Korogi Y

INSTITUCIÓN / INSTITUTION: - Department of Radiology, University of Occupational and Environmental Health, Kitakyushu, Japan.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the toxicity and efficacy of thoracic stereotactic body radiotherapy (SBRT) in patients with subclinical interstitial lung disease (ILD). METHODS AND MATERIALS: One hundred patients with 124 lung tumors
were treated with SBRT at our institution according to our own protocols; patients with subclinical (untreated and oxygen-free) ILD were treated with SBRT, while those with clinical ILD (post- or under treatment) were not. The administration of 48Gy in four fractions was used in 103 (83%) of the 124 tumors. The presence of subclinical ILD in the pre-SBRT CT findings was reviewed by two chest radiologists. The relationships between radiation pneumonitis (RP) and clinical factors were investigated. RESULTS: Subclinical ILD was recognized in 16 (16%) of 100 patients. Grade 2-5 RP was recognized in 13 (13%) of 100 patients. Grade 2-5 RP was observed in three (19%) of 16 patients with subclinical ILD. Subclinical ILD was not found to be a significant factor influencing Grade 2-5 RP; however, extensive RP beyond the irradiated field, including the contralateral lung, was recognized in only three patients with subclinical ILD, and the rate of extensive RP was significantly high in the patients with subclinical ILD. Grade 4 or 5 extensive RP was recognized in only two patients with subclinical ILD. Dosimetric factors of the lungs (V5, V10, V15, V20, V25, MLD) were significantly associated with Grade 2-5 RP. The three-year overall survival and local control rates of all patients were 53% and 86%, respectively. No significant differences were seen in either overall survival or local control rates between the patients with ILD and those without ILD. CONCLUSIONS: Subclinical ILD was not found to be a significant factor for Grade 2-5 RP or clinical outcomes in the current study; however, uncommon extensive RP can occur in patients with subclinical ILD.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhai R; Yu X; Shafer A; Wain JC; Christiani DC
RESUMEN / SUMMARY: - BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a recognized risk factor for lung cancer, but studies of coexisting COPD in relation to lung cancer outcomes are limited. We assessed the impact of COPD on overall survival (OS) and progression-free survival (PFS) in patients with early-stage non-small cell lung cancer (NSCLC). METHODS: Patients (n = 902) with early-stage (stage IA-IIB) NSCLC, treated with surgical resection, were retrospectively analyzed. The association of self-reported, physician-diagnosed COPD with survivals of NSCLC was assessed using the log-rank and Cox regression models, adjusting for age, gender, BMI, smoking, stages, and performance status. RESULTS: Among this cohort of NSCLC patients, 330 cases had physician-diagnosed COPD and 572 did not have COPD. The 5-year OS in patients with COPD (54.4%) was significantly (P = .0002) lower than that in patients without
COPD (69.0%). The 5-year PFS rates for patients with COPD and without COPD were 50.1% and 60.6%, respectively (P = .007). Compared with patients without COPD, patients with COPD had increased risk of worse OS (adjusted hazard ratio [HRadj] = 1.41; P = .002) and PFS (HRadj = 1.67; P = .003). The associations between COPD and worse survival outcomes were stronger in male and in squamous cell carcinoma (SCC). CONCLUSIONS: Co-existing COPD is associated with worse survival outcomes in early-stage NSCLC patients, particularly for men and for SCC.

[27]


RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1007/s13277-013-1132-1

AUTORES / AUTHORS - Zhong R; Han B; Zhong H

INSTITUCIÓN / INSTITUTION - Department of Pulmonary Disease, Shanghai Chest Hospital, Shanghai Jiao Tong University, No. 241, Huaihai Road (W), Shanghai, People’s Republic of China.

RESUMEN / SUMMARY - Dendritic cells (DC) play a crucial role in the induction of an effective antitumor immune response. Cytokine-induced killer (CIK) cells, a subset of T lymphocytes, have the capacity to eliminate cancer cells. This study was to evaluate the correlation between the frequency of DC/CIK immunotherapies following regular chemotherapy, the time-to-progression (TTP), and overall survival (OS) of advanced non-small lung cancer patients. Sixty patients with IIIB-IV non-small-cell lung carcinoma (NSCLC) were enrolled from August 2007 to December 2009 and were randomized into two groups. All 60 patients received four courses of navelbine-platinum (NP) chemotherapy. In one group, 30 patients were treated with adoptive autologous DC/CIK cell transfusion twice every 30 days. In the other group, the patients received immunotherapies more than twice every 30 days. The adverse effects, TTP, and OS were evaluated between the two groups. Median survival time of all 60 patients was 13.80 months. The 1-, 2-, and 3-year overall survival rates were 60.0, 21.7, and 15.0 %, respectively. The 1-, 2-, and 3-year overall survival rates of patients receiving more than two immunotherapies were 63.3, 30.0, and 23.3 %, and the rates of those receiving two immunotherapies were 56.7, 13.3, and 6.7 %, respectively. The difference between the two groups was statistically significant (P = 0.037). Compared with patients in the fewer immunotherapies group, TTP in the group receiving more immunotherapies significantly prolonged, with the median improving from 6.2 months (95 % CI, 5.35-9.24) to 7.3 months (95 % CI, 5.45-6.95; P = 0.034). The adverse effects of chemoimmunotherapy were tolerable. Advanced NSCLC patients can benefit from
the combination of DC/CIK immunotherapies following conventional chemotherapy. More than two immunotherapies improved TTP and OS of those patients in this study.

[28]

TÍTULO / TITLE: - Phase I/II trial of pemetrexed plus nab-paclitaxel in advanced solid tumor patients with emphasis on non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Ho C; Davies AM; Sangha RS; Lau D; Lara P Jr; Chew HK; Beckett L; Mack PC; Riess JW; Gandara DR

INSTITUCIÓN / INSTITUTION: - British Columbia Cancer Agency, 600 W 10th Avenue, Vancouver, BC, V5Z 4E6, Canada, cho@bccancer.bc.ca.

RESUMEN / SUMMARY: - Background Despite advances in targeted therapies, there is an ongoing need to develop new and effective cytotoxic drug combinations in non-small cell lung cancer (NSCLC). Based on preclinical demonstration of additive cytotoxicity, we evaluated the safety and efficacy of combining pemetrexed and nanoparticle albumin bound (nab) paclitaxel with a focus on NSCLC for phase II expansion. Methods A 3 + 3 dose-escalation design was used to determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D). Three dose levels were tested: pemetrexed 500 mg/m2 day 1 and nab-paclitaxel day 1 at 180, 220, & 260 mg/m2 every 21 days. Phase II eligibility included advanced NSCLC, =<2 line prior therapy, PS 0-1, adequate organ function. Primary endpoint for further study was response rate (RR) =/> 25 %. Results Planned dose escalation was completed without reaching the MTD. The RP2D was pemetrexed 500 mg/m2 and nab-paclitaxel 260 mg/m2. The phase II portion accrued 37 pts before early closure due to increasing first-line pemetrexed/platinum doublet use in non-squamous NSCLC. In 31 assessable phase II patients there were 5 partial responses, 12 stable disease, 14 progressive disease. The median overall survival was 8.8 months; progressive disease 4.4 months and disease control 15.6 months. Conclusions Pemetrexed 500 mg/m2 day 1 with nab-paclitaxel 260 mg/m2 was feasible and well tolerated. The phase II component demonstrated activity in second/third-line therapy of advanced NSCLC; response rate 14 % and disease control rate 46 %. Treatment practice patterns of advanced NSCLC have evolved; further trials of this regimen are not planned.

[29]

TÍTULO / TITLE: - Uveal Metastasis from Lung Cancer: Clinical Features, Treatment, and Outcome in 194 Patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Shah SU; Mashayekhi A; Shields CL; Walia HS; Hubbard GB 3rd; Zhang J; Shields JA

INSTITUCIÓN / INSTITUTION: - Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the clinical features, treatment, and prognosis of patients with uveal metastasis from lung cancer. DESIGN: Retrospective chart review. PARTICIPANTS: There were 194 patients with a diagnosis of uveal metastasis from lung cancer. INTERVENTION: Radiotherapy, chemotherapy, enucleation, or observation. MAIN OUTCOME MEASURES: Ocular tumor control, final visual acuity, and tumor-related death. RESULTS: There were 374 uveal metastatic tumors originating from primary lung cancer in 229 eyes of 194 patients. Tumor location included choroid (88%), ciliary body (2%), and iris (10%), with bilateral involvement in 18%. Diagnosis of uveal metastasis preceded the diagnosis of primary lung cancer in 44% of patients. The choroidal metastatic focus had a mean basal diameter of 8 mm and mean thickness of 3 mm, and were mostly located posterior to the equator (91%). The choroidal metastasis commonly had yellow or orange color (98%), had plateau (61%) or dome (38%) configuration, and displayed associated subretinal fluid (85%). Choroidal tumors were multifocal in 49 cases (23%). Ciliary body tumors were commonly dome shaped (75%) with an episcleral sentinel vessel (75%). Iris tumors were multifocal in 2 cases (13%), had visible intrinsic vessels (97%), and were associated with tumor seeding in the angle (38%) or on the iris stroma (25%). The uveal metastases were treated with teletherapy (31%), chemotherapy (18%), brachytherapy (9%), chemotherapy combined with teletherapy or brachytherapy (14%), enucleation (3%), or observation (21%). At last visit, eyes with follow-up showed tumor regression (66%), stability (12%), growth (14%), recurrence (3%), or new metastasis (5%). Visual acuity improved or remained stable in 59% eyes. One-year mortality from the time of detection of uveal metastasis was 54%. CONCLUSIONS: Of 194 patients with uveal metastasis from lung cancer, 44% did not have a history of known lung cancer. Current methods of ocular treatment allow globe salvage in 92% of patients and improved/stable vision in 59% of patients. Systemic prognosis remains poor with tumor-related death in 54% of patients at 1 year. FINANCIAL DISCLOSURE(S): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

[30]
First clinical results of adaptive radiotherapy based on 3D portal dosimetry for lung cancer patients with atelectasis treated with volumetric-modulated arc therapy (VMAT).

RESUMEN / SUMMARY: Abstract Atelectasis in lung cancer patients can change rapidly during a treatment course, which may displace the tumor/healthy tissues, or change tissue densities locally. This may result in differences between the planned and the actually delivered dose. With complex delivery techniques treatment verification is essential and inter-fractional adaptation may be necessary. We present the first clinical results of treatment adaptation based on an in-house developed three-dimensional (3D) portal dose measurement (PDM) system. Material and methods. A method was developed for 3D PDM combined with cone beam computed tomography (kV-CBCT) imaging. Lung cancer patients are monitored routinely with this imaging technique. During treatment, the first three fractions are analyzed with 3D PDM and weekly thereafter. The reconstructed measured dose is compared to the planned dose using dose-volume histograms and a gamma evaluation. Patients having $|\gamma| > 1$ in more than 5% of the (primary tumor or organ at risk) volume were subjected to further analysis. In this study we show the PDM dose changes for five patients. Results. We detected relevant dose changes induced by changes in atelectasis in the presented cases. Two patients received two treatment adaptations after being detected with PDM confirmed by visual inspection of the kV-CBCTs, and in two other patients the radiation treatment plan was adapted once. In one case no dose delivery change was detected with PDM. Conclusion. The first clinical patients show that 3D PDM combined with kV-CBCT is a valuable quality assurance tool for detecting anatomical alterations and their dosimetric consequences during the course of radiotherapy. In our clinic, 3D PDM is fully automated for ease and speed of the procedure, and for minimization of human error. The technique is able to flag patients with suspected dose discrepancies for potential adaptation of the treatment plan.

Gene expression signature of non-involved lung tissue associated with survival in lung adenocarcinoma patients.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Galvan A; Frullanti E; Anderlini M; Manenti G; Noci S; Dugo M; Ambrogi F; De Cecco L; Spinelli R; Piazza R; Pirola A; Gambacorti-Passerini C; Incarbone M; Alloiso M; Tosi D; Nosotti M; Santambrogio L; Pastorino U; Dragani TA

INSTITUCIÓN / INSTITUTION: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

RESUMEN / SUMMARY: Lung adenocarcinoma patients of similar clinical stage and undergoing the same treatments often have marked interindividual variations in prognosis. These clinical discrepancies may be due to the genetic background modulating an individual’s predisposition to fighting cancer. Herein, we hypothesized that the lung microenvironment, as reflected by its expression profile, may affect lung adenocarcinoma patients’ survival. The transcriptome of non-involved lung tissue, excised from a discovery series of 204 lung adenocarcinoma patients, was evaluated using whole-genome expression microarrays (with probes corresponding to 28,688 well-annotated coding sequences). Genes associated with survival status at 60 months were identified by Cox regression analysis (adjusted for gender, age and clinical stage) and retested in a validation series of 78 additional cases. RNA-Seq analysis from non-involved lung tissue of 12 patients was performed to characterize the different isoforms of candidate genes. Ten genes for which the loge-transformed hazard ratios expressed the same direction of effect in the discovery (P < 1.0 x 10^-3) and validation series comprised the gene expression signature associated with survival: CNTNAP1, PKNOX1, FAM156A, FRMD8, GALNT1, TXNDC12, SNTB1, PPP3R1, SNX10 and SERPINH1. RNA sequencing highlighted the complex expression pattern of these genes in non-involved lung tissue from different patients and permitted the detection of a read-through gene fusion between PPP3R1 and the flanking gene (CNRIP1) as well as a novel isoform of CNTNAP1. Our findings support the hypothesis that individual genetic characteristics, evidenced by the expression pattern of non-involved tissue, influence the outcome of lung adenocarcinoma patients.

[32]


RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Gagnon B; Agulnik JS; Gioulbasanis I; Kasymjanova G; Morris D; Macdonald N
Background: For evidence-based medical practice, well-defined risk scoring systems are essential to identify patients with a poor prognosis. The objective of this study was to develop a prognostic score, the Montreal prognostic score (MPS), to improve prognostication of patients with incurable non-small cell lung cancer (NSCLC) in everyday practice.

Methods: A training cohort (TC) and a confirmatory cohort (CC) of newly diagnosed patients with NSCLC planning to receive chemotherapy were used to develop the MPS. Stage and clinically available biomarkers were entered into a Cox model and risk weights were estimated. C-statistics were used to test the accuracy.

Results: The TC consisted of 258 patients and the CC consisted of 433 patients. Montreal prognostic score classified patients into three distinct groups with median survivals of 2.5 months (95% confidence interval (CI): 1.8, 4.2), 8.2 months (95% CI: 7.0, 9.4) and 18.2 months (95% CI: 14.0, 27.5), respectively (log-rank, P<0.001). Overall, the C-statistics were 0.691 (95% CI: 0.685, 0.697) for the TC and 0.665 (95% CI: 0.661, 0.670) for the CC.

Conclusion: The MPS, by classifying patients into three well-defined prognostic groups, provides valuable information, which physicians could use to better inform their patients about treatment options, especially the best timing to involve palliative care teams.


[33]

- Air pollution: a potentially modifiable risk factor for lung cancer.

Economic growth and increased urbanization pose a new risk for cancer development: the exposure of high numbers of people to ambient air pollution. Epidemiological evidence that links air pollution to mortality from lung cancer is robust. An ability to produce high-quality scientific research that addresses these risks and the ability of local health authorities to understand and respond to these risks are basic requirements to solve the conflict between economic
development and the preservation of human health. However, this is currently far from being achieved. Thus, this Science and Society article addresses the possibilities of expanding scientific networking to increase awareness of the risk of lung cancer that is promoted by air pollution.

[34]

TÍTULO / TITLE: - Locoregional Small Cell Carcinoma of the Bladder: Clinical Characteristics and Treatment Patterns in Over 600 Patients from the National Cancer Database.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Patel SG; Stimson CJ; Zaid HB; Resnick MJ; Cookson MS; Barocas DA; Chang SS

INSTITUCIÓN / INSTITUTION: - Department of Urology, Vanderbilt University Medical Center, Nashville TN. Electronic address: sanjay.g.patel@vanderbilt.edu.

RESUMEN / SUMMARY: - INTRODUCTION: Small cell carcinoma (SCC) of the bladder is a relatively rare tumor type, and consequently, the volume of literature surrounding its treatment remains limited. We sought to elaborate patterns of care and survival after treatment in the largest series of patients with locoregional SCC of the bladder to date. METHODS: We identified patients with localized/locally advanced (cTis-cT4, cN0, cM0) bladder SCC diagnosed between 1998 and 2010 from the National Cancer Database (NCDB). Treatment was categorized as bladder preservation therapy (BPT), radical cystectomy alone (RC), BPT with multimodal treatment (BSS/MMT), or RC with multimodal treatment (RC/MMT). We performed a Kaplan-Meier overall survival (OS) analysis to evaluate for differential survival between treatment groups. RESULTS: A total of 625 patients met our inclusion criteria. The median age at diagnosis was 73 years (range 36-90) and 65% of patients presented with cT2 disease. When stratified by treatment type 174 (27.8%) underwent BPT, 333 (53.3%) underwent BPT+MMT, 46 (7.4%) underwent RC, and 72 (11.5%) underwent RC+MMT. The 3-year OS was 23% [95% CI: 15%-32%], 35% [30%-45%], 38% [17%-60%], and 30.1% [16%-47%] for BPT, BPT+MMT, RC, and RC+MMT respectively. The OS was most favorable with RC+ neoadjuvant chemotherapy with a 3-year OS of 53% [95%CI: 19%-79%]. CONCLUSION: In the US, locoregional small cell carcinoma of the bladder predominantly occurs in Caucasian males with treatment in Metropolitan, Comprehensive Community Cancer Centers. The majority of patients were managed with BPT and most receive multimodal therapy. Patients receiving neoadjuvant chemotherapy followed by RC had the most favorable survival.
BACKGROUND: Experimental models of cancer cachexia have indicated that systemic inflammation induces muscle-protein breakdown and wasting via muscular nuclear transcription factor kappa B (NF-κappa B) activation. This process may limit the efficacy of nutritional intervention. OBJECTIVES: We assessed muscle NF-kappa B activity and protein turnover signaling in progressive stages of clinical lung cancer cachexia and assessed whether circulating factors can induce muscular NF-kappa B activity. DESIGN: Patients with lung cancer precachexia (n = 10) and cachexia (n = 16) were cross-sectionally compared with 22 healthy control subjects. mRNA transcripts of muscle proteolytic (ubiquitin proteasome system and autophagy lysosomal pathway) and myogenic markers and protein expression of PI3K/Akt, myostatin, and autophagy signaling were measured. A multiplex analysis showed the systemic inflammatory status, whereas plasma exposure to stable NF-κappa B-luciferase-reporter muscle cells revealed NF-κappa B inducibility. RESULTS: Compared with healthy control subjects, cachectic patients had reduced (appendicular) muscle mass (-10%), muscle fiber atrophy (-27%), and decreased quadriceps strength (-31%). Subtle alterations in the muscle morphology were also detectable in precachectic patients, without changes in body composition. Despite increased Akt phosphorylation, downstream phosphosubstrates glycogen synthase kinase 3 beta, mammalian target of rapamycin, and Forkhead box protein were unaltered. The expression of autophagy effectors B cell lymphoma 2/adenovirus E1B 19-kDa protein-interacting protein 3 and microtubule-associated proteins 1B light chain 3B gradually increased from precachectic to cachectic patients, without differences in E3 ubiquitin ligases. Systemic and local inflammation was evident in cachexia and intermediate in precachexia, but the plasma of both patients groups caused ex vivo muscle NF-κappa B activation. CONCLUSIONS: In lung cancer, muscular NF-κappa B activity is induced by factors contained within the circulation. Autophagy may contribute to increased muscle proteolysis in lung cancer cachexia, whereas the
absence of downstream changes in phosphosubstrates despite increased Akt phosphorylation suggests impaired anabolic signaling that may require targeted nutritional intervention.

[36]

**TÍTULO / TITLE** - Identification of Transcriptional Subgroups in EGFR-Mutated and EGFR/KRAS Wild-Type Lung Adenocarcinoma Reveals Gene Signatures Associated with Patient Outcome.

**RESUMEN / SUMMARY** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS**: Planck M; Isaksson S; Veerla S; Staaf J

**INSTITUCIÓN / INSTITUTION**: Authors’ Affiliations: Department of Oncology, Clinical Sciences, Skane University Hospital; and CREATE Health Strategic Center for Translational Cancer Research, Lund University, Lund, Sweden.

**RESUMEN / SUMMARY**: PURPOSE: In lung adenocarcinoma, EGFR and KRAS mutations dominate the mutational spectrum and have clear therapeutic implications. We sought to determine whether transcriptional subgroups of clinical relevance exist within EGFR-mutated, KRAS-mutated, or EGFR and KRAS wild-type (EGFRwt/KRASwt) adenocarcinomas. EXPERIMENTAL DESIGN: Gene expression profiles from 1,186 adenocarcinomas, including 215 EGFR-mutated, 84 KRAS-mutated, and 219 EGFRwt/KRASwt tumors, were assembled and divided into four discovery (n = 522) and four validation cohorts (n = 664). Subgroups within the mutation groups were identified by unsupervised consensus clustering, significance analysis of microarrays (SAM) analysis, and centroid classification across discovery cohorts. Genomic alterations in identified mutation subgroups were assessed by integration of genomic profiles for 158 cases with concurrent data. Multicohort expression subgroup predictors were built for each mutation group using the discovery cohorts, and validated in the four validation cohorts. RESULTS: Consensus clustering within the mutation groups identified reproducible transcriptional subgroups in EGFR-mutated and EGFRwt/KRASwt tumors, but not in KRAS-mutated tumors. Subgroups displayed differences in genomic alterations, clinicopathologic characteristics, and overall survival. Multicohort gene signatures derived from the mutation subgroups added independent prognostic information in their respective mutation group, for adenocarcinoma in general and stage I tumors specifically, irrespective of mutation status, when applied to the validation cohorts. Consistent with their worse clinical outcome, high-risk subgroups showed higher expression of proliferation-related genes, higher frequency of copy number alterations/amplifications, and association with a poorly differentiated tumor phenotype. CONCLUSIONS: We identified transcriptional...
subgroups in EGFR-mutated and EGFRwt/KRASwt adenocarcinomas with significant differences in clinicopathologic characteristics and patient outcome, not limited to a mutation-specific setting. Clin Cancer Res; 19(18); 5116-26. ©2013 AACR.

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**RESUMEN / SUMMARY**: Excision-repair-cross-complement-1 (ERCC1) protein expression in tumor cells has been associated with resistance to platinum compounds, the backbone of treatment in NSCLC. In the current study the impact of the tumoral ERCC1 protein expression on the outcome of patients with advanced stage NSCLC treated with platinum-based chemotherapy, was investigated. Ninety-four patients with inoperable stage III-IV NSCLC, treated with platinum-based first-line chemotherapy, were retrospectively analyzed. Pretreatment tumor samples were analyzed for ERCC1 protein expression using immunohistochemistry. Response to treatment, time to tumor progression (TTP), and overall survival (OS) were correlated with patients’ clinicopathological characteristics and ERCC1 protein expression on tumor cells. ERCC1 protein low expression was detected in 39 (41.5%) patients and did not correlate with patients’ clinicopathological characteristics or response to chemotherapy. However, ERCC1 protein low expression showed a trend for better disease control rate (p=0.059), longer TTP (5.3 vs. 3.2 months; p=0.051) and significantly longer OS (18.7 vs. 9.7 months; p=0.009). ERCC1 could have a role in refining prognosis and thus individualizing chemotherapy for advanced stage NSCLC.

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[38] **TÍTULO / TITLE**: Needs regarding care and factors associated with unmet needs in disease-free survivors of surgically treated lung cancer.

**RESUMEN / SUMMARY**: Needs regarding care and factors associated with unmet needs in disease-free survivors of surgically treated lung cancer.
[39] **TITULO / TITLE:** Proline-rich tyrosine kinase 2 and its phosphorylated form pY881 are novel prognostic markers for non-small-cell lung cancer progression and patients’ overall survival.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Kuang BH; Zhang MQ; Xu LH; Hu LJ; Wang HB; Zhao WF; Du Y; Zhang X

**INSTITUCIÓN / INSTITUTION:** State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, 651 East Dongfeng Road, Guangzhou 510060, China.

**RESUMEN / SUMMARY:** Background: Our previous study revealed that proline-rich tyrosine kinase 2 (Pyk2) is implicated in both anchorage-independent growth and anoikis resistance in lung cancer cells. This study aims to explore the expression and clinical significance of Pyk2 and its phosphorylated forms in non-small-cell lung cancer (NSCLC).

**Methods:** The mRNA and protein levels of Pyk2 or cancer stem cell markers (ALDH1a1, ABCG2 and Bmi-1) were either examined by reverse transcription-PCR or western blotting. An immunohistochemistry (IHC) assay was conducted to analyse the expression of Pyk2 and its phosphorylated forms in 128 NSCLC cases.

**Results:** The levels of Pyk2 mRNA, total protein, and its phosphorylated form pY881 were higher in lung cancer lesions than in the paired noncancerous tissues. The IHC analysis showed the levels of the Pyk2 and Pyk2[pY881] proteins were highly expressed in 70 (54.7%) and 77 (60.2%) cases, respectively. Both Pyk2 and Pyk2[pY881] were independent prognostic factors for NSCLC patients. The gain and loss study of Pyk2 function revealed that Pyk2 could upregulate the expression of ALDH1a1, ABCG2 and Bmi-1 and enhance the ability of colony formation in soft agar assay in A549 and H460 cells.

**Conclusion:** Both Pyk2 and phosphorylated Pyk2[pY881] are potential prognostic factors and therapeutic targets for NSCLC.

[40]

**TITULO / TITLE:** Mechanism for activation of mutated epidermal growth factor receptors in lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Red Brewer M; Yun CH; Lai D; Lemmon MA; Eck MJ; Pao W
The initiation of epidermal growth factor receptor (EGFR) kinase activity proceeds via an asymmetric dimerization mechanism in which a “donor” tyrosine kinase domain (TKD) contacts an “acceptor” TKD, leading to its activation. In the context of a ligand-induced dimer, identical wild-type EGFR TKDs are thought to assume the donor or acceptor roles in a random manner. Here, we present biochemical reconstitution data demonstrating that activated EGFR mutants found in lung cancer preferentially assume the acceptor role when coexpressed with WT EGFR. Mutated EGFRs show enhanced association with WT EGFR, leading to hyperphosphorylation of the WT counterpart. Mutated EGFRs also hyperphosphorylate the related erythroblastic leukemia viral oncogene (ErbB) family member, ErbB-2, in a similar manner. This directional “superacceptor activity” is particularly pronounced in the drug-resistant L834R/T766M mutant. A 4-A crystal structure of this mutant in the active conformation reveals an asymmetric dimer interface that is essentially the same as that in WT EGFR. Asymmetric dimer formation induces an allosteric conformational change in the acceptor subunit. Thus, superacceptor activity likely arises simply from a lower energetic cost associated with this conformational change in the mutant EGFR compared with WT, rather than from any structural alteration that impairs the donor role of the mutant. Collectively, these findings define a previously unrecognized mode of mutant-specific intermolecular regulation for ErbB receptors, knowledge of which could potentially be exploited for therapeutic benefit.
**RESUMEN / SUMMARY:** - BACKGROUND: Icotinib, an oral EGFR tyrosine kinase inhibitor, had shown antitumour activity and favourable toxicity in early-phase clinical trials. We aimed to investigate whether icotinib is non-inferior to gefitinib in patients with non-small-cell lung cancer. METHODS: In this randomised, double-blind, phase 3 non-inferiority trial we enrolled patients with advanced non-small-cell lung cancer from 27 sites in China. Eligible patients were those aged 18-75 years who had not responded to one or more platinum-based chemotherapy regimen. Patients were randomly assigned (1:1), using minimisation methods, to receive icotinib (125 mg, three times per day) or gefitinib (250 mg, once per day) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival, analysed in the full analysis set. We analysed EGFR status if tissue samples were available. All investigators, clinicians, and participants were masked to patient distribution. The non-inferiority margin was 1.14; non-inferiority would be established if the upper limit of the 95% CI for the hazard ratio (HR) of gefitinib versus icotinib was less than this margin. This study is registered with ClinicalTrials.gov, number NCT01040780, and the Chinese Clinical Trial Registry, number ChiCTR-TRC-09000506. FINDINGS: 400 eligible patients were enrolled between Feb 26, 2009, and Nov 13, 2009; one patient was enrolled by mistake and removed from the study, 200 were assigned to icotinib and 199 to gefitinib. 395 patients were included in the full analysis set (icotinib, n=199; gefitinib, n=196). Icotinib was non-inferior to gefitinib in terms of progression-free survival (HR 0.84, 95% CI 0.67-1.05; median progression-free survival 4.6 months [95% CI 3.5-6.3] vs 3.4 months [2.3-3.8]; p=0.13). The most common adverse events were rash (81 [41%] of 200 patients in the icotinib group vs 98 [49%] of 199 patients in the gefitinib group) and diarrhoea (43 [22%] vs 58 [29%]). Patients given icotinib had less drug-related adverse events than did those given gefitinib (121 [61%] vs 140 [70%]; p=0.046), especially drug-related diarrhoea (37 [19%] vs 55 [28%]; p=0.033). INTERPRETATION: Icotinib could be a new treatment option for pretreated patients with advanced non-small-cell lung cancer. FUNDING: Zhejiang Beta Pharma (China), the Chinese National Key Special Program for Innovative Drugs, the 863 Project, and Zhejiang Provincial Key Special Program.
Cross-validation analysis of the prognostic significance of mucin expression in patients with resected non-small cell lung cancer treated with adjuvant chemotherapy: Results from IALT, JBR.10 and ANITA.

INTRODUCTION: CALGB 9633 was a randomized trial of observation versus adjuvant chemotherapy for patients with stage IB non-small cell lung cancer (NSCLC). In CALGB 9633, the presence of mucin in the primary tumor was associated with shorter disease-free survival (DFS; hazard ratio (HR)=1.9, p=0.002) and overall survival (OS; HR=1.9, p=0.004). METHODS: To validate these results, mucin staining was performed on primary tumor specimens from 780 patients treated on IALT, 351 on JBR.10 and 150 on ANITA. The histochemical technique using mucicarmine was performed. The prognostic value of mucin for DFS and OS was tested in a Cox model stratified by trial and adjusted for clinical and pathological factors. A pooled analysis of all 4 trials was performed for the predictive value of mucin for benefit from adjuvant chemotherapy. RESULTS: The cross-validation group had 48% squamous, 37% adenocarcinoma and 15% other NSCLC compared with 29%, 56%, and 15%, respectively in CALGB. Among 1262 patients with assessable results, mucin was positive in IALT 24%, JBR.10 30%, ANITA 22% compared with 45% in CALGB. Histology was the only significant covariate (p<0.0001) in multivariate analysis with mucin seen more commonly in adenocarcinoma (56%) compared with squamous (5%) and other NSCLC (15%). Mucin was a borderline negative prognostic factor for DFS (HR=1.2 [1.0-1.5], p=0.06) but not significantly so for OS (HR=1.1 [0.9-1.4], p=0.25). Prognostic value did not vary according to histology: HR=1.3 [1.0-1.6] in adenocarcinoma vs. 1.6 [1.2-2.2] for DFS in other histology (interaction p=0.69). Mucin status was not predictive for benefit from adjuvant chemotherapy (test of interaction: DFS p=0.27; OS p=0.49). CONCLUSIONS: Mucin was less frequent in the cross-validation group due to its higher percentage of squamous cell carcinomas. The negative impact of mucin was confirmed for DFS but not for OS. Mucin expression was not predictive of overall survival benefit from adjuvant chemotherapy.
A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: the NVALT-10 study.

BACKGROUND: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) administered concurrently with chemotherapy did not improve outcome in non-small-cell lung cancer (NSCLC). However, in preclinical models and early phase noncomparative studies, pharmacodynamic separation of chemotherapy and TKIs did show a synergistic effect. PATIENTS AND METHODS: A randomized phase II study was carried out in patients with advanced NSCLC who had progressed on or following first-line chemotherapy. Erlotinib 150 mg daily (monotherapy) or erlotinib 150 mg during 15 days intercalated with four 21-day cycles docetaxel for squamous (SQ) or pemetrexed for nonsquamous (NSQ) patients was administered (combination therapy). After completion of chemotherapy, erlotinib was continued daily. Primary end point was progression-free survival (PFS). RESULTS: Two hundred and thirty-one patients were randomized, 115 in the monotherapy arm and 116 in the combination arm. The adjusted hazard ratio for PFS was 0.76 [95% confidence interval (CI) 0.58-1.02; P = 0.06], for overall survival (OS) 0.67 (95% CI 0.49-0.91; P = 0.01) favoring the combination arm. This improvement was primarily observed in NSQ subgroup. Common Toxicity Criteria grade 3+ toxic effect occurred in 20% versus 56%, rash in 7% versus 15% and febrile neutropenia in 0% versus 6% in monotherapy and combination therapy, respectively. CONCLUSIONS: PFS was not significantly different between the arms. OS was significantly improved in the combination arm, an effect restricted to NSQ histology. STUDY REGISTRATION NUMBER: NCT00835471.

Video-assisted thoracoscopic lobectomy in non-small-cell lung cancer patients with chronic obstructive pulmonary disease is associated with lower pulmonary complications than open lobectomy: a propensity score-matched analysis.

BACKGROUND: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) administered concurrently with chemotherapy did not improve outcome in non-small-cell lung cancer (NSCLC). However, in preclinical models and early phase noncomparative studies, pharmacodynamic separation of chemotherapy and TKIs did show a synergistic effect. PATIENTS AND METHODS: A randomized phase II study was carried out in patients with advanced NSCLC who had progressed on or following first-line chemotherapy. Erlotinib 150 mg daily (monotherapy) or erlotinib 150 mg during 15 days intercalated with four 21-day cycles docetaxel for squamous (SQ) or pemetrexed for nonsquamous (NSQ) patients was administered (combination therapy). After completion of chemotherapy, erlotinib was continued daily. Primary end point was progression-free survival (PFS). RESULTS: Two hundred and thirty-one patients were randomized, 115 in the monotherapy arm and 116 in the combination arm. The adjusted hazard ratio for PFS was 0.76 [95% confidence interval (CI) 0.58-1.02; P = 0.06], for overall survival (OS) 0.67 (95% CI 0.49-0.91; P = 0.01) favoring the combination arm. This improvement was primarily observed in NSQ subgroup. Common Toxicity Criteria grade 3+ toxic effect occurred in 20% versus 56%, rash in 7% versus 15% and febrile neutropenia in 0% versus 6% in monotherapy and combination therapy, respectively. CONCLUSIONS: PFS was not significantly different between the arms. OS was significantly improved in the combination arm, an effect restricted to NSQ histology. STUDY REGISTRATION NUMBER: NCT00835471.
El objetivo de este estudio fue identificar si la lobectomía con ayuda de videoasistida transoperatoria (VATS) puede reducir las complicaciones pulmonares posoperatorias comparadas con las lobectomías por toracotomía en pacientes con NSCLC y COPD. Métodos: En un total de 1502 pacientes con NSCLC que realizaron lobectomía en el Hospital Universitario Nacional de Seúl, de abril de 2005 a junio de 2012, 446 (29.7%) fueron diagnosticados con COPD, basándose en los criterios espirométricos del Global Initiative for COPD. Entre los 446 pacientes, 283 presentaron con NSCLC de estadio I y fueron seleccionados para este estudio. Los pacientes fueron divididos en dos grupos: pacientes sometidos a VATS (n = 160) y pacientes sometidos a lobectomía por toracotomía (n = 123). Se realizó un análisis de propensión que incluyó variables preoperatorias, como la edad, el sexo, el índice de comorbilidad de Charlson, el grado de fumador, la función pulmonar preoperatoria, el tamaño de la masa, el tipo histológico del tumor y la resección adicional de pulmón, y se compararon los resultados posoperatorios. Resultados: El análisis de los resultados posoperatorios produjo 91 pacientes en cada grupo. Sólo hubo tres mortalidades operatorias en el grupo de toracotomía, y todas estas pacientes murieron por neumonía postoperatoria. La incidencia general de las complicaciones pulmonares posoperatorias fue del 32.9% (30 de 91) en el grupo de toracotomía y del 22.0% (20 de 91) en el grupo de VATS (P = 0.14). En comparación con la lobectomía por toracotomía, la VATS lobectomía se asoció con una incidencia más baja de complicaciones pulmonares (1.1 vs 12.1%; P < 0.01), un tiempooperatorio más corto (165 vs 201 min; P < 0.01) y un tiempo de hospitalización más corto (6.0 vs 9.0 días; P = 0.04). Conclusión: La VATS lobectomía se asocia con una incidencia más baja de complicaciones pulmonares en pacientes con NSCLC y COPD. La VATS lobectomía puede ser una estrategia preferida para adecuados pacientes con NSCLC y COPD.

[46]

TÍTULO / TITLE: - Investigación de Complemento Activación Producto C4d como un biomarcador diagnóstico y pronóstico para el cáncer de pulmón.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1093/jnci/djt205
**RESUMEN / SUMMARY:** - BACKGROUND: There is a medical need for diagnostic biomarkers in lung cancer. We evaluated the diagnostic performance of complement activation fragments. METHODS: We assessed complement activation in four bronchial epithelial and seven lung cancer cell lines. C4d, a degradation product of complement activation, was determined in 90 primary lung tumors; bronchoalveolar lavage supernatants from patients with lung cancer (n = 50) and nonmalignant respiratory diseases (n = 22); and plasma samples from advanced (n = 50) and early lung cancer patients (n = 84) subjects with inflammatory lung diseases (n = 133), and asymptomatic individuals enrolled in a lung cancer computed tomography screening program (n = 190). Two-sided P values were calculated by Mann-Whitney U test.

RESULTS: Lung cancer cells activated the classical complement pathway mediated by C1q binding that was inhibited by phosphomonoesters. Survival was decreased in patients with high C4d deposition in tumors (hazard ratio [HR] = 3.06; 95% confidence interval [CI] = 1.18 to 7.91). C4d levels were increased in bronchoalveolar lavage fluid from lung cancer patients compared with patients with nonmalignant respiratory diseases (0.61+/-0.87 vs 0.16+/-0.11 microg/mL; P < .001). C4d levels in plasma samples from lung cancer patients at both advanced and early stages were also increased compared with control subjects (4.13+/-2.02 vs 1.86+/-0.95 microg/mL, P < 0.001; 3.18+/-3.20 vs 1.13+/-0.69 microg/mL, P < .001, respectively). C4d plasma levels were associated with shorter survival in patients at advanced (HR = 1.59; 95% CI = 0.97 to 2.60) and early stages (HR = 5.57; 95% CI = 1.60 to 19.39). Plasma C4d levels were reduced after surgical removal of lung tumors (P < .001) and were associated with increased lung cancer risk in asymptomatic individuals with (n = 32) or without lung cancer (n = 158) (odds ratio = 4.38; 95% CI = 1.61 to 11.93). CONCLUSIONS: Complement fragment C4d may serve as a biomarker for early diagnosis and prognosis of lung cancer.
TÍTULO / TITLE: - Phase II Trial of a GM-CSF-producing and CD40L-expressing Bystander Cell Line Combined With an Allogeneic Tumor Cell-based Vaccine for Refractory Lung Adenocarcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Creelan BC; Antonia S; Noyes D; Hunter TB; Simon GR; Bepler G; Williams CC; Tanvetyanon T; Haura EB; Schell MJ; Chiappori A

INSTITUCIÓN / INSTITUTION: - *Department of Oncologic Sciences, University of South Florida daggerH. Lee Moffitt Cancer Center & Research Institute, Tampa, FL double daggerMD Anderson Cancer Center, Houston, TX section signKarmanos Cancer Institute, Wayne State University, Detroit, MI.

RESUMEN / SUMMARY: - We created a vaccine in which irradiated allogeneic lung adenocarcinoma cells are combined with a bystander K562 cell line transfected with hCD40L and hGM-CSF. By recruiting and activating dendritic cells, we hypothesized that the vaccine would induce tumor regression in metastatic lung adenocarcinoma. Intradermal vaccine was given q14 days x 3, followed by monthly x 3. Cyclophosphamide (300 mg/m² IV) was administered before the first and fourth vaccines to deplete regulatory T cells. All-trans retinoic acid was given (150 mg/m²/d) after the first and fourth vaccines to enhance dendritic cell differentiation. Twenty-four participants were accrued at a single institution from October 2006 to June 2008, with a median age 64 years and median of 4 previous lines of systemic therapy. A total of 101 vaccines were administered. Common toxicities were headache (54%) and site reaction (38%). No radiologic responses were observed. Median overall survival was 7.9 months and median progression-free survival was 1.7 months. Of 14 patients evaluable for immunological study, 5 had peptide-induced CD8 T-cell activation after vaccination. Overall, vaccine administration was feasible in an extensively pretreated population of metastatic lung cancer. Despite a suggestion of clinical activity in the subset with immune response, the trial did not meet the primary endpoint of inducing radiologic tumor regression.

TÍTULO / TITLE: - High CC chemokine receptor 7 expression improves postoperative prognosis of lung adenocarcinoma patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
**RESUMEN / SUMMARY:**

Background: Chemokines and chemokine receptors not only have significant roles in cancer metastasis and tumorigenesis but also act as antitumour agents. The interaction between the Crk-like adaptor protein (CrkL), which is encoded by the CRKL gene, and non-receptor tyrosine kinase c-ABL is reported to transform many cells into malignant cells. We examined the effects of CC chemokine receptor 7 (CCR7), CCR7 ligands and CrkL and c-ABL in lung adenocarcinoma.

Methods: One hundred and twenty patients with lung adenocarcinoma were included in this historical cohort analysis. We examined CCR7 and CCR7 ligands and CrkL and c-ABL mRNA expressions in surgically resected lung adenocarcinoma specimens and evaluated their contribution to prognosis, and the relationship with epidermal growth factor receptor (EGFR) and TP53 mutations.

Results: High CCR7 mRNA expressions indicated better prognoses than those of the groups with low CCR7 mRNA expressions (P=0.007, HR=2.00, 95% CI of ratio: 1.22 -3.31). In lung adenocarcinoma, CrkL and c-ABL mRNAs were related to CCR7 mRNA expression (P<0.0001). CrkL and c-ABL mRNA expressions were influenced by EGFR mutations. A high expression of CCL19 was a good prognostic factor of lung adenocarcinoma.

Conclusion: We propose that CCR7 and CCL19 are clinically good prognostic factors and that CCR7 is strongly related to CrkL and c-ABL kinase mRNA expression in lung adenocarcinoma.

[49]
The contribution of TSP-1 upregulation to the modulation of tumorigenesis in the lung is unclear. Using a mouse model of lung cancer, we have shown that TSP-1 plays a critical and cell-autonomous role in suppressing Kras-induced lung tumorigenesis independent of its antiangiogenic function. Overall survival was decreased in a Kras-driven mouse model of lung cancer on a Tsp-1/- background. We found that oncogenic Kras-induced TSP-1 upregulation in a p53-dependent manner. TSP-1 functioned in a positive feedback loop to stabilize p53 by interacting directly with activated ERK. TSP-1 tethering of ERK in the cytoplasm promoted a level of MAPK signaling that was sufficient to sustain p53 expression and a senescence response. Our data identify TSP-1 as a p53 target that contributes to maintaining Ras-induced senescence in the lung.
Título / Title: - Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: a health economics analysis of the ASTER trial from a European perspective.

Resumen / Summary: - In the ASTER study, mediastinal staging was more accurate for patients randomised to combined endobronchial and endoscopic ultrasound, followed by surgical staging if endoscopy was negative, versus surgical staging alone. Here, we report survival, quality of life and cost effectiveness up to 6 months, for the UK, The Netherlands and Belgium, separately. Survival in the two arms of the study was similar. In all three countries, the endosonography strategy had slightly higher quality-adjusted life years over 6 months, and was cheaper. Therefore, based on clinical accuracy and cost effectiveness, we conclude that mediastinal staging should commence with endosonography.

Título / Title: - A prediction model for pathologic n2 disease in lung cancer patients with a negative mediastinum by positron emission tomography.

Resumen / Summary: - INTRODUCTION: Guidance is limited for invasive staging in patients with lung cancer without mediastinal disease by positron emission tomography (PET). We developed and validated a prediction model for pathologic N2 disease (pN2), using six previously described risk factors: tumor location and size by
computed tomography (CT), nodal disease by CT, maximum standardized uptake value of the primary tumor, N1 by PET, and histology. METHODS: A cohort study (2004-2009) was performed in patients with T1/T2 by CT and N0/N1 by PET. Logistic regression analysis was used to develop a prediction model for pN2 among a random development set (n = 625). The model was validated in both the development set, which comprised two thirds of the patients and the validation set (n = 313), which comprised the remaining one third. Model performance was assessed in terms of discrimination and calibration. RESULTS: Among 938 patients, 9.9% had pN2 (9 detected by invasive staging and 84 intraoperatively). In the development set, univariate analyses demonstrated a significant association between pN2 and increasing tumor size (p < 0.001), nodal status by CT (p = 0.007), maximum standardized uptake value of the primary tumor (p = 0.027), and N1 by PET (p < 0.001); however, only N1 by PET was associated with pN2 (p < 0.001) in the multivariate prediction model. The model performed reasonably well in the development (c-statistic, 0.70; 95% confidence interval, 0.63-0.77; goodness of fit p = 0.61) and validation (c-statistic, 0.65; 95% confidence interval, 0.56-0.74; goodness-of-fit p = 0.19) sets. CONCLUSION: A prediction model for pN2 based on six previously described risk factors has reasonable performance characteristics. Observations from this study may guide prospective, multicenter development and validation of a prediction model for pN2.

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[TÍTULO / TITLE: - The national lung screening trial: Results stratified by demographics, smoking history, and lung cancer histology.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pinsky PF; Church TR; Izmirlian G; Kramer BS
INSTITUCIÓN / INSTITUTION: - Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland.
RESUMEN / SUMMARY: - BACKGROUND: The National Lung Screening Trial (NLST), which compared lung cancer screening with low-dose computed tomography (LDCT) versus chest radiography (CXR), demonstrated a statistically significant mortality benefit of LDCT screening. In the current study, the authors performed a post hoc analysis to examine whether the benefit was affected by various baseline factors, including age, sex, and smoking status, and whether it differed by tumor histology. METHODS: Lung cancer death rates were computed as events over person-years of observation; the mortality risk ratio (RR) was calculated as the lung cancer death rate in the LDCT versus CXR trial arms. Poisson regression was used to test for interactions of sex, age (< 65 years vs >/= 65 years), and smoking status (current vs former) with trial arm. Mortality
RRs were also computed for specific lung cancer histologies. RESULTS: The overall mortality RR was 0.92 in men and 0.73 in women, with a P value for interaction of .08. RRs were similar for individuals aged < 65 years versus those aged >/= 65 years (0.82 vs 0.87), and for current versus former smokers (0.81 vs 0.91). By tumor histology, mortality RRs were 0.75 for adenocarcinoma, 0.71 for all non-small cell lung cancers except squamous, 1.23 for squamous cell carcinoma, and 0.90 for small cell carcinoma. RRs were similar for men and women for nonsquamous non-small cell lung cancers (0.71 and 0.70, respectively); women were found to have lower RRs for small cell and squamous cell carcinoma. CONCLUSIONS: A benefit of LDCT did not appear to vary substantially by age or smoking status; there was weak evidence of a differential benefit by sex. A differential benefit across lung cancer histologies may exist. Cancer 2013. Published 2013. This article is a U.S. Government work and is in the public domain in the USA.
paired t test). MiR-31 was then validated as a marker for lymph node metastasis in an external validation cohort of 233 lung adenocarcinoma cases of the TCGA (P = 0.031, t test). In vitro functional assays showed that miR-31 increases cell migration, invasion, and proliferation in an ERK1/2 signaling-dependent manner. Notably, miR-31 was a significant predictor of survival in a multivariate cox regression model even when controlling for cancer staging. Exploratory in silico analysis showed that low expression of miR-31 is associated with excellent survival for T2N0 patients. CONCLUSIONS: We applied miRNA-seq to study microRNomes in lung adenocarcinoma tissue samples for the first time and potentially identified a miRNA predicting the presence of lymph node metastasis and survival outcomes in patients of lung adenocarcinoma. Clin Cancer Res; 19(19); 5423-33. © 2013 AACR.

[55]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lester JF; Agulnik J; Akerborg O; Chouaid C; De Geer A; Finnern HW; Herder GJ; Lungershausen J; Mitchell PL; Vansteenkiste J; Ziske C; Goker E
INSTITUCIÓN / INSTITUTION: - Velindre Hospital, United Kingdom. Electronic address: Jason.lester2@wales.nhs.uk.
RESUMEN / SUMMARY: - BACKGROUND: A significant proportion of advanced non-small cell lung cancer (NSCLC) patients receive supportive treatments to manage disease-related symptoms either separately or combined with systemic anti-cancer therapy (SACT). This supportive treatment is commonly referred to as best supportive care (BSC). Definition of BSC in clinical trials and its description in published comparative and real-life NSCLC studies is limited. The lack of a consensus BSC definition makes detailed evaluations of clinical trials and comparisons between clinical trials problematic. METHODS: Data were collected as part of the lung cancer economics and outcomes research (LUCEOR) study. Information on treatment and treatment outcomes from deceased stage IIIb/IV NSCLC patients across ten countries was retrospectively collected from medical records. BSC was defined as the best care available as judged by the attending physicians. RESULTS: A total of 1327 patients’ data were analyzed. Of those, 774/1327 (58%), 316/631 (50%), 123/259 (47%), 25/56 (45%) and 15/26 (58%) were administered treatment defined as BSC with first, second, third, fourth and fifth-line SACT respectively. In total, 346/678 (51%), 149/335 (45%), 86/176 (49%), 11/28 (39%) and 13/25 (52%) of patients were administered treatment defined
as BSC in the end-of-life setting after finishing first, second, third, fourth and fifth-line SACT respectively. BSC therapies could be grouped into 24 different categories. The most common elements did not vary substantially whether given with SACT (irrespective of treatment line), in the end-of-life setting, or between countries. The commonest categories of BSC were narcotic and non-narcotic analgesics, corticosteroids and gastrointestinal medication. CONCLUSION: There were no major differences in what constituted BSC. BSC included in all instances narcotic and non-narcotic analgesics, corticosteroids and gastrointestinal medication. To our knowledge this is the first study attempting to describe BSC in routine clinical practice. This study’s results could help define a practical, up to date, evidence-based definition of BSC.

[56]

**TÍTULO / TITLE:** - Prognostic value of metabolic tumor volume and total lesion glycolysis from 18F-FDG PET/CT in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Vu CC; Matthews R; Kim B; Franceschi D; Bilfinger TV; Moore WH

**INSTITUCIÓN / INSTITUTION:** - Departments of aRadiology bRadiation Oncology cSurgery, Division of Cardiothoracic Surgery, Stony Brook University Medical Center, Stony Brook, New York, USA.

**RESUMEN / SUMMARY:** - OBJECTIVES: The aim of this study was to evaluate the prognostic value of pretreatment F-fluorodeoxyglucose PET/computed tomography (CT), particularly in the assessment of metabolic tumor burden markers such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), with respect to clinical outcomes in stage I non-small-cell lung cancer (NSCLC) patients undergoing stereotactic body radiation therapy (SBRT). METHODS: This retrospective study evaluated 50 patients who underwent SBRT for stage I NSCLC from May 2007 to December 2012. The maximum standardized uptake value (SUVmax), average SUV (SUVavg), MTV, and TLG were measured from the PET/CT scan. The study population was dichotomized at the median into high and low groups. Kaplan-Meier log-rank tests were then used to compare high with low PET/CT parameter groups, and univariate Cox proportional hazards regression analysis was carried out to identify predictors of overall survival. RESULTS: The 2-year local control rate was 93.7%. After a median follow-up of 25.1 months, the 2-year overall survival was 79.3%. Eight patients (16%) had disease recurrence. There were three local failures (6%), three mediastinal failures...
(6%), and six cases of distant metastases (12%). Both Kaplan-Meier actuarial analysis and Cox proportional hazards regression found no correlation between SUVmax, SUVavg, MTV, and TLG and overall survival. CONCLUSION: Standard PET/CT measures, such as SUVmax, as well as newer measures of metabolic tumor burden, such as MTV and TLG, were not correlated with overall survival in our study population of stage I NSCLC patients undergoing SBRT. Larger studies with longer follow-up periods are needed to confirm these results.

[57]

**TÍTULO / TITLE:** - Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors.

**RESUMEN / SUMMARY:** - Metastatic non-small cell lung carcinoma (NSCLC) generally carries a poor prognosis, and systemic therapy is the mainstay of treatment. However, extended survival has been reported in patients presenting with a limited number of metastases, termed oligometastatic disease. We retrospectively reviewed the outcomes of such patients treated at two centers. MATERIALS AND METHODS: From September 1999-July 2012, a total of 61 patients with 1-3 synchronous metastases, who were treated with radical intent to all sites of disease, were identified from records of two cancer centers. Treatment was considered radical if it involved surgical resection and/or delivery of radiation doses >/=13x3Gy. RESULTS: Besides the primary tumor, 50 patients had a solitary metastasis, 9 had two metastases, and 2 had three metastases. Locations of metastases included the brain (n=36), bone (n=11), adrenal (n=4), contralateral lung (n=4), extra-thoracic lymph nodes (n=4), skin (n=2) and colon (n=1). Only one patient had metastases in two different organs. Median follow-up was 26.1 months (m), median overall survival (OS) was 13.5m, median progression free survival (PFS) was 6.6m and median survival after first progression (SAFP) was 8.3m. The 1- and 2-year OS were, 54% and 38%, respectively. Significant predictors of improved OS were: smaller radiotherapy planning target volume (PTV) (p=0.004) and surgery for the primary lung tumor (p<0.001). Factors associated with improved SAFP included surgery for the primary lung tumor, presence of brain metastases, and absence of bone metastases. No significant differences in outcomes
were observed between the two centers. CONCLUSION: Radical treatment of selected NSCLC patients presenting with 1-3 synchronous metastases can result in favorable 2-year survivals. Favorable outcomes were associated with intra-thoracic disease status: patients with small radiotherapy treatment volumes or resected disease had the best OS. Future prospective clinical trials, ideally randomized, should evaluate radical treatment strategies in such patients.

[58]

TÍTULO / TITLE: - Outcome of Surgical Resection as a First Line Therapy in T3 Non-small Cell Lung Cancer Patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Takenaka T; Katsura M; Shikada Y; Takeo S

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RESUMEN / SUMMARY: - BACKGROUND: The T3 category of the 7th Edition of the TNM classification of non-small cell lung cancer (NSCLC) has added two factors that do not appear in the 6th Edition, large tumor size (>7 cm) and pulmonary metastasis of the same lobe. These factors are considered to have different biological and clinical features. In the present study we assessed the outcome of surgical resection as a first line therapy for T3 NSCLC. METHODS: A total of 145 patients who were diagnosed according to the TNM 7th Edition with pathologic T3 NSCLC received surgical resection in our institution as a first line treatment. The outcomes of their treatment were analyzed. RESULTS: The 5-year survival rate was 46.9 %. On the basis of the 6th TNM Edition, the 5-year survival rate was 63.1 % for patients diagnosed with T2 disease (large tumor size), 44.3 % for patients diagnosed with T3 disease, and 33.1 % for patients diagnosed with T4 disease (pulmonary metastasis of the same lobe). There were no significant correlations between these categories and overall survival (OS). Nevertheless, 6th Edition T factors were found to be significantly correlated with lymph node status (p < 0.01). The univariate analyses showed that age, lymph node metastasis, and curative resection had significant effects on OS. In addition, the multivariate analysis identified age and N factor as independent prognostic factors in this cohort. CONCLUSIONS: Indications for surgical resection as a first line therapy in T3 NSCLC should be based on N factors and patient age. Lymph node metastasis, especially N2 disease, was increasingly frequent in patients with 6th Edition T classifications.
- TÍTULO / TITLE: - Effect of prophylactic cranial irradiation on survival in elderly patients with limited-stage small cell lung cancer.

- RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


- AUTORES / AUTHORS: - Eaton BR; Kim S; Marcus DM; Prabhu R; Chen Z; Ramalingam SS; Curran WJ Jr; Higgins KA

- INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia.

- RESUMEN / SUMMARY: - BACKGROUND: Prophylactic cranial irradiation (PCI) improves survival in patients with limited-stage small cell lung cancer (SCLC) who have a complete response to chemotherapy and radiotherapy, yet to the best of the authors’ knowledge, data specific to the elderly population are lacking. METHODS: Using the Surveillance, Epidemiology, and End Results (SEER) database, the authors identified 1926 patients aged >/= 70 years who were diagnosed with limited-stage SCLC between 1988 and 1997. Overall survival (OS) for patients who received PCI versus those who did not were estimated using the Kaplan-Meier method and compared with the log-rank test. A Cox proportional hazards model was further fitted to estimate the effect of PCI on OS after adjusting for age, race, sex, tumor size, lymph node status, stage of disease, and receipt of thoracic radiotherapy and surgery. RESULTS: The median age of the patients was 75 years (range, 70 years-94 years) and 138 patients (7.2 %) received PCI. The 2-year and 5-year OS rates were 33.3% (95% confidence interval [95% CI], 25.6%-41.2%) and 11.6% (95% CI, 6.9%-17.6%), respectively, among patients who received PCI versus 23.1% (95% CI, 21.2%-25.1%) and 8.6% (95% CI, 7.3%-9.9%), respectively, among patients who did not receive PCI (P = .028). On multivariable analysis, PCI was found to be an independent predictor of OS (hazards ratio, 0.72; 95% CI, 0.54-0.97 [P = .032]). On subgroup analysis, PCI remained an independent predictor of OS among patients aged >/= 75 years, but not among patients aged >/= 80 years. CONCLUSIONS: The receipt of PCI is associated with improved OS in patients aged >/= 70 years with SCLC, suggesting that the benefit of PCI is maintained in the elderly population. Cancer 2013. © 2013 American Cancer Society.

- TÍTULO / TITLE: - Preoperative Consolidation-to-Tumor Ratio and SUVmax Stratify the Risk of Recurrence in Patients Undergoing Limited Resection for Lung Adenocarcinoma </=2 cm.

- RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


- AUTORES / AUTHORS: - Eaton BR; Kim S; Marcus DM; Prabhu R; Chen Z; Ramalingam SS; Curran WJ Jr; Higgins KA

- INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia.
AUTORES / AUTHORS: Nitadori JI; Bograd AJ; Morales EA; Rizk NP; Dunphy MP; Sima CS; Rusch VW; Adusumilli PS
INSTITUCIÓN / INSTITUTION: Division of Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.
RESUMEN / SUMMARY: PURPOSE: Limited resection is an increasingly utilized option for treatment of clinical stage IA lung adenocarcinoma (ADC) \( \leq 2 \) cm (T1aN0M0), yet there are no validated predictive factors for postoperative recurrence. We investigated the prognostic value of preoperative consolidation/tumor (C/T) ratio [on computed tomography (CT) scan] and maximum standardized uptake value (SUVmax) on 18F-fluorodeoxyglucose-positron emission tomography (PET) scan. METHODS: We retrospectively reviewed 962 consecutive patients who underwent limited resection for lung cancer at Memorial Sloan-Kettering between 2000 and 2008. Patients with available CT and PET scans were included in the analysis. C/T ratio of 25 % (in accordance with the Japan Clinical Oncology Group 0201) and SUVmax of 2.2 (cohort median) were used as cutoffs. Cumulative incidence of recurrence (CIR) was assessed. RESULTS: A total of 181 patients met the study inclusion criteria. Patients with a low C/T ratio (n = 15) had a significantly lower 5-year recurrence rate compared with patients with a high C/T ratio (n = 166) (5-year CIR, 0 vs. 33 %; \( p = 0.015 \)), as did patients with low SUVmax (n = 86) compared with patients with high SUVmax (n = 95; 5-year CIR, 18 vs. 40 %; \( p = 0.002 \)). Furthermore, within the high C/T ratio group, SUVmax further stratified risk of recurrence [5-year CIR, 22 % (low) vs. 40 % (high); \( p = 0.018 \)]. CONCLUSIONS: With the expected increase in diagnoses of small lung ADC as a result of more widespread use of CT screening, C/T ratio and SUVmax are widely available markers that can be used to stratify the risk of recurrence among cT1aN0M0 patients after limited resection.

[61] TÍTULO / TITLE: The influence of TP53 mutations on the prognosis of patients with early stage non-small cell lung cancer may depend on the intratumor heterogeneity of the mutations.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Lee SY; Jeon HS; Hwangbo Y; Jeong JY; Park JY; Lee EJ; Jin G; Shin KM; Yoo SS; Lee J; Lee EB; Cha SI; Kim CH; Park JY
INSTITUCIÓN / INSTITUTION: Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea.
RESUMEN / SUMMARY: A large number of studies have evaluated the impact of TP53 mutations on the prognosis of patients with non-small cell lung cancer (NSCLC); however, the results of these studies are still controversial. Recently, considerable
intratumor heterogeneity for genetic alterations has been demonstrated in various human cancers, including lung cancer. In the present study, we evaluated TP53 mutations in NSCLCs by direct sequencing and observed remarkable variation in the values of relative intensity (RI, the height of the peak of mutated allele/the height of the peak of non-mutated allele) of the mutations. We also examined whether the RI values were associated with intratumor heterogeneity of TP53 mutations. In addition, we evaluated the relationship between TP53 mutations and survival outcome. The patients with a TP53 mutation did not have significantly worse survival compared to those without the mutation. However, when tumors with a TP53 mutation were categorized into two groups, those with a low and those with a high RI, the latter group had significantly worse survival compared to those with wild-type TP53 (adjusted hazard ratio = 2.58, 95% confidence interval = 1.21-5.48, P = 0.01), whereas the former group did not. These results suggest that intratumor genetic heterogeneity may be an important factor in determining the role of TP53 mutations on the prognosis of NSCLC patients. © 2013 Wiley Periodicals, Inc.

[62]

**Título / Title:** - Effectiveness of radiation therapy alone for elderly patients with unresected stage III non-small cell lung cancer.

**Resumen / Summary:** - Enlace al Resumen / Link to its Summary


**Autores / Authors:** - Sigel K; Lurslurchachai L; Bonomi M; Mhango G; Bergamo C; Kale M; Halm E; Wisnivesky J

**Institución / Institution:** - Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY, United States. Electronic address: Keith.Sigel@mssm.edu.

**Resumen / Summary:** - PURPOSE: Chemoradiotherapy is the standard of care for unresectable stage III non-small cell lung cancer (NSCLC). Elderly patients, who are often considered unfit for combined chemoradiotherapy, frequently receive radiation therapy (RT) alone. Using population-based data, we evaluated the effectiveness and tolerability of lone RT in unresected elderly stage III NSCLC patients. METHODS AND MATERIALS: Using the Surveillance, Epidemiology and End Results (SEER) registry linked to Medicare records we identified 10,376 cases of unresected stage III NSCLC that were not treated with chemotherapy, diagnosed between 1992 and 2007. We used logistic regression to determine propensity scores for RT treatment using patients’ pre-treatment characteristics. We then compared survival of patients who underwent lone RT vs. no treatment using a Cox regression model adjusting for propensity scores. The adjusted odds for toxicity among patients treated with and without RT were also estimated. RESULTS: Overall, 6468 (62%) patients received lone
RT. Adjusted analyses showed that RT was associated with improved overall survival in unresected stage III NSCLC (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.74-0.79) after controlling for propensity scores. RT treated patients had an increased adjusted risk of hospitalization for pneumonitis (odds ratio [OR]: 89, 95% CI: 12-636), and esophagitis (OR: 8, 95% CI: 3-21). CONCLUSIONS: These data suggest that use of RT alone may improve the outcomes of elderly patients with unresected stage III NSCLC. Severe toxicity, however, was considerably higher in the RT treated group. The potential risks and benefits of RT should be carefully discussed with eligible elderly NSCLC patients.

[63]
TÍTULO / TITLE: - Surveillance with computed tomography after curative treatment of early-stage lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Senti S; Senan S
INSTITUCIÓN / INSTITUTION: - Vrije Universiteit University Medical Center, Amsterdam, the Netherlands.

[64]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Huang T; Jia CP; Jun-Yang; Sun WJ; Wang WT; Cong H; Jing FX; Mao HJ; Jin QH; Zhang Z; Chen YJ; Li G; Mao GX; Zhao JL
INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Transducer Technology and the Science and Technology on Micro-system Laboratory, Shanghai Institute of Microsystem and Information Technology, Chinese Academy of Sciences, 865 Changning Road, Shanghai 200050, China; Department of Tumor Chemotherapy, The Affiliated Hospital of Nantong University, No. 20 Xisi Road, Nantong, Jiangsu 226001, China; Department of Oncology, The People’s Hospital of Chizhou, No. 3 Baiya Middle Road, Chizhou, Anhui 247100, China. Electronic address: ahwwh0416@163.com.
- Insulin growth factor signaling is regulated by microRNA-486, an underexpressed microRNA in lung cancer.

**TÍTULO / TITLE:** Insulin growth factor signaling is regulated by microRNA-486, an underexpressed microRNA in lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Peng Y; Dai Y; Hitchcock C; Yang X; Kassis ES; Liu L; Luo Z; Sun HL; Cui R; Wei H; Kim T; Lee TJ; Jeon YJ; Nuovo GJ; Volinia S; He Q; Yu J; Nana-Sinkam P; Croce CM

**INSTITUCIÓN / INSTITUTION:** Department of Molecular Virology, Immunology, and Medical Genetics and Division of Hematology, Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210.

**RESUMEN / SUMMARY:** MicroRNAs (miRNAs) are small 19- to 24-nt noncoding RNAs that have the capacity to regulate fundamental biological processes essential for cancer initiation and progression. In cancer, miRNAs may function as oncogenes or tumor suppressors. Here, we conducted global profiling for miRNAs in a cohort of stage 1 nonsmall cell lung cancers (n = 81) and determined that miR-486 was the most down-regulated miRNA in tumors compared with adjacent uninvolved lung tissues, suggesting that miR-486 loss may be important in lung cancer development. We report that miR-486 directly targets components of insulin growth factor (IGF) signaling including insulin-like growth factor 1 (IGF1), IGF1 receptor (IGF1R), and phosphoinositide-3-kinase, regulatory subunit 1 (alpha) (PIK3R1, or p85a) and functions as a potent tumor suppressor of lung cancer both in vitro and in vivo. Our findings support the role for miR-486 loss in lung cancer and suggest a potential biological link to p53.

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- Risk of seizure and its clinical implication in the patients with cerebral metastasis from lung cancer.

**TÍTULO / TITLE:** Risk of seizure and its clinical implication in the patients with cerebral metastasis from lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Lee MH; Kong DS; Seol HJ; Nam DH; Lee JI

**INSTITUCIÓN / INSTITUTION:** Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** BACKGROUND: The prevalence, risk factors, and clinical implication of seizure development were investigated in patients with metastatic brain tumors. METHODS: Medical records and radiological findings were analyzed.
retrospectively in 258 patients with brain metastasis from lung cancer who underwent Gamma Knife radiosurgery (GKS) between January 2008 and December 2009. RESULTS: During the follow-up period 32 patients (12.4 %) experienced seizure episodes. Coexistence of leptomeningeal seeding was a significant risk factor related to development of seizure (p < 0.001). Prophylactic use of anticonvulsants was not correlated with reduction of seizure incidence (p = 0.818). Continued use of anticonvulsants was necessary in nine of the 258 patients (3.5 %) because of recurrent seizures. Imaging studies performed immediately after seizure attacks in the patients with known metastatic brain lesions revealed tumor progression or complications related to treatment in 35 of 42 episodes of seizure (77.8 %). CONCLUSIONS: Patients with metastatic lesions have a substantial risk of developing seizure. Seizure in known metastatic brain tumor patients are usually related to disease progression or complications of treatment. Follow-up imaging should be considered for each seizure episode and adequate multimodal treatment needs to be added to antiepileptic medication.

[67]

TÍTULO / TITLE: Lung cancer, histologic stratification, and resection extent: something for surgeons to think about.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Pass HI
INSTITUCIÓN / INSTITUTION: Affiliation of author: Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York, NY.

[68]

TÍTULO / TITLE: Impact of Micropapillary Histologic Subtype in Selecting Limited Resection vs Lobectomy for Lung Adenocarcinoma of 2cm or Smaller.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Nitadori J; Bograd AJ; Kadota K; Sima CS; Rizk NP; Morales EA; Rusch VW; Travis WD; Adusumilli PS
INSTITUCIÓN / INSTITUTION: Affiliations of authors: Division of Thoracic Surgery (JN, A JB, KK, NPR, EAM, VWR, PSA), Center for Cell Engineering (AJB, PSA), Department of Epidemiology and Biostatistics (CSS), and Department of Pathology (WDT), Memorial
RESUMEN / SUMMARY: - BACKGROUND: We sought to analyze the prognostic significance of the new International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) lung adenocarcinoma (ADC) classification for patients undergoing resection for small (≤2cm) lung ADC and to investigate whether histologic subtyping can predict recurrence after limited resection (LR) vs lobectomy (LO). METHODS: Comprehensive histologic subtyping was performed according to the IASLC/ATS/ERS classification on all consecutive patients who underwent LR or LO for small lung ADC between 1995 and 2009 at Memorial Sloan-Kettering Cancer Center. Clinical characteristics and pathologic data were retrospectively evaluated for 734 consecutive patients (LR: 258; LO: 476). Cumulative incidence of recurrence (CIR) was calculated using competing risks analysis and compared across groups using Grey’s test. All statistical tests were two-sided. RESULTS: Application of IASLC/ATS/ERS lung ADC histologic subtyping to predict recurrence demonstrates that, in the LR group but not in the LO group, micropapillary (MIP) component of 5% or greater was associated with an increased risk of recurrence, compared with MIP component of less than 5% (LR: 5-year CIR = 34.2%, 95% confidence interval [CI] = 23.5% to 49.7% vs 5-year CIR = 12.4%, 95% CI = 6.9% to 22.1%, P < .001; LO: 5-year CIR = 19.1%, 95% CI = 12.0% to 30.5% vs 15-year CIR = 12.9%, 95% CI = 7.6% to 21.9%, P = .13). In the LR group, among patients with tumors with an MIP component of 5% or greater, most recurrences (63.4%) were locoregional; MIP component of 5% or greater was statistically significantly associated with increased risk of local recurrence when the surgical margin was less than 1cm (5-year CIR = 32.0%, 95% CI = 18.6% to 46.0% for MIP ≥ 5% vs 5-year CIR = 7.6%, 95% CI = 2.3% to 15.6% for MIP < 5%; P = .007) but not when surgical margin was 1cm or greater (5-year CIR = 13.0%, 95% CI = 4.1% to 22.1% for MIP ≥ 5% vs 5-year CIR = 3.4%, 95% CI = 0% to 7.7% for MIP < 5%; P = .10). CONCLUSIONS: Application of the IASLC/ATS/ERS classification identifies the presence of an MIP component of 5% or greater as independently associated with the risk of recurrence in patients treated with LR.

[69]

TÍTULO / TITLE: - REG lalpha gene expression is linked with the poor prognosis of lung adenocarcinoma and squamous cell carcinoma patients via discrete mechanisms.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kimura M; Naito H; Tojo T; Itaya-Hironaka A; Dohi Y; Yoshimura M; Nakagawara KI; Takasawa S; Taniguchi S
The aim of the present study was to evaluate the effects of the REG Ialpha and REG Ibeta genes on lung cancer cell lines, and thereafter, the expression of REG family genes (REG Ialpha, REG Ibeta, REG III, HIP/PAP and REG IV) in lung cancer in relation to patient prognosis was evaluated. Lung adenocarcinoma (AD) and squamous cell carcinoma (SCC) cell lines expressing REG Ialpha or REG Ibeta (HLC-1 REG Ialpha/Ibeta and EBC-1 REG Ialpha/Ibeta) were established, and cell number, cell invasive activity, and anchorage-independent cell growth were compared with these variables in the control cells. The expression levels of REG family genes were evaluated by real-time RT-PCR in surgically resected lung cancers, and disease-specific survival (DSS) curves were generated. The HLC-1 REG Ialpha/Ibeta cell line showed significant increases in cell number and anchorage-independent cell growth compared with the control cells. EBC-1 REG Ialpha/Ibeta cells showed significant increases in cell invasive activity and anchorage-independent cell growth as compared with the control cells. Except for the REG Ibeta gene, expression of other REG family genes was observed in the surgically resected samples; however, DSS was significantly worse only in stage I patients who were positive for REG Ialpha expression than in patients who were negative for REG Ialpha expression. The effects of REG Ialpha on AD and SCC cells were different in the in vitro study, and a correlation between REG Ialpha expression and patient prognosis was noted in the in vivo study. Therefore, overexpression of REG Ialpha is a risk factor for poor prognosis caused by discrete mechanisms in AD and SCC patients.

[70]

**TÍTULO / TITLE:** - Prognostic value of EpCAM/MUC1 mRNA-positive cells in non-small cell lung cancer patients.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** - Tumour Biol. 2013 Sep 7.

**AUTORES / AUTHORS:** - Zhu WF; Li J; Yu LC; Wu Y; Tang XP; Hu YM; Chen YC

**INSTITUCIÓN / INSTITUTION:** - Department of Pulmonary Medicine, Affiliated Hospital of Jiangsu University, No. 438 North Jiefang Street, Zhenjiang, China.

**RESUMEN / SUMMARY:** - The aim of this study was to assess the prognostic value of EpCAM/MUC1 mRNA-positive circulating tumor cells (CTCs) in patients with non-small cell lung cancer (NSCLC). The presence of EpCAM/MUC1 mRNA-positive CTCs was evaluated in 74 NSCLC patients before the initiation of any therapy, from which 61 patients with surgical resection of tumor were also evaluable for EpCAM/MUC1 mRNA-positive CTC analysis after surgery, by quantitative real-time PCR assay. Sixty patients with benign lung disease (BLD) entered this study as controls. The results
showed that blood levels of EpCAM and MUC1 mRNA in NSCLC patients before and after surgery were significantly higher than those in BLD patients (P = 0.001 and P = 0.015, respectively, for EpCAM; P = 0.003 and P = 0.026, respectively, for MUC1), and the levels of the two gene mRNA in NSCLC patients significantly decreased after surgery (P = 0.025 and P = 0.033, respectively). Disease recurrence significantly increased in NSCLC patients with EpCAM/MUC1 mRNA-positive CTC preoperation and postoperation (P = 0.004 and P = 0.001, respectively). Disease-free survival and overall survival significantly reduced in patients with EpCAM/MUC1 mRNA-positive CTC preoperation and postoperation (P = 0.012 and P = 0.002, respectively, for preoperation; both P < 0.001 for postoperation). Multivariate analysis demonstrated that the presence of EpCAM/MUC1 mRNA-positive CTCs before and after surgery was an independent factor associated with disease recurrence. In conclusion, the detection of EpCAM/MUC1 mRNA-positive CTCs in the blood before and after surgery is useful for predicting a poor prognosis in NSCLC patients who undergo curative surgery.
carbonic anhydrases CAIX and CAXII is well established, the effect of re-oxygenation on these proteins remains to be elucidated. A549 and H1975 human lung cancer cell lines were exposed to hypoxia for 24h and then re-oxygenated. CAIX or CAXII expression and cell cycle progression at different time-points were monitored. A549-shCA9 cells were analyzed for cell cycle progression in the same conditions. We demonstrate for the first time an association between the stability of CAIX and restoration of the S/G2 phase of hypoxia-arrested cells subjected to re-oxygenation. In exchange, we have found that the loss of CA9 did not cause a decreased progression into S/G2 phase during re-oxygenation, but rather affected the hypoxic growth arrest. We previously demonstrated that CAIX expression is a poor prognostic factor and that CAXII expression is a good prognostic factor in non-small cell lung cancer (NSCLC) patients. We further detail the relevance of the combined expression of these proteins for predicting outcome in a large population of NSCLC patients after long-term follow-up. The high CAIX/low CAXII expression sub-group was associated with a high cumulative incidence of relapse and with poor overall survival of NSCLC patients (P<0.0001). Our results demonstrate a critical role for re-oxygenation on CAIX and CAXII levels that may select for an aggressive lung cancer phenotype. These findings suggest that CAIX and CAXII play dual roles in tumour progression and emphasize their significant prognostic and potential therapeutic value.

[73] - Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Nalbantov G; Kietselaer B; Vandecasteele K; Oberije C; Berbee M; Troost E; Dingemans AM; Baardwijk AV; Smits K; Dekker A; Bussink J; Ruysscher DD; Lievens Y; Lambin P

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology (Maastro Clinic), GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands. Electronic address: georgi.nalbantov@maastro.nl.

RESUMEN / SUMMARY: - PURPOSE: To test the hypothesis that cardiac comorbidity before the start of radiotherapy (RT) is associated with an increased risk of radiation-induced lung toxicity (RILT) in lung cancer patients. MATERIAL AND METHODS: A retrospective analysis was performed of a prospective cohort of 259 patients with locoregional lung cancer treated with definitive radio(chemo)therapy between 2007 and 2011 (ClinicalTrials.gov Identifiers: NCT00572325 and NCT00573040). We defined
RILT as dyspnea CTCv.3.0 grade 2 within 6 months after RT, and cardiac comorbidity as a recorded treatment of a cardiac pathology at a cardiology department. Univariate and multivariate analyses, as well as external validation, were performed. The model-performance measure was the area under the receiver operating characteristic curve (AUC). RESULTS: Prior to RT, 75/259 (28.9%) patients had cardiac comorbidity, 44% of whom (33/75) developed RILT. The odds ratio of developing RILT for patients with cardiac comorbidity was 2.58 (p<0.01). The cross-validated AUC of a model with cardiac comorbidity, tumor location, forced expiratory volume in 1s, sequential chemotherapy and pretreatment dyspnea score was 0.72 (p<0.001) on the training set, and 0.67 (p<0.001) on the validation set. CONCLUSION: Cardiac comorbidity is an important risk factor for developing RILT after definite radio(chemo)therapy of lung cancer patients.

[74]

TÍTULO / TITLE: Why Do Pathological Stage IA Lung Adenocarcinomas Vary from Prognosis?: A Clinicopathologic Study of 176 Patients with Pathological Stage IA Lung Adenocarcinoma Based on the IASLC/ATS/ERS Classification.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Zhang J; Wu J; Tan Q; Zhu L; Gao W

INSTITUCIÓN / INSTITUTION: Departments of *Pathology, daggerThoracic Surgery, Shanghai Chest Hospital, Shanghai, China.

RESUMEN / SUMMARY: BACKGROUND: Patients with pathological stage IA adenocarcinoma (AC) have a variable prognosis, even if treated in the same way. The postoperative treatment of pathological stage IA patients is also controversial. METHODS: We identified 176 patients with pathological stage IA AC who had undergone a lobectomy and mediastinal lymph node dissection at the Shanghai Chest Hospital, Shanghai, China, between 2000 and 2006. No patient had preoperative treatment. The histologic subtypes of all patients were classified according to the 2011 International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) international multidisciplinary lung AC classification. Patients’ 5-year overall survival (OS) and 5-year disease-free survival (DFS) were calculated using Kaplan-Meier and Cox regression analyses. RESULTS: One hundred seventy-six patients with pathological stage IA AC had an 86.6% 5-year OS and 74.6% 5-year DFS. The 10 patients with micropapillary predominant subtype had the lowest 5-year DFS (40.0%). The 12 patients with solid predominant with mucin production subtype had the lowest 5-year OS (66.7%). Univariate and multivariate analysis showed that sex and prognostic groups of the IASLC/ATS/ERS histologic
classification were significantly associated with 5-year DFS of pathological stage IA AC. CONCLUSION: Our study revealed that sex was an independent prognostic factor of pathological stage IA AC. The IASLC/ATS/ERS classification of lung AC identifies histologic categories with prognostic differences that could be helpful in clinical therapy.

[75]
TÍTULO / TITLE: - Transformation to small-cell lung cancer following treatment with EGFR tyrosine kinase inhibitors in a patient with lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

[76]
TÍTULO / TITLE: - EGFR lung cancer mutants get specialized.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Littlefield P; Jura N
INSTITUCIÓN / INSTITUTION: - Cardiovascular Research Institute and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94158.

Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 3892/or.2013.2696

Enlace a Enlace al texto completo (gratuito o de pago) 3892/or.2013.2696

Platinum-based chemotherapy with third generation drugs (such as gemcitabine) is an efficacious regimen of first-line treatment of patients with advanced, unresectable non-small cell lung cancer (NSCLC), without activating EGFR mutations. Mechanism of action of cytostatics are distortions in the DNA. ERCC1 and RRM1 are key proteins involved in the repair of DNA, thus, they may be responsible for the ineffectiveness of therapy. We investigated whether ERCC1 (19007C>T) and RRM1 (-37C>A) polymorphisms impact response to chemotherapy and survival in 62 patients with NSCLC treated with platinum and gemcitabine. Single nucleotide polymorphisms (SNPs) were assessed using a PCR-RFLP method in DNA isolated from PBLs. There were no statistically significant relationships between ERCC1 genotypes and response to therapy (p=0.581, chi2=1.09) as well as patient overall survival (OS). Carriers of the RRM1 AC genotype showed disease progression significantly more frequently (p=0.019, chi2=5.473) compared to carriers of the AA or CC genotypes. Carriers of the ERCC1/RRM1TT/CC genotype combination showed disease control significantly more frequently (p=0.047, chi2=3.95) compared to carriers of other genotype combinations. Patients with AA or CC genotypes of RRM1 showed significantly higher progression-free survival probability (p=0.0001, HR=0.39, 95% CI, 0.22-0.70) and OS probability (p=0.0104, HR=0.39, 95% CI, 0.18-0.82) compared to those with the AC genotype. In Cox regression model, poor performance status (p=0.0016, HR=4.78, 95% CI, 1.82-12.56), AC genotype of RRM1 gene (p=0.0414, HR=2.47, 95% CI, 1.04-5.87), lack of prior surgical treatment (p=0.0425, HR=4.71, 95% CI, 1.06-20.92) and lack of subsequent lines of treatment (p=0.0127, HR=3.23, 95% CI, 1.29-8.11) were significantly associated with shortening of patient survival. The analysis of RRM1 (-37C>A) more than ERCC1 (19007C>T) polymorphism may be a promising tool in the qualification of NSCLC patients for chemotherapy containing platinum compounds and gemcitabine.
TÍTULO / TITLE: Methadone as an additional opioid for a cancer patient with severe neuropathic and bone pain not responsive to other opioids and adjuvant analgesics.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Leppert W; Kowalski G
INSTITUCIÓN / INSTITUTION: Department of Palliative Medicine, Poznan University of Medical Sciences, Osiedle Rusa 25 A, 61-245 Poznan, Poland. wojciechleppert@wp.pl

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: De Couck M; van Brummelen D; Schallier D; De Greve J; Gidron Y
INSTITUCIÓN / INSTITUTION: Faculty of Medicine and Pharmacy, Free University of Brussels (VUB), Brussels, Belgium.
RESUMEN / SUMMARY: Recent studies suggest that vagal nerve activity, indexed by heart rate variability (HRV), could have a prognostic role in cancer. However, most studies did not control adequately for confounders and included cardiac patients. Furthermore, the validity of this prognostic role needs to be tested in different types of cancer. The present study tested the prognostic role of HRV in prostate cancer (PC) and non-small cell lung cancer (NSCLC) patients, using a historical prospective design. HRV was derived from brief 10 sec ECGs obtained at approximately the time of diagnosis in 113 PC patients and 133 NSCLC patients. Outcomes included prostate-specific antigen (PSA) at 6 and 24 months in PC, and overall survival (OS) (for the full sample) and survival time (for the deceased patients) in NSCLC. Furthermore, the possible mediating role of C-reactive protein (CRP) was tested (in NSCLC), as well as whether age and stage moderated the relationship between HRV and prognosis in both types of cancer. In the PC patients, HRV significantly inversely predicted PSA levels at 6 and 24 months, independent of confounders. Furthermore, this was particularly significant in metastatic PC patients, indicating moderation by stage. In NSCLC patients, HRV did not predict OS and survival time, but it did positively predict survival time in patients under the age of 65, independent of confounders. Additionally, CRP was not found to mediate the relationship between HRV and OS or survival time in NSCLC. The present results partly support previous studies and extend them to two additional common types of cancer, using a more rigorous control over
confounders. Together with recent experimental findings, these results propose a modulatory role of vagal nerve activity in cancer. Therefore, routine measurement of HRV in estimating prognosis in cancer may be considered.
**TÍTULO** - Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer?

**RESUMEN** - Enlace al Resumen / Link to its Summary


**AUTORES** - Langer CJ

**INSTITUCIÓN** - Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.

**TÍTULO** - Cost effectiveness of first-line pemetrexed plus platinum compared with other regimens in the treatment of patients with nonsquamous non-small cell lung cancer in the US outpatient setting.

**RESUMEN** - Enlace al Resumen / Link to its Summary


**AUTORES** - Shah M; Winfree KB; Peterson P; Gruschkus SK; Eaddy M; Green MR

**INSTITUCIÓN** - Xcenda, 4114 Woodlands Parkway, Palm Harbor, FL 34685, USA.

**RESUMEN** - This retrospective observational study evaluated cost effectiveness of first-line treatment of advanced nonsquamous non-small cell lung cancer (NSCLC) with pemetrexed/platinum (Pem/Plat) relative to paclitaxel/carboplatin (Pac/Carbo) and paclitaxel/carboplatin/bevacizumab (Pac/Carbo/Bev). Patients initiating first-line treatment from 2006 to 2009 were identified in electronic medical records of 20 US oncology practices. Pem/Plat patients were matched 1:1 on important characteristics with Pac/Carbo and Pac/Carbo/Bev patients and followed for 1 year to assess progression, survival, and costs. Bootstraping was used to calculate the probability of falling within quadrants of the incremental cost-effectiveness plane. Kaplan-Meier analysis and Cox proportional hazards regression modeling were also performed. Three hundred Pem/Plat patients (mean age, 67.6 years; male, 56.0%; PS 0/1, 71.0%) were matched with 300 patients in the other cohorts. Median PFS was 134 days (Pem/Plat) versus 106 days (Pac/Carbo) (hazard ratio [HR]: 0.67, P<0.001) and 126 days (Pac/Carbo/Bev) (HR: 0.68, P<0.001). Median OS was 298 days (Pem/Plat) versus 218 days (Pac/Carbo) (HR: 0.88, P=0.08) and 271 days (Pac/Carbo/Bev) (HR: 0.93, P=0.31). Pem/Plat therapy costs were higher versus Pac/Carbo ($21,841 higher PFS; $19,137 higher OS; P<0.05) and lower versus Pac/Carbo/Bev ($15,160 lower PFS; $19,946 lower OS; P<0.05). Pem/Plat had a
greater probability of higher costs/higher effectiveness versus Pac/Carbo (PFS, 90.1%; OS, 96.3%) and lower costs/higher effectiveness versus Pac/Carbo/Bev (PFS, 69.5%; OS, 85.0%). Pem/Plat had higher cost and effectiveness than Pac/Carbo; depending on a payer’s or society’s willingness to pay, Pem/Plat may be considered cost effective compared with Pac/Carbo. Pem/Plat yielded greater effectiveness with lower costs than Pac/Carbo/Bev.

[83]

**TITULO / TITLE:** - Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** - Support Care Cancer. 2013 Sep 1.

- Enlace al texto completo (gratuito o de pago) 1007/s00520-013-1925-1

**AUTORES / AUTHORS:** - Henke CC; Cabri J; Fricke L; Pankow W; Kandilakis G; Feyer PC; de Wit M

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Hematology and Oncology, Vivantes Clinic Neukoelln, Rudower Strasse 48, 12351, Berlin, Germany.

**RESUMEN / SUMMARY:** - PURPOSE: This randomized controlled trial tested the effects of a specially designed strength and endurance training on the independence and quality of life in lung cancer patients in stages IIIA/IIIB/IV during palliative chemotherapy.

**METHODS:** Between August 2010 and December 2011, 46 patients were randomized into two groups receiving either conventional physiotherapy or special physiotherapeutic training. The Barthel Index served as primary endpoint. The secondary endpoints were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ C-30/LC-13) questionnaire, the 6-Minute Walk Test (6MWT), stair walking, the Modified Borg Scale, and muscle strength. Nonparametrical data were analyzed with the Wilcoxon and Mann-Whitney U test. For parametric, data student t tests were used. A p value of </=.05 was accepted. RESULTS: Twenty-nine patients completed the trial (Intervention group (IG), n = 18; control group (CG), n = 11). Significant differences were detectable in the Barthel Index (IGmean = 92.08; CGmean = 81.67; p = .041), in single scores of the EORTC QLQ C-30/LC-13 questionnaire (physical functioning, p = .025; hemoptysis, p = .019; pain in arms or shoulder, p = .048; peripheral neuropathy, p = .050; cognitive functioning, p = .050), in the 6MWT, stair walking, strength capacity, and in the patient’s dyspnoea perception during submaximal walking activities (IG > CG).

**CONCLUSION:** According to these findings, lung cancer patients should receive enhanced physical activity intervention during palliative chemotherapy.
The Impact of EGFR Mutation Status on Outcomes in Patients With Resected Stage I Non-Small Cell Lung Cancers.

Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago)
1016/j.athoracsur.2013.05.091

Autores / Authors: Izar B; Sequist L; Lee M; Muzikansky A; Heist R; Iafrate J; Dias-Santagata D; Mathisen D; Lanuti M

Institución / Institution: Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Resumen / Summary: BACKGROUND: Mutations of the epidermal growth factor hormone receptor (EGFR) gene have been associated with improved treatment response and prognosis in advanced non-small lung cancer (NSCLC). However, their prognostic role in early-stage NSCLC is not well defined. In this study we sought to identify the pure prognostic role of EGFR mutation in patients with completely resected stage I NSCLC who received no adjuvant therapy. METHODS: Mutation status was tested in treatment-naive patients who had complete resection of stage I (T1-2aN0) NSCLC (from 2004 to 2011) using direct sequencing or multiplex polymerase chain reaction-based assay. Recurrence rates, disease-free survival, and overall survival were compared between EGFR-mutant and wild-type patients using Kaplan-Meier methods and Cox regression models. RESULTS: Three hundred seven patients were included in this study; 62 harbored tumors with EGFR mutations and 245 had wild-type EGFR. Tumors in patients with EGFR mutations were associated with a significantly lower recurrence rate (9.7% versus 21.6%; p = 0.03), greater median disease-free survival (8.8 versus 7.0 years; p = 0.0085), and improved overall 5-year survival (98% versus 73%; p = 0.003) compared with wild-type tumors. Lobectomy was the most frequently performed procedure, accounting for 209 of 307 operations. Among these patients, EGFR mutation was associated with superior overall survival (hazard ratio, 0.45; 95% confidence interval, 0.13 to 0.83; p = 0.017), with an estimated 5-year survival of 98% versus 70%. The presence of EGFR mutation (p = 0.026) and tumor size less than 2 cm (p = 0.04) were identified as independent prognostic markers for disease-free survival, whereas age, sex, and smoking status were not.

Conclusions: Completely resected stage I EGFR mutation-positive NSCLC patients have a significant survival advantage compared with EGFR wild-type patients. Mutation of the EGFR gene is a positive prognostic marker in completely resected stage I NSCLC.

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TÍTULO / TITLE: Identification of subgroup patients with stage IIIB/IV non-small cell lung cancer at higher risk for brain metastases.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Hsiao SH; Chung CL; Chou YT; Lee HL; Lin SE; Liu HE

INSTITUCIÓN / INSTITUTION: Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Medical University Hospital, 252, Wu-Xin Street, 110 Taipei, Taiwan.

RESUMEN / SUMMARY: PURPOSE: Brain metastases (BM), a common occurrence in non-small cell lung cancer (NSCLC), usually lead to a poor prognosis. Recently, the selection of treatment modalities for BM has modestly improved patient survival and quality of life. Treatment choice is largely based on the number of BM, the presence of BM-related symptoms, and performance status. Therefore, early BM detection is crucial. In this study, we aimed to elucidate the factors associated with BM and identify subgroups of patients at higher risk for BM.

METHODS AND PATIENTS: The medical records of 596 consecutive patients with stage I-IV NSCLC were reviewed between January 2006 and November 2011. A multivariate logistic regression (MLR) model was used to identify factors associated with BM.

RESULTS: Among 482 eligible stage IIIB/IV NSCLC patients, 173 (36%) experienced BM during their disease course. On MLR analysis, female gender, age <60 years and adenocarcinoma were associated with BM (OR=1.71, 95% CI=1.06-2.75, P=0.028; OR=2.11, 95% CI=1.38-3.22, P=0.001; and OR=2.39, 95% CI=1.16-4.92, P=0.018, respectively). The actuarial incidence of BM varied widely from 14% to 59% in different subgroups; younger patients with adenocarcinoma tended to experience BM more than older patients with squamous cell carcinoma (OR=6.88, 95% CI=2.97-15.94, P<0.001). Furthermore, the incidence of BM correlated closely with survival after NSCLC diagnosis, and it was 42%, 54% and 64% in patients who survived more than 3, 12 and 24 months, respectively. Notably, the number of BM, the size of the largest BM and the proportion of multiple BM, defined as more than 4 metastatic tumors in brain, were significantly different in NSCLC patients with and without BM-related symptoms or signs (4.0+/−2.1 vs 2.7+/−1.9, P<0.001; 2.6+/−1.5 vs 1.3+/−1.0 CM, P<0.001, and 50% vs 21%, P<0.001, respectively). CONCLUSION: We found that subgroups of NSCLC patients characterized by younger age, female gender and adenocarcinoma are at higher risks for BM. These findings might be helpful to detect BM earlier and facilitate the design of clinical trials aiming at their prevention.

[86]

TÍTULO / TITLE: Clinical significance of serum BAP, TRACP 5b and ICTP as bone metabolic markers for bone metastasis screening in lung cancer patients.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Tang C; Liu Y; Qin H; Li X; Guo W; Li J; Wang W; Qu L; Hu H; Xu C; Zheng L; Huang Y; Liu B; Gao H; Halleen JM; Liu X

INSTITUCIÓN / INSTITUTION: Department of Lung Cancer, Affiliated Hospital of Academy of Military Medical Sciences, No. 8 Dongdajie, Beijing 100071, China. Electronic address: gallanttang@126.com.

TÍTULO / TITLE: A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC).

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Goto K; Nishio M; Yamamoto N; Chikamori K; Hida T; Maemondo M; Katakami N; Kozuki T; Yoshioka H; Seto T; Fukuyama T; Tamura T

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RESUMEN / SUMMARY: INTRODUCTION: The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib is associated with survival benefits in patients with EGFR mutation-positive non-small-cell lung cancer (NSCLC). This phase II, single-arm study examined the efficacy and safety of first-line erlotinib in Japanese patients with EGFR mutation-positive NSCLC. METHODS: Eligible patients received erlotinib 150mg/day until disease progression or unacceptable toxicity. The primary endpoints were progression-free survival (PFS) and safety. RESULTS: A high degree of concordance was observed between different mutation testing methodologies, suggesting feasibility of early, rapid detection of EGFR mutations. Median PFS was 11.8 months (95% confidence interval [CI]: 9.7-15.3) at data cut-off (1 June 2012) (n=102). Exon 19 deletions seemed to be associated with longer PFS compared with L858R mutations; T790M mutations were tentatively linked with shorter PFS. The safety profile was as expected: rash (any grade; 83%) and diarrhea (any grade; 81%) were most common. Six interstitial lung disease (ILD)-like cases were reported, and 5 were confirmed as ILD-like events by the extramural committee. Two patients died of treatment-related pneumonitis (JAPIC Clinical Trials Information number: Japic CTI-101085). CONCLUSION: Erlotinib should be considered for first-line treatment in this subset of Japanese patients, with close monitoring for ILD-like events.
A retrospective analysis of 335 Japanese lung cancer patients who responded to initial gefitinib treatment.

BACKGROUND: Gefitinib treatment results in considerably better progression-free survival compared with that of platinum doublets in the first line treatment of nonsmall-cell lung cancer (NSCLC) carrying an activating epidermal growth factor receptor (EGFR) mutation. Some patients who respond to gefitinib have an overall survival (OS) of more than 5 years, whereas other initial responders do less well. Although there has been considerable effort made to elucidate the mechanisms of acquired resistance, there have only been a few studies that addressed the effect of clinical backgrounds and treatment histories on the survival of the patients who had responded to an EGFR-tyrosine kinase inhibitor (TKI). In this study, we especially focused on the clinical benefit of EGFR-TKI administration after progression.

PATIENTS AND METHODS: We retrospectively analyzed consecutive patients with advanced NSCLC who were diagnosed before October 2010, treated with gefitinib after July 2002, and responded to it. The primary objective of this study was to evaluate how clinical backgrounds and treatment histories influence survival of the patients who respond to gefitinib. The secondary objectives were to evaluate the safety of long-term gefitinib use and to establish the optimal treatment sequence using a dynamic treatment regimen analysis (DTRA).

RESULTS: A total of 335 patients were recruited. Twenty-eight (8.4%) patients survived more than 5 years. Sixty-five and 93 patients received gefitinib as rechallenge and beyond progressive disease (BPD), respectively. A statistically significant difference in OS was observed between the patients who underwent gefitinib rechallenge and those who did not rechallenge (median: 1272 days vs. 774 days; p<0.001), a result supported by a DTRA. Patients treated with gefitinib BPD also showed a tendency of longer survival.

CONCLUSIONS: Gefitinib rechallenge and BPD played a central role in long term survival of the patients who initially responded to gefitinib.
Hepatocyte Nuclear Factor 6 suppresses the migration and invasive growth of lung cancer cells through p53 and the inhibition of epithelial-mesenchymal transition.

Epithelial-mesenchymal transition plays an important role in many patho-physiological processes, including cancer invasion and metastatic progression. Hepatocyte Nuclear Factor 6 (HNF6) has been known to be an important factor for both physiological and pathological functions in liver and pancreas. However, its role in EMT and lung cancer progression remains unidentified. We observed that HNF6 level can be downregulated by TGF-beta1 in human lung cancer cells. Knockdown of HNF6 induced EMT and increased cell migration. In contrast, ectopically expression of HNF6 inhibited cell migration and attenuated TGF-beta1-induced EMT. The data suggest that HNF6 plays a role in maintaining epithelial phenotype, which suppresses EMT. HNF6 also inhibits both colony formation and proliferation of lung cancer cells. It pronouncedly reduced the formation of tumor xenograft in nude mice. In addition, HNF6 can activate the promoter activity of p53 by directly binding to a specific region of its promoter, and therefore increase the protein level of tumor suppressor p53. p53 knockdown induced EMT and increased cell migration, whereas the opposite effect was generated by p53 overexpression. p53 knockdown also inhibited the effect of HNF6 on EMT and cell migration, indicating that p53 is required for HNF6’s functions herein. Moreover, there is a high positive correlation among the expression levels of HNF6, p53, and E-cadherin in human lung cancer cells and tissues. The data suggest that HNF6 inhibits EMT, cell migration, and invasive growth through a mechanism involving the transcriptional activation of p53.
Treatment with epidermal growth factor receptor (EGFR) tyrosine inhibitors (EGFR-TKIs) provides encouraging outcomes for advanced non-small cell lung cancer (NSCLC) patients with EGFR mutations. Pleural effusion is a common complication of NSCLC. We compared direct DNA sequencing and ADx Amplification Refractory Mutation System (ADx-ARMS) to detect EGFR mutations in malignant pleural effusion samples. We obtained 24 samples from pleural effusion fluid of NSCLC patients. Three common types of EGFR mutations were examined by direct sequencing and ADx-ARMS analysis. The sensitivity of the methods was compared and the relationship between EGFR mutations and response rates of the patients determined.

In 14/24 patients, we detected EGFR mutations (58.3%) by ADx-ARMS, and in 10 samples (41.7%) by direct sequencing. In 6 samples, EGFR mutations were on exon 19, and in 8 samples, mutations were on exon 21 by ADx-ARMS. By contrast, we found EGFR mutations in 4 samples on exon 19, and in 6 samples on exon 21 by direct sequencing. Neither method showed mutations on exon 20. Among the 24 patients, there was 83.3% concordance for the methods. In 18/24 patients, gefitinib treatment was administered, including 10 patients with mutations who showed improved response compared to 8 of the wild-type patients (P<0.05). In conclusion, EGFR mutation analysis by ADx-ARMS was the most sensitive compared to direct sequencing, and provided more reliable EGFR mutation assessments. ADx-ARMS could be introduced into the clinical practice to identify NSCLC patients likely to benefit from TKI treatment, especially those with malignant pleural effusion.
with NSCLC between 1996 and 2007. We used conditional probability function (CPF) analyses to compare survival by HIV status accounting for an increased risk of non-lung cancer death (competing risks) in HIV-infected patients. We used multivariable CPF regression to evaluate lung cancer prognosis by HIV status adjusted for confounders.

Results: Stage at presentation and use of stage-appropriate lung cancer treatment did not differ by HIV status. Median survival was 6 months (95% confidence interval (CI): 5-8 months) among HIV-infected NSCLC patients compared with 20 months (95% CI: 17-23 months) in patients without evidence of HIV. Multivariable CPF regression showed that HIV was associated with a greater risk of lung cancer-specific death after controlling for confounders and competing risks.

Conclusion: NSCLC patients with HIV have a poorer prognosis than patients without evidence of HIV. NSCLC may exhibit more aggressive behaviour in the setting of HIV.

[92]

TÍTULO / TITLE: - Treatment of central type lung cancer by combined cryotherapy: Experiences of 47 patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhikai Z; Lizhi N; Liang Z; Jianying Z; Fei Y; Jibing C; Jialiang L; Kecheng X

INSTITUCIÓN / INSTITUTION: - Fuda Cancer Hospital, Jinan University School of Medicine, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China.

RESUMEN / SUMMARY: - Most patients with central type lung cancer (CTLC) are not candidates for surgery; systemic chemotherapy and external beam radiotherapy are the main treatments but have not greatly affected patient outcome. Combined percutaneous and endobronchial cryotherapy has been used successfully to treat CTLC; this study aimed to determine its feasibility and safety. Forty-seven patients with unresectable CTLC (22 endotracheal, 26 tracheal wall and 21 extratracheal tumors) underwent 69 sessions of combined percutaneous cryosurgery, endobronchial cryosurgery and airway stenting. The long diameter of all tumors was <5cm. Biopsy showed non-small cell lung cancer (NSCLC) in 40 patients (medium or well differentiated in 20 cases, poorly differentiated in 20) and small cell lung cancer (SCLC) in seven. Within 3 days after treatment, ventilatory capacity and performance status had obviously increased and cough, signs of dyspnea, hemoptysis and atelectasis improved significantly, but symptoms of pneumothorax and pleural effusion emerged. After 2 weeks, all complications had disappeared completely, as had cough. Progression-free survival (PFS) for endotraheal tumors (8+/−4 months) was shorter than that for tracheal wall (13+/−6 months, P<0.05) and extratracheal (14+/−8 months,
The PFS of NSCLC (11+/−5 months) was significantly longer than that of SCLC (4+/−2 months, P<0.0001). The PFS of medium or well differentiated CTLC (15+/−8 months) was significantly longer than that of poorly differentiated CTLC (7+/−3 months, P<0.0001). In conclusion, combined cryotherapy is a safe and effective treatment for CTLC, with PFS largely influenced by tumor location and pathologic type.
chemoradiotherapy. CONCLUSIONS:: Because of study design, efficacy comparisons cannot be made. However, both combinations with concurrent RT were active and well tolerated.
AUTORES / AUTHORS: - Gahr S; Stoehr R; Geissinger E; Ficker JH; Brueckl WM; Gschwendtner A; Gattenloehner S; Fuchs FS; Schulz C; Rieker RJ; Hartmann A; Ruemmele P; Dietmaier W
INSTITUCIÓN / INSTITUTION: - 1] Klinikum Nuernberg, Department of Respiratory Medicine, Allergology and Sleep Medicine, Nuremberg, Germany [2] Paracelsus Medical University Nuremberg, Nuremberg, Germany.
RESUMEN / SUMMARY: - Background: The prognosis of metastatic non-small cell lung cancer (NSCLC) is still poor. Activating epithelial growth factor receptor (EGFR) mutations are important genetic alterations with dramatic therapeutical implications. Up to now, in contrast to Asian populations only limited data on the prevalence of those mutations are available from patients with Caucasian and especially European ethnicity. Methods: In this multicentre study, 1201 unselected NSCLC patients from Southern Germany were tested in the daily clinical routine for EGFR mutation status. Results: Activating EGFR mutations were found in 9.8% of all tumours. Mutations in exons 18, 19 and 21 accounted for 4.2%, 61.9% and 33.1% of all mutations, respectively. Non-smokers had a significantly higher rate of EGFR mutations than smokers or ex-smokers (24.4% vs 4.2%; P<0.001). Non-lepidic-non-mucinous adenocarcinomas (G2) accounted for 45.5% of all activating EGFR mutations and 3.5% of all squamous cell carcinomas were tested positive. Thyroid transcription factor 1 protein expression was significantly associated with EGFR mutational status. Conclusion: These comprehensive data from clinical routine in Germany add to the knowledge of clinical and histopathological factors associated with EGFR mutational status in NSCLC.

[96]

TÍTULO / TITLE: - Increased BCAR1 Predicts Poor Outcomes of Non-small Cell Lung Cancer in Multiple-Center Patients.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Deng B; Sun Z; Jason W; Yang P
INSTITUCIÓN / INSTITUTION: - Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, College of Medicine, Rochester, MN, USA.
RESUMEN / SUMMARY: - OBJECTIVE: This study was designed to determine the prognostic value of BCAR1 expression and its associations with clinical-demographical characteristics in multiple centers of non-small cell lung cancer (NSCLC) patients. METHODS: Gene expression microarray (mRNA) of 77 adenocarcinomas from Mayo Clinic, RNA-sequencing of 508 NSCLC from The Cancer Genome Atlas (TCGA), and immunohistochemistry stain of BCAR1-protein expression in 150 cases from Daping Hospital were included in the study. The association of mRNA or protein expression
with patient clinical characteristics and overall survival was assessed in each dataset. We also predicted microRNAs (miRNA) that target BCAR1 using bioinformatics prediction tools and evaluated miRNA expression patterns with BCAR1 expression in miRNA-sequencing data of 74 lung cancer cases from TCGA dataset. RESULTS: In the Mayo Clinic dataset, a higher BCAR1 mRNA level correlated significantly with more advanced tumor-stage and lymphatic metastasis. Similar changes were observed in the TCGA RNA-seq dataset. Additionally, higher BCAR1 mRNA levels predicted poorer survival in adenocarcinoma and squamous carcinoma from the TCGA dataset. The protein levels in the adenocarcinoma cases with lymphatic metastasis were significantly higher than of those without metastasis. Tumor tissues demonstrated remarkably higher levels of protein compared with matched normal tissues although there was no significant difference in BCAR1 mRNA expression between tumor and matched normal tissues was detected. In miRNAs that were downregulated in the tumors, Let-7f-2 and miR-22 differed the most (P < 0.001 and P = 0.007, respectively).

CONCLUSIONS: We confirmed that increased BCAR1 expression predicts poorer prognosis in NSCLC. We postulate that mRNA-protein decoupling of BCAR1 may be a result of reduced inhibition of specific miRNAs in tumor tissues, which warrants further study.

[97]
TÍTULO / TITLE: - Smoking and smoking cessation in relation to the development of coexisting non-small cell lung cancer with chronic obstructive pulmonary disease.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhai R; Yu X; Wei Y; Su L; Christiani DC
INSTITUCIÓN / INSTITUTION: - Department of Environmental Health, Harvard School of Public Health, Boston, MA.
RESUMEN / SUMMARY: - Previous studies have identified a mixed-phenotype of non-small cell lung cancer (NSCLC) with co-existing chronic obstructive pulmonary disease (COPD). Although NSCLC and COPD share a common risk factor in smoking, whether and how smoking may contribute to the coexistence of NSCLC with COPD (NSCLC-COPD) is unclear. Our study suggests that cigarette smoking is the major risk factor for the development of NSCLC-COPD, especially in females and among patients with squamous cell carcinoma subtype.

[98]
Choline is essential for the synthesis of the major membrane phospholipid phosphatidylcholine and the neurotransmitter acetylcholine (ACh). Elevated levels of choline and up-regulated choline kinase activity have been detected in cancer cells. Thus, the intracellular accumulation of choline through choline transporters is the rate-limiting step in phospholipid metabolism and a prerequisite for cancer cell proliferation. However, the uptake system for choline and the functional expression of choline transporters in lung cancer cells are poorly understood. We examined the molecular and functional characterization of choline uptake in the small cell lung carcinoma cell line NCI-H69. Choline uptake was saturable and mediated by a single transport system. Interestingly, removal of Na(+) from the uptake buffer strongly enhanced choline uptake. This increase in choline uptake under the Na(+)-free conditions was inhibited by dimethylamiloride (DMA), a Na(+)/H(+) exchanger (NHE) inhibitor. Various organic cations and the choline analog hemicholinium-3 (HC-3) inhibited the choline uptake and cell viability. A correlation analysis of the potencies of organic cations for the inhibition of choline uptake and cell viability showed a strong correlation (R=0.8077). RT-PCR revealed that choline transporter-like protein 1 (CTL1) mRNA and NHE1 are mainly expressed. HC-3 and CTL1 siRNA inhibited choline uptake and cell viability, and increased caspase-3/7 activity. The conversion of choline to ACh was confirmed, and this conversion was enhanced under Na(+)-free conditions, which in turn was sensitive to HC-3. These results indicate that choline uptake through CTL1 is used for ACh synthesis. Both an acetylcholinesterase inhibitor (eserine) and a butyrylcholinesterase inhibitor (ethopropazine) increased cell proliferation, and these effects were inhibited by 4-DAMP, a mAChR3 antagonist. We conclude that NCI-H69 cells express the choline transporter CTL1 which uses a directed H(+) gradient as a driving force, and its transport functions in co-operation with NHE1. This system primarily supplies choline for the synthesis of ACh and secretes ACh to act as an autocrine/paracrine growth factor, and the functional inhibition of CTL1 could promote apoptotic cell death. Identification of this new CTL1-mediated choline transport system provides a potential new target for therapeutic intervention.
Comparison of the utility of whole-body MRI with and without contrast-enhanced Quick 3D and double RF fat suppression techniques, conventional whole-body MRI, PET/CT and conventional examination for assessment of recurrence in NSCLC patients.

PURPOSE: The purpose of this study was to compare diagnostic capabilities for assessment of recurrence in non-small cell lung cancer (NSCLC) patients by contrast-enhanced whole-body MRI (CE-WB-MRI) with and without CE-Quick 3D and double RF fat suppression technique (DFS), FDG-PET/CT and conventional radiological examinations. MATERIALS AND METHODS: A total of 134 pathologically proven and completely resected NSCLC patients (78 males, 56 females; mean age: 72 years) underwent FDG-PET/CT, CE-WB-MRI with and without Quick 3D and DFS at 3T as well as conventional radiological examinations. The probability of recurrence was assessed with a 5-point scoring system on a per-patient basis, and final diagnosis was made by consensus between two readers. The capability for overall recurrence assessment by all the methods was compared by means of ROC analysis and their sensitivity, specificity and accuracy by means of McNemar’s test. RESULTS: Although areas under the curve did not show any significant differences, specificity (100%) and accuracy (95.5%) of CE-WB-MRI with CE-Quick 3D and DFS were significantly higher than those of FDG-PET/CT (specificity: 93.6%, p=0.02; accuracy: 89.6%, p=0.01) and conventional radiological examinations (specificity: 92.7%, p=0.01; accuracy: 91.0%, p=0.03). In addition, specificity of CE-WB-MRI without CE-Quick 3D and DFS (100%) was significantly higher than that of FDG-PET/CT (p=0.02) and conventional radiological examinations (p=0.01). CONCLUSION: Specificity and accuracy of CE-WB-MRI with CE-Quick 3D and DFS for assessment of recurrence in NSCLC patients are at least as high as, or higher than those of others.
Various ion channels are expressed in human cancers where they are intimately involved in proliferation, angiogenesis, invasion and metastasis. Expression of functional voltage-gated sodium channels (Nav) is implicated in the metastatic potential of breast, prostate, lung and colon cancer cells. However, the cellular mechanisms that regulate Nav expression in cancer remain largely unknown. Growth factors are attractive candidates; they not only play crucial roles in cancer progression but are also key regulators of ion channel expression and activity in non-cancerous cells. Here, we examine the role of epidermal growth factor receptor (EGFR) signalling and Nav in non-small cell lung carcinoma (NSCLC) cell lines. We show unequivocally, that functional expression of Nav1.7 promotes invasion in H460 NSCLC cells. Inhibition of Nav1.7 activity (tetrodotoxin), or, expression (small interfering RNA), reduces H460 cell invasion by up to 50%. Crucially, non-invasive wild type A549 cells lack functional Nav whereas exogenous over-expression of Nav1.7 is sufficient to promote TTX-sensitive invasion of these cells. EGF/EGFR signalling enhances proliferation, migration and invasion of H460 cells but we find that EGFR-mediated up-regulation of Nav1.7 specifically, is necessary for invasive behaviour in these cells. Examination of Nav1.7 expression at the mRNA, protein and functional levels further reveals that EGF/EGFR signalling via the ERK1/2 pathway controls transcriptional regulation of channel expression to promote cellular invasion. Immunohistochemistry of patient biopsies confirms the clinical relevance of Nav1.7 expression in NSCLC. Thus, Nav1.7 has significant potential as a novel target for therapeutic intervention and/or as a diagnostic/prognostic marker in NSCLC.
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[102]

TÍTULO / TITLE: - Notch1 Is Required for Kras-Induced Lung Adenocarcinoma and Controls Tumor Cell Survival via p53.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Licciulli S; Avila JL; Hanlon L; Troutman S; Cesaroni M; Kota S; Keith B; Simon MC; Pure E; Radtke F; Capobianco AJ; Kissil JL

INSTITUCIÓN / INSTITUTION: - Authors’ Affiliations: Department of Cancer Biology, The Scripps Research Institute, Jupiter; Molecular Oncology Program, DeWitt Daughtry Family Department of Surgery and Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, Florida; The Wistar Institute; Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine; Department of Cancer Biology, Abramson Family Cancer Research Institute; and Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and Ecole Polytechnique Federale de Lausanne, EPFL SV ISREC, Lausanne, Switzerland.

RESUMEN / SUMMARY: - The Notch pathway has been implicated in a number of malignancies with different roles that are cell- and tissue-type dependent. Notch1 is a putative oncogene in non-small cell lung cancer (NSCLC) and activation of the pathway represents a negative prognostic factor. To establish the role of Notch1 in lung adenocarcinoma, we directly assessed its requirement in Kras-induced tumorigenesis in vivo using an autochthonous model of lung adenocarcinoma with concomitant expression of oncogenic Kras and deletion of Notch1. We found that Notch1 function is required for tumor initiation via suppression of p53-mediated apoptosis through the regulation of p53 stability. These findings implicate Notch1 as a critical effector in Kras-driven lung adenocarcinoma and as a regulator of p53 at a posttranslational level. Moreover, our study provides new insights to explain, at a molecular level, the correlation between Notch1 activity and poor prognosis in patients with NSCLC carrying wild-type p53. This information is critical for design and implementation of new therapeutic strategies in this cohort of patients representing 50% of NSCLC cases. Cancer Res; 73(19); 5974-84. ©2013 AACR.

[103]
Hypoxia imaging with [F]HX4 PET in NSCLC patients: Defining optimal imaging parameters.

BACKGROUND AND PURPOSE: [18F]HX4 is a promising hypoxia PET-tracer. Uptake, spatio-temporal stability and optimal acquisition parameters for [18F]HX4 PET imaging were evaluated in non-small cell lung cancer (NSCLC) patients.

MATERIALS AND METHODS: [18F]HX4 PET/CT images of 15 NSCLC patients were acquired 2h and 4h after injection (p.i.). Maximum standardized-uptake-value (SUVmax), tumor-to-blood-ratio (TBRmax), hypoxic fraction (HF) and contrast-to-noise-ratio (CNR) were determined for all lesions. To evaluate spatio-temporal stability, DICE-similarity and Pearson correlation coefficients were calculated. Optimal acquisition-duration was assessed by comparing 30, 20, 10 and 5min acquisitions.

RESULTS: Considerable uptake (TBR >1.4) was observed in 18/25 target lesions. TBRmax increased significantly from 2h (1.6+-0.3) to 4h p.i. (2.0+-0.6). Uptake patterns at 2h and 4h p.i. showed a strong correlation (R=0.77+/-0.10) with a DICE similarity coefficient of 0.69+/-0.08 for the 30% highest uptake volume. Reducing acquisition-time resulted in significant changes in SUVmax and CNR. TBRmax and HF were only affected for scan-times of 5min. CONCLUSIONS: The majority of NSCLC lesions showed considerable [18F]HX4 uptake. The heterogeneous uptake pattern was stable between 2h and 4h p.i. [18F]HX4 PET imaging at 4h p.i. is superior to 2h p.i. to reach highest contrast. Acquisition time may be reduced to 10min without significant effects on TBRmax and HF.

Expression of TLR9 in tumor-infiltrating mononuclear cells enhances angiogenesis and is associated with a worse survival in lung cancer.

BACKGROUND AND PURPOSE: [18F]HX4 is a promising hypoxia PET-tracer. Uptake, spatio-temporal stability and optimal acquisition parameters for [18F]HX4 PET imaging were evaluated in non-small cell lung cancer (NSCLC) patients.

MATERIALS AND METHODS: [18F]HX4 PET/CT images of 15 NSCLC patients were acquired 2h and 4h after injection (p.i.). Maximum standardized-uptake-value (SUVmax), tumor-to-blood-ratio (TBRmax), hypoxic fraction (HF) and contrast-to-noise-ratio (CNR) were determined for all lesions. To evaluate spatio-temporal stability, DICE-similarity and Pearson correlation coefficients were calculated. Optimal acquisition-duration was assessed by comparing 30, 20, 10 and 5min acquisitions.

RESULTS: Considerable uptake (TBR >1.4) was observed in 18/25 target lesions. TBRmax increased significantly from 2h (1.6+-0.3) to 4h p.i. (2.0+-0.6). Uptake patterns at 2h and 4h p.i. showed a strong correlation (R=0.77+/-0.10) with a DICE similarity coefficient of 0.69+/-0.08 for the 30% highest uptake volume. Reducing acquisition-time resulted in significant changes in SUVmax and CNR. TBRmax and HF were only affected for scan-times of 5min. CONCLUSIONS: The majority of NSCLC lesions showed considerable [18F]HX4 uptake. The heterogeneous uptake pattern was stable between 2h and 4h p.i. [18F]HX4 PET imaging at 4h p.i. is superior to 2h p.i. to reach highest contrast. Acquisition time may be reduced to 10min without significant effects on TBRmax and HF.
**INSTITUCIÓN / INSTITUTION:** Service de Pneumologie, AP-HP, Hopital Tenon, Paris, France; Equipe de Recherche 2, GRC UPMC-04, Universite Paris 6 Pierre et Marie Curie, Service de Pneumologie, Hopital Tenon, Paris, France.

**RESUMEN / SUMMARY:** Toll-like receptors (TLRs) play a crucial role in the innate and adaptive immune responses against microbial infection, tissue injury and cancer. Ligands of TLR9 have been developed as therapy in non-small-cell lung carcinoma (NSCLC). However, phase III clinical trials in metastatic NSCLC were negative. Our objective was to determine whether TLR9 affects tumor growth. We generated a mouse model of lung adenocarcinoma (ADC) mutated for K-ras (K-rasLA1), with and without TLR9 inactivation (K-rasLA1 TLR9-/- and K-rasLA1 TLR9+/+, respectively). TLR9 was functionally expressed only in mononuclear cells of K-rasLA1 TLR9+/+ mice. These mice had significantly worse survival and a higher tumor burden than K-rasLA1 TLR9-/- mice. Lung tumors were analyzed for 24 cytokines/growth factors using Bio-Plex multiplex bead-based assays. Factor VIII was assessed by immunochemistry. Tumors from K-rasLA1 TLR9+/+ mice were characterized by an angiogenic phenotype with higher concentrations of vascular endothelial growth factor (VEGF) and higher microvessel density than from K-rasLA1 TLR9-/- mice. LKR13 cells, an ADC cell line derived from K-rasLA1 mice, were subcutaneously injected into TLR9-/- and TLR9+/+ mice. Syngeneic tumors regressed in TLR9-/- but not in TLR9+/+ mice. Peripheral blood mononuclear cells from TLR9-/- mice released less VEGF than those from TLR9+/+ mice. In 61 patients with early-stage NSCLC, TLR9 was expressed in mononuclear cells that infiltrated tumors, as assessed by immunochemistry, and contributed to worse survival. Our results suggest that TLR9 expression in mononuclear cells was associated with an angiogenic phenotype and promoted lung cancer progression. These findings may aid clinical development of TLR9 ligands to treat cancers.

[105]

**TÍTULO / TITLE:** How do social factors explain outcomes in non-small-cell lung cancer among hispanics in California? Explaining the Hispanic paradox.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Patel MI; Schupp CW; Gomez SL; Chang ET; Wakelee HA

**INSTITUCIÓN / INSTITUTION:** Manali I. Patel, Scarlett L. Gomez, Ellen T. Chang, and Heather A. Wakelee, Stanford University; Scarlett L. Gomez and Heather A. Wakelee, Stanford Cancer Institute, Stanford; Clayton W. Schupp and Scarlett L. Gomez, Cancer Prevention Institute of California, Fremont; and Ellen T. Chang, Exponent Health Sciences Practices, Menlo Park, CA.
RESUMEN / SUMMARY: - PURPOSE: Hispanics in the United States have lower age-adjusted mortality resulting from non-small-cell lung cancer (NSCLC) compared with non-Hispanic whites (NHWs). The purpose of this study was to evaluate individual, clinical, and neighborhood factors in survival among Hispanics with NSCLC. PATIENTS AND METHODS: We performed a retrospective analysis of NHWs and Hispanics with NSCLC between 1998 and 2007 in the California Cancer Registry (follow-up to December 2009). Kaplan-Meier curves depict survival by nativity for Hispanics with NSCLC. Cox proportional hazards models estimated hazard of mortality by race with adjustment for individual (age, sex, marital status), clinical (histologic grade, surgery, irradiation, chemotherapy), and neighborhood factors (neighborhood socioeconomic status, ethnic enclave). RESULTS: We included 14,280 Hispanic patients with NSCLC. Foreign-born Hispanics had 15% decreased risk of disease-specific mortality resulting from NSCLC compared with NHWs (hazard ratio [HR], 0.85; 95% CI, 0.83 to 0.88) after adjustment for individual, clinical, and neighborhood factors. After adjustment for individual factors, compared with US-born Hispanics, foreign-born Hispanics had 10% decreased risk of disease-specific mortality (HR, 0.90; 95% CI, 0.87 to 0.96). Clinical and neighborhood factors slightly moderated the survival benefit for foreign-born patients. A modestly more pronounced survival advantage was seen for foreign-born Hispanics living in low socioeconomic and high Hispanic enclave neighborhoods as compared with US-born Hispanics (HR, 0.86; 95% CI, 0.81 to 0.90). CONCLUSION: Foreign-born Hispanics with NSCLC have a decreased risk of disease-specific mortality compared with NHWs and US-born Hispanics with NSCLC. Neighborhood factors slightly moderate this survival advantage. This survival advantage is slightly more pronounced in lower socioeconomic and higher Hispanic enclave neighborhoods.

[106]

TÍTULO / TITLE: - Cetuximab response of lung cancer-derived EGF receptor mutants is associated with asymmetric dimerization.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Cho J; Chen L; Sangji N; Okabe T; Yonesaka K; Francis JM; Flavin RJ; Johnson W; Kwon J; Yu S; Greulich HE; Johnson BE; Eck MJ; Janne PA; Wong KK; Meyerson M

INSTITUCIÓN / INSTITUTION: - Samsung Genome Institute, Samsung Medical Center.

RESUMEN / SUMMARY: - Kinase domain mutations of the epidermal growth factor receptor (EGFR) are common oncogenic events in lung adenocarcinoma. Here we explore the dependency upon asymmetric dimerization of the kinase domain for activation of lung cancer-derived EGFR mutants. We show that while wild-type EGFR and the L858R mutant require dimerization for activation and oncogenic
transformation, the exon 19 deletion, exon 20 insertion, and L858R/T790M EGFR mutants do not require dimerization. In addition, treatment with the monoclonal antibody, cetuximab, shrinks mouse lung tumors induced by the dimerization-dependent L858R mutant, but exerts only a modest effect on tumors driven by dimerization-independent EGFR mutants. These data imply that different EGFR mutants show differential requirements for dimerization, and that disruption of dimerization may be among the antitumor mechanisms of cetuximab.
patients compared to control subjects. Systemic levels of oxidatively damaged DNA, superoxide anion, and TNF-alpha and bronchial levels of TGF-beta and TNF-alpha showed high sensitivity and specificity for LC among patients. Regardless of the presence of an underlying respiratory condition (COPD), protein oxidation, oxidatively damaged DNA, and inflammation were remarkably increased in the normal airways and blood of patients with LC. Furthermore, the potential predictive value for LC development of these molecular events warrants attention and should be explored in future larger longitudinal studies.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
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RESUMEN / SUMMARY: PURPOSE: To explore the potential of a novel dose-volume based metric to assist in the selection of optimal fractionation schedules for lung cancer patients. METHODS: Selecting the dose per fraction that maximizes the therapeutic ratio via a linear-quadratic effect on normal tissue complication probability and tumor cell survival is an optimization problem. The mathematical solution reveals that the optimal fractionation schedule is determined by a generalized dose ratio between the normal tissue and the tumor, here termed the bifurcation number B, that can be derived from the dose-volume histogram of the normal tissue. The bifurcation number characterizes the volume effect of a normal tissue and its dependency on the fractionation schedule. The clinical relevance of the bifurcation number was evaluated in 46 patients previously treated for nonsmall cell lung cancer (NSCLC) according to various fractionation protocols. Bifurcation numbers were computed for both lung and esophagus as the normal tissues. RESULTS: The value of the bifurcation number determines whether the volume effect reverses the traditional radiobiological advantage of small dose per fraction for the normal tissue. If B is smaller than the ratio of alpha/beta ratios between normal tissue and tumor, then a single fraction is optimal; otherwise the optimal treatment is an infinite number of doses (hence the name “bifurcation” number). These fractionation schedules correspond clinically to hypo- and standard/hyperfractionation, respectively. Compared with traditional dose-volume metrics, the bifurcation number is a unitless ratio and independent of dose fractionation. The B-numbers derived from the clinical treatment plans are also strongly consistent with historically prescribed clinical fractionation protocols for
NSCLC treatments. The B-numbers for esophagus and lung for all patients receiving a high dose per fraction protocol (>7.5 Gy/fraction) were all smaller than the B-numbers for the patients receiving standard 2 Gy/fraction, with the numbers for the 3 Gy/fraction group in between. CONCLUSIONS: The bifurcation numbers are strongly consistent with prescribed clinical fractionation protocols for NSCLC treatments. Due to their scale-free property the B-numbers may assist in the selection of an appropriate fractionation once the dose distribution has been optimized.

[109]

TÍTULO / TITLE: A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

Enlace al texto completo (gratuito o de pago) 1038/bjc.2013.467
AUTORES / AUTHORS: Sun JM; Kim JR; Do IG; Lee SY; Lee J; Choi YL; Ahn JS; Ahn MJ; Park K
INSTITUCIÓN / INSTITUTION: Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea.
RESUMEN / SUMMARY: Background: The mammalian target of rapamycin (mTOR) pathway is dysregulated in small-cell lung cancer (SCLC) and everolimus is an oral mTOR inhibitor. Methods: This phase-1b study assessed everolimus safety at the levels of 2.5, 5, or 10 mg once daily in combination with paclitaxel (175 mg m(-2)) once every 3 weeks in previously treated SCLC patients. The primary end point was to determine the maximum tolerated dose of everolimus. Results: Among 21 enrolled patients, common drug-related adverse events were anaemia, neutropenia, thrombocytopenia, pain, hyperglycemia, and stomatitis. Out of 11 evaluable patients treated with everolimus at the level of 5 mg, 1 patient experienced dose-limiting toxicity (DLT) of grade 4 febrile neutropenia and grade 3 thrombocytopenia. The other two DLTs (grade 4 thrombocytopenia and grade 3 hyperglycemia) occurred in two out of three patients receiving everolimus 10 mg. The overall objective response rate was 28%. Conclusion: Everolimus showed an acceptable safety profile and preliminary antitumour activity at the dose of 5 mg once daily when combined with 3-weekly paclitaxel 175 mg m(-2) in patients with SCLC.

[110]

TÍTULO / TITLE: Does age influence the symptom experience of lung cancer patients prior to surgery?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Oksholm T; Miaskowski C; Kongerud JS; Cooper B; Paul SM; Laerum L; Rustoen T

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RESUMEN / SUMMARY: - OBJECTIVES: Older patients with lung cancer are less likely to be offered surgery than younger patients. Although higher preoperative symptom burden is associated with poorer postoperative outcomes, few studies have examined age-related differences in symptom experience of lung cancer patients prior to surgery. This study evaluated for differences in symptom occurrence, severity, and distress between older (>65 years) and younger (<65 years) patients prior to surgery.

MATERIALS AND METHODS: Data were collected through chart review and a symptom assessment scale (i.e., Memorial Symptom Assessment Scale (MSAS)) that evaluated multiple dimensions of 32 symptoms. Descriptive statistics were used to present demographic and clinical characteristics of the sample. Logistic regression analyses were used to evaluate for age-related differences in each dimension of the symptom experience. RESULTS: A total of 270 patients completed the MSAS prior to surgery (113 younger and 157 older patients). Few age-related differences were identified. When age differences were identified, older patients reported lower occurrence rates and lower severity and distress ratings. Cough, lack of energy, feeling drowsy and worrying was the four most common symptoms in both age groups. In the younger patients, feeling nervous was ranked fourth. Shortness of breath was ranked third by the older patients. The study confirmed the high occurrence rates for cough, pain, fatigue, shortness of breath, and sleep disturbance found in previous studies. However, “new” symptoms were identified including feeling nervous, worrying, sweats, feeling bloated, and problems with sexual interest. These “new” symptoms were reported by over 40% of the patients. CONCLUSIONS: Measurement of symptoms in lung cancer patients before surgery is important, because patients reported an average of 10 symptoms. Few age-related differences in the patients’ symptom experience were identified. Psychological symptoms were common and warrant consideration.

[111]

TÍTULO / TITLE: - Digital tomosynthesis (DTS) for verification of target position in early stage lung cancer patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Purpose: The ability to verify intrafraction tumor position is clinically useful for hypofractionated treatments. Short arc kV digital tomosynthesis (DTS) could facilitate more frequent target verification. The authors used DTS combined with triangulation to determine the mean temporal position of small-volume lung tumor targets treated with stereotactic radiotherapy. DTS registration results were benchmarked against online clinical localization using registration between free-breathing cone-beam computed tomography (CBCT) and the average intensity projection (AvIP) of the planning 4DCT.

Methods: In this retrospective study, 76 sets of kV-projection images from online CBCT scans of 13 patients were used to generate DTS image slices (CB-DTS) with nonclinical research software (DTS Toolkit, Varian Medical Systems). Three-dimensional tumor motion was 1.3-4 mm in six patients and 6.1-25.4 mm in seven patients on 4DCT (significant difference in the mean of the groups, P < 0.01). The 4DCT AvIP was used to digitally reconstruct the Reference-DTS. DTS registration and DTS registration combined with triangulation were investigated. Progressive shortening of total DTS arc lengths from 95 degrees to 35 degrees around 0 degrees gantry position was evaluated for different scenarios: DTS registration using the entire arc; DTS registration plus triangulation using two nonoverlapping arcs; and for 55 degrees and 45 degrees total gantry rotation, DTS registration plus triangulation using two overlapping arcs. Finally, DTS registration plus triangulation performed at eight gantry angles, each separated by 45 degrees was evaluated using full fan kV projection data for one patient with an immobile tumor and five patients with mobile tumors.

Results: For DTS registration alone, shortening arc length did not influence accuracy in X- and Y-directions, but in Z-direction, mean deviations from online CBCT localization systematically increased for shorter arc length (P < 0.05). For example, using a 95 degrees arc mean DTS-CBCT difference was 0.8 mm (1 SD = 0.6 mm) and for a 35 degrees arc the mean was 2.4 mm (1 SD = 1.7 mm). DTS plus triangulation using nonoverlapping-arcs increased accuracy in Z-direction for tested arc lengths <=55 degrees (P < 0.01). Overlapping arcs increased accuracy in Y-direction for tumors with motion >4 mm (P < 0.02) but increased Z-direction accuracy was only observed with 55 degrees total gantry rotation. The 95th percentile deviations with this overlapping technique in X-, Y-, and Z-directions were 1.3, 2.0, and 2.5 mm, respectively. For the five patients with mobile tumors where DTS + triangulation was performed with 45 degrees intervals, the pooled deviation from online CBCT correction showed, for X-, Y-, and Z-directions, mean of 1.1 mm, standard deviations (SD) of 0.9, 1.0, and 0.9 mm, respectively. The mean + 2 SD was <3 mm for
Conclusions: Short-arc DTS verification of time averaged lung tumor position is feasible using free-breathing kV projection data and the AviP of the 4DCT as a reference. Observed differences between DTS and online CBCT registration with AviP were <=3 mm (mean + 2 SD), however, the increased temporal resolution of DTS + triangulation also identified short period deviations from the average target position on the CBCT. Short-arc DTS appears promising for intrafraction tumor position monitoring during stereotactic lung radiotherapy delivered with a rotational technique.
3DCRT. IMRT was associated with a lower rate of esophagitis-related percutaneous feeding tube placements.
between the arms. Exploratory analyses demonstrated no DFS (HR, 1.28; 95% CI, 0.92 to 1.76; P = .14) or OS benefit (HR, 1.24; 95% CI, 0.90 to 1.71; P = .18) from gefitinib for 344 patients with epidermal growth factor receptor (EGFR) wild-type tumors. Similarly, there was no DFS (HR, 1.84; 95% CI, 0.44 to 7.73; P = .395) or OS benefit (HR, 3.16; 95% CI, 0.61 to 16.45; P = .15) from gefitinib for the 15 patients with EGFR mutation-positive tumors. Adverse events were those expected with an EGFR inhibitor. Serious adverse events occurred in \( \leq 5\% \) of patients, except infection, fatigue, and pain. One patient in each arm had fatal pneumonitis. CONCLUSION: Although the trial closed prematurely and definitive statements regarding the efficacy of adjuvant gefitinib cannot be made, these results indicate that it is unlikely to be of benefit.

[114]

--- CASTELLANO ---

**TÍTULO / TITLE:** Überleben von Patienten mit Knochenmetastasen der Wirbelsäule eines nichtkleinzelligen Bronchialkarzinoms : Eine retrospektive Analyse von 303 Patienten.

**RESUMEN / SUMMARY:** - Survival and prognostic factors in non-small cell lung cancer patients with spinal bone metastases: A retrospective analysis of 303 patients.

**REVISTA / JOURNAL:** - Enlace al Resumen / Link to its Summary

**AUTORES / AUTHORS:** - Rief H; Muley T; Bruckner T; Welzel T; Rieken S; Bischof M; Lindel K; Combs SE; Debus J

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**RESUMEN / SUMMARY:** - BACKGROUND AND PURPOSE: For palliative care of spinal bone metastases, stability assessment is of crucial importance. Pathological fractures, instability-related patient immobility and the extent of bone metastasis have been reported to affect patient outcome and these parameters have therefore been used for treatment stratification. We report on stability-dependent fracture and survival rates in over 300 non-small cell lung cancer (NSCLC) patients.

**METHODS:** Data from 303 patients with 868 osteolytic metastases treated with radiotherapy (RT) between 2000 and 2012 were evaluated retrospectively. RESULTS: In NSCLC patients with bone metastases only, the retrospective 6- and 12-month overall survival (OS) rates were 76.7 and 47.2 %, respectively. In patients with additional non-bone distant metastases, these values were 60.0 and 34.0 %, respectively. Survival rates were significantly lower in patients with multiple bone metastases and in those suffering pathological fractures (p = 0.017). No significant impact of histological type, location of spinal lesions or treatment regime was detected. Furthermore, stability assessment revealed no influence of vertebral column stability on patient outcome (p
CONCLUSION: Our analysis demonstrated a correlation between the pathological fractures of bone lesions, the number of bone metastases, additional distant metastases and survival. The results offer a rationale for future prospective investigations.

[115]

TÍTULO / TITLE: - Proton arc reduces range uncertainty effects and improves conformity compared with photon volumetric modulated arc therapy in stereotactic body radiation therapy for non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Seco J; Gu G; Marcelos T; Kooy H; Willers H

INSTITUCIÓN / INSTITUTION: - Francis H. Burr Proton Therapy Center, Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA. jseco@partners.org

RESUMEN / SUMMARY: - PURPOSE: To describe, in a setting of non-small cell lung cancer (NSCLC), the theoretical dosimetric advantages of proton arc stereotactic body radiation therapy (SBRT) in which the beam penumbra of a rotating beam is used to reduce the impact of range uncertainties. METHODS AND MATERIALS: Thirteen patients with early-stage NSCLC treated with proton SBRT underwent repeat planning with photon volumetric modulated arc therapy (Photon-VMAT) and an in-house-developed arc planning approach for both proton passive scattering (Passive-Arc) and intensity modulated proton therapy (IMPT-Arc). An arc was mimicked with a series of beams placed at 10 degrees increments. Tumor and organ at risk doses were compared in the context of high- and low-dose regions, represented by volumes receiving >50% and <50% of the prescription dose, respectively. RESULTS: In the high-dose region, conformity index values are 2.56, 1.91, 1.31, and 1.74, and homogeneity index values are 1.29, 1.22, 1.52, and 1.18, respectively, for 3 proton passive scattered beams, Passive-Arc, IMPT-Arc, and Photon-VMAT. Therefore, proton arc leads to a 30% reduction in the 95% isodose line volume to 3-beam proton plan, sparing surrounding organs, such as lung and chest wall. For chest wall, V30 is reduced from 21 cm(3) (3 proton beams) to 11.5 cm(3), 12.9 cm(3), and 8.63 cm(3) (P=.005) for Passive-Arc, IMPT-Arc, and Photon-VMAT, respectively. In the low-dose region, the mean lung dose and V20 of the ipsilateral lung are 5.01 Gy(relative biological effectiveness [RBE]), 4.38 Gy(RBE), 4.91 Gy(RBE), and 5.99 Gy(RBE) and 9.5%, 7.5%, 9.0%, and 10.0%, respectively, for 3-beam, Passive-Arc, IMPT-Arc, and Photon-VMAT, respectively.

CONCLUSIONS: Stereotactic body radiation therapy with proton arc and Photon-VMAT generate significantly more conformal high-dose volumes than standard proton SBRT,
without loss of coverage of the tumor and with significant sparing of nearby organs, such as chest wall. In addition, both proton arc approaches spare the healthy lung from low-dose radiation relative to photon VMAT. Our data suggest that IMPT-Arc should be developed for clinical use.

[116] TÍTULO / TITLE: - Expulsion of micronuclei containing amplified genes contributes to a decrease in double minute chromosomes from malignant tumor cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ji W; Bian Z; Yu Y; Yuan C; Liu Y; Yu L; Li C; Zhu J; Jia X; Guan R; Zhang C; Meng X; Jin Y; Bai J; Yu J; Lee KY; Sun W; Fu S
INSTITUCIÓN / INSTITUTION: - Laboratory of Medical Genetics, Harbin Medical University, Harbin, China.
RESUMEN / SUMMARY: - Double minute chromosomes (DMs) are a hallmark of gene amplification. The relationship between the formation of DMs and the amplification of DM-carried genes remains to be clarified. The human colorectal cancer cell line NCI-H716 and human malignant primitive neuroectodermal tumor cell line SK-PN-DW are known to contain many DMs. To examine the amplification of DM-carried genes in tumor cells, we performed Affymetrix SNP Array 6.0 analyses and verified the regions of amplification in NCI-H716 and SK-PN-DW tumor cells. We identified the amplification regions and the DM-carried genes that were amplified and overexpressed in tumor cells. Using RNA interference, we downregulated seven DM-carried genes, (NDUF9, MTSS1, NSMCE2, TRIB1, FAM84B, MYC, and FGFR2) individually and then investigated the formation of DMs, the amplification of the DM-carried genes, DNA damage, and the physiological function of these genes. We found that suppressing the expression of DM-carried genes led to a decrease in the number of DMs and reduced the amplification of the DM-carried genes through the micronuclei (MN) expulsion of DMs from the tumor cells. We further detected an increase in the number of gammaH2AX foci in the knockdown cells, which provides a strong link between DNA damage and the loss of DMs. In addition, the loss of DMs and the reduced amplification and expression of the DM-carried genes resulted in a decrease in cell proliferation and invasion ability. © 2013 Wiley Periodicals, Inc.

[117] TÍTULO / TITLE: - ASCL1 and RET expression defines a clinically relevant subgroup of lung adenocarcinoma characterized by neuroendocrine differentiation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
ASCL1 is an important regulatory transcription factor in pulmonary neuroendocrine (NE) cell development, but its value as a biomarker of NE differentiation in lung adenocarcinoma (AD) and as a potential prognostic biomarker remains unclear. We examined ASCL1 expression in lung cancer samples of varied histologic subtype, clinical outcome and smoking status and compared with expression of traditional NE markers. ASCL1 mRNA expression was found almost exclusively in smokers with AD, in contrast to non-smokers and other lung cancer subtypes. ASCL1 protein expression by immunohistochemical (IHC) analysis correlated best with synaptophysin compared with chromogranin and CD56/NCAM. Analysis of a compendium of 367 microarray-based gene expression profiles in stage I lung adenocarcinomas identified significantly higher expression levels of the RET oncogene in ASCL1-positive tumors (ASCL1+) compared with ASCL1- tumors (q-value <10^{-9}). High levels of RET expression in ASCL1+ but not in ASCL1- tumors was associated with significantly shorter overall survival (OS) in stage 1 (P=0.007) and in all AD (P=0.037). RET protein expression by IHC had an association with OS in the context of ASCL1 expression. In silico gene set analysis and in vitro experiments by ASCL1 shRNA in AD cells with high endogenous expression of ASCL1 and RET implicated ASCL1 as a potential upstream regulator of the RET oncogene. Also, silencing ASCL1 in AD cells markedly reduced cell growth and motility. These results suggest that ASCL1 and RET expression defines a clinically relevant subgroup of approximately 10% of AD characterized by NE differentiation.
RESUMEN / SUMMARY: Lung cancer is the most frequent cancer in China and all over the world. Recent studies have shown that long noncoding RNAs play critical roles in multiple biological processes including oncogenesis. In this study, we reported a new lncRNA GAS6-AS1 (GAS6 antisense RNA 1), whose expression was downregulated in tumor tissues in 50 patients with non-small cell lung cancer (NSCLC) compared with those in the adjacent normal tissues (P < 0.001). Furthermore, decreased GAS6-AS1 expression was negatively correlated with lymph node metastasis (P = 0.032) and advanced tumor node metastasis stage (P = 0.003). Univariate and multivariate analyses showed that GAS6-AS1 expression served as an independent predictor for overall survival (P = 0.036). Also, GAS6-AS1 level was inversely correlated with GAS6 (growth-arrest-specific gene 6) mRNA level (Pearson’s correlation -0.620). In conclusion, our study demonstrated that altered lncRNA GAS6-AS1 expression might be involved in the development and progression of NSCLC by influencing its host gene and promised to be a potential diagnostic target in patients with NSCLC.

[119]

TÍTULO / TITLE: Clinical evaluation of targeted arterial perfusion of verapamil and chemotherapeutic drugs in interventional therapy of advanced lung cancer.

RESUMEN / SUMMARY: PURPOSE: To assess the clinical efficacy of targeted arterial perfusion of verapamil and chemotherapeutic agents in the interventional therapy of lung cancer. METHODS: Forty patients with advanced lung cancer underwent treatment with targeted arterial perfusion of verapamil and chemotherapeutic agents using Seldinger technique. Interventional therapy was performed once a month, and each subject received interventional treatment for 2 or more cycles. The therapeutic efficacy was evaluated 2 months post-treatment. RESULTS: Out of 40 patients with advanced lung cancer, 5 cases achieved complete remission (CR) and 29 cases achieved partial remission (PR), with a total effectiveness (CR + PR) rate of 85%. Besides, 32 cases achieved significantly alleviated clinical symptoms, and 29 cases had...
decreased clinical tumor stage. All subjects had stable Karnofsky performance status score and body weight. Among the 40 patients, 13 cases had leucopenia, 10 cases had gastrointestinal reactions, 3 cases presented with elevated alanine aminotransferase/aspartate aminotransferase ratio, and 3 cases had fever. However, all these side effects relieved quickly. No elevation of BUN/Cr ratio and allergic reactions was observed. No significant changes in cardiac function and electrocardiogram were noticed after the treatment. CONCLUSIONS: Targeted arterial perfusion of verapamil and chemotherapeutic drugs can improve the clinical symptoms of patients with advanced lung cancer and increase the efficacy of chemotherapeutic agents, thereby providing an opportunity for radiotherapy or surgical treatment for advanced lung cancer.
RESUMEN / SUMMARY: - Background: Early-stage non-small cell lung cancer (NSCLC) patients have a high risk of disease relapse despite curatively intended surgical resection, and the detection of tumour cells in the bone marrow could be one method of determining the presence of the disseminated disease in its early stages. Methods: Bone marrow aspirates were collected from 296 patients at the time of surgery, and the presence of disseminated tumour cells was determined with the help of immunomagnetic selection (IMS) using the MOC31-antibody recognising EpCAM and with the help of standard immunocytochemistry (ICC) using the anti-cytokeratin (CK) antibodies AE1/AE3. Results: Disseminated tumour cells were found in 152 of 252 (59%) bone marrow samples using IMS and in 25 of 234 (11%) samples using ICC. No association between the two detection methods was observed. The presence of EpCAM(+) cells was not associated with any clinicopathological parameters, whereas a higher frequency of CK(+) cells was found in patients with an advanced pT status. Disseminated tumour cells, as detected using IMS, had no prognostic impact. Patients with CK(+) cells in the bone marrow had a reduced relapse-free survival, but the difference was not statistically significant. Conclusion: Our findings do not support the further development of DTC detection for clinical use in early-stage NSCLC. Future studies should include the molecular characterisation of DTCs, along with an attempt to identify subpopulations of cells with biological and clinical significance.

[122]

TÍTULO / TITLE: - Prognostic value of the IASLC/ATS/ERS classification in stage I lung adenocarcinoma patients-Based on a hospital study in China.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Song Z; Zhu H; Guo Z; Wu W; Sun W; Zhang Y

INSTITUCIÓN / INSTITUTION: - Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou 310022, China; Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Hangzhou 310022, Zhejiang Province, China.
AIMS: We investigated the relationship between predominant subtype, according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Lung Adenocarcinoma Classification, and prognosis in stage I lung adenocarcinoma in Zhejiang Cancer Hospital. METHODS: Two hundred and sixty-one patients with stage I lung adenocarcinoma, operated in Zhejiang Cancer Hospital, were identified between 2000 and 2010. Survival curves were plotted using the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analysis. RESULTS: None of the cases were adenocarcinoma in situ and six were minimally invasive adenocarcinomas. Two hundred and fifty-five cases were invasive adenocarcinoma. Of those, 80, 76, 42, 34, 19, and 4 were papillary predominant, acinar predominant, micropapillary predominant, solid predominant, lepidic predominant subtypes, and variants of invasive adenocarcinoma, respectively. Patients with micropapillary and solid predominant tumors had a significantly worse disease-free survival as compared to those with other subtypes predominant tumors (p < 0.001). Multivariate analysis revealed that the new classification was an independent predictor of the disease-free and overall survival (p = 0.002 and 0.015). CONCLUSION: The predominant subtype in the primary tumor was associated with prognosis in resected stage I lung adenocarcinoma.

TÍTULO / TITLE: - Effect of Temozolomide in Patients with Metastatic Bronchial Carcinoids.

RESUMEN / SUMMARY: - Contact to its Summary


AUTORES / AUTHORS: - Crona J; Fanola I; Lindholm DP; Antonodimitrakis P; Oberg K; Eriksson B; Granberg D

INSTITUCIÓN / INSTITUTION: - Department of Medical Sciences, Uppsala University, Uppsala, Sweden.

RESUMEN / SUMMARY: - Introduction: Metastatic bronchial carcinoids are rare neoplasms, where efforts of medical treatment so far have been disappointing. A previous study from our center indicated that temozolomide might be of value. Materials and Methods: All patients with progressive metastatic bronchial carcinoid treated with temozolomide as monotherapy at our center between 2004 and 2010 (n = 31) were included in this retrospective study. 14 tumors were classified as typical and 15 as atypical carcinoids, whereas 2 tumors could not be classified. Temozolomide was given on 5 consecutive days every 4 weeks. Toxicity was evaluable in 28 of 31 patients, and 22 patients were evaluable by RECIST 1.1. Results: There were no complete responses. A partial response was seen in 3 patients (14%), stable disease in 11 (52%)
and progressive disease in 7 patients (33%). Median progression-free survival was 5.3 months and median overall survival was 23.2 months from the start of temozolomide. Toxicities grade 3-4 were noted in 4 patients, thrombocytopenia (n = 3) and leukopenia (n = 1). Conclusion: Temozolomide as monotherapy shows activity in metastatic bronchial carcinoids. Regimens combining temozolomide with other agents (e.g. capecitabine and/or bevacizumab, everolimus, radiolabeled somatostatin analogues) should be further studied in these patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chen R; Li J; Hu WW; Wang ML; Zou SL; Miao LY
INSTITUCIÓN / INSTITUTION: - Department of Pharmacy and Oncology, The Third Affiliated Hospital of Soochow University, Changzhou, Jiang Su, China.
RESUMEN / SUMMARY: - PURPOSE: The aim of this study was to describe the nonlinear pharmacokinetics of total and unbound plasma cisplatin under different administered time in patients with non-small-cell lung carcinoma. METHODS: Patients receiving chemotherapy with cisplatin were included in this analysis. Patients were divided into two groups depending on the administrated time of cisplatin: 6:00 (Group A) and 18:00 (Group B). The population pharmacokinetics of cisplatin was calculated using nonlinear mixed-effects modeling (NONMEM) method, and the possible influence of covariates on the population pharmacokinetics of cisplatin was also explored. RESULTS: The pharmacokinetics of total and unbound cisplatin could be described well by a linear two-compartment model. The mean population estimates for total and unbound drug were, respectively, 0.463 (17.0 %) and 25.4 (14.0 %) l h^{-1} for clearance (CL), 24.2 (19.9 %) and 20.5 (27.1 %) l for central distribution volume (V 1), 10.2 (18.2 %) and 9.82 (28.1) l h^{-1} for intercompartmental clearance (Q) and 32.0 (24.1 %) and 6.77 (25.4 %) l for peripheral compartment volume (V 2). The CL for total and unbound cisplatin was dependent on body surface area (BSA). When cisplatin was administered at 18:00, the CL was 1.38- and 1.22-fold higher than those administered at 6:00 for total and unbound cisplatin, respectively (P < 0.05). The mean parameter estimates from a nonparametric bootstrap procedure were comparable and within 5 % of the estimates from NONMEM. CONCLUSIONS: The results showed that circadian could influence the metabolism of cisplatin and suggested the conventional dose adjustment of cisplatin based on BSA.
Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma.

Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1007/s00432-013-1495-0

AUTORES / AUTHORS: Yoshida T; Ishii G; Goto K; Yoh K; Niho S; Umemura S; Matsumoto S; Ohmatsu H; Nagai K; Ohe Y; Ochiai A

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BACKGROUND: The efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) differs in patients with lung adenocarcinoma harboring EGFR-activating mutations. Although lung adenocarcinoma with EGFR-activating mutations has heterogeneous morphologic features, the predictive role of histologic subtype of lung adenocarcinoma with regard to the effectiveness of EGFR-TKIs in patients with EGFR-activating mutations has not been well defined. METHODS: Among 134 postoperative recurrence patients with lung adenocarcinoma harboring EGFR-activating mutation (L858R or exon 19 deletion) treated with EGFR-TKIs, we retrospectively analyzed 61 patients treated with EGFR-TKIs as first-line chemotherapy. All the tumors were classified according to the new histologic classification proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) into the following subtypes: lepidic, papillary, acinar, micropapillary, or solid predominant subtype. We evaluated the correlation between the histologic subtype and the clinical efficacy of EGFR-TKIs. RESULTS: In overall response rate, adenocarcinoma with solid predominant subtype is significantly worse than with non-solid predominant subtype (61 vs. 88 %, P = 0.03). The median progression-free survival (PFS) and overall survival after EGFR-TKI treatment were significantly shorter for the patients with solid predominant subtype than for those with non-solid predominant subtype (median PFS of 7.7 vs. 13.5 months, P = 0.002, and median OS of 21.5 vs. 31.0 months, P = 0.028). CONCLUSIONS: This study indicated that among patients with lung adenocarcinoma harboring activating EGFR mutations treated with EGFR-TKIs, solid predominant subtype according to IASLC/ATS/ERS classification is a response predictor for EGFR-TKI.
Depletion of hepatoma-derived growth factor-related protein-3 induces apoptotic sensitization of radioresistant A549 cells via reactive oxygen species-dependent p53 activation.

Biomarkers based on functional signaling have the potential to provide greater insight into the pathogenesis of cancer and may offer additional targets for anticancer therapeutics. Here, we identified hepatoma-derived growth factor-related protein-3 (HRP-3) as a radioresistance-related gene and characterized the molecular mechanism by which its encoded protein regulates the radio- and chemoresistant phenotype of lung cancer-derived A549 cells. Knockdown of HRP-3 promoted apoptosis of A549 cells and potentiated the apoptosis-inducing action of radio- and chemotherapy. This increase in apoptosis was associated with a substantial generation of reactive oxygen species (ROS) that was attributable to inhibition of the Nrf2/HO-1 antioxidant pathway and resulted in enhanced ROS-dependent p53 activation and p53-dependent expression of PUMA (p53 upregulated modulator of apoptosis). Therefore, the HRP-3/Nrf2/HO-1/ROS/p53/PUMA cascade is an essential feature of the A549 cell phenotype and a potential radiotherapy target, extending the range of targets in multimodal therapies against lung cancer.

Therapeutic outcomes of combining cryotherapy, chemotherapy and DC-CIK immunotherapy in the treatment of metastatic non-small cell lung cancer.

Biomarkers based on functional signaling have the potential to provide greater insight into the pathogenesis of cancer and may offer additional targets for anticancer therapeutics. Here, we identified hepatoma-derived growth factor-related protein-3 (HRP-3) as a radioresistance-related gene and characterized the molecular mechanism by which its encoded protein regulates the radio- and chemoresistant phenotype of lung cancer-derived A549 cells. Knockdown of HRP-3 promoted apoptosis of A549 cells and potentiated the apoptosis-inducing action of radio- and chemotherapy. This increase in apoptosis was associated with a substantial generation of reactive oxygen species (ROS) that was attributable to inhibition of the Nrf2/HO-1 antioxidant pathway and resulted in enhanced ROS-dependent p53 activation and p53-dependent expression of PUMA (p53 upregulated modulator of apoptosis). Therefore, the HRP-3/Nrf2/HO-1/ROS/p53/PUMA cascade is an essential feature of the A549 cell phenotype and a potential radiotherapy target, extending the range of targets in multimodal therapies against lung cancer.
Currently there are no effective therapies for the treatment of metastatic non-small cell lung cancer (NSCLC). Here, we conducted a retrospective study of 161 patients to evaluate the therapeutic effects of combining cryosurgery, chemotherapy and dendritic cell-activated cytokine-induced killer cells (DC-CIK) immunotherapy. The overall survival (OS) after diagnosis of metastatic NSCLC to patient death was assessed during a 5-years follow-up period. OS of patients who received comprehensive cryotherapy was (median OS, 20 months; n=86) significantly longer than that of patients who did not receive cryotherapy (median OS, 10 months; n=75; P<0.0001). Five treatment combinations were selected: chemotherapy (n=44); chemo-immunotherapy (n=31); cryo-chemotherapy (n=32); cryo-immunotherapy (n=21); and cryo-chemo-immunotherapy (n=33). A combination of cryotherapy with either chemotherapy or immunotherapy lead to significantly longer OS (18 months and 17 months, respectively) compared to chemotherapy and chemo-immunotherapy (8.5 months and 12 months, respectively; P<0.001); however, the median OS of patients who underwent cryo-chemo-immunotherapy was significantly longer (27 months) compared to the other treatment programs (P<0.001). In conclusion, a combination of cryotherapy, chemotherapy and DC-CIK immunotherapy proved the best treatment option for metastatic NSCLC in this group of patients.

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**RESUMEN / SUMMARY:** - Currently there are no effective therapies for the treatment of metastatic non-small cell lung cancer (NSCLC). Here, we conducted a retrospective study of 161 patients to evaluate the therapeutic effects of combining cryosurgery, chemotherapy and dendritic cell-activated cytokine-induced killer cells (DC-CIK) immunotherapy. The overall survival (OS) after diagnosis of metastatic NSCLC to patient death was assessed during a 5-years follow-up period. OS of patients who received comprehensive cryotherapy was (median OS, 20 months; n=86) significantly longer than that of patients who did not receive cryotherapy (median OS, 10 months; n=75; P<0.0001). Five treatment combinations were selected: chemotherapy (n=44); chemo-immunotherapy (n=31); cryo-chemotherapy (n=32); cryo-immunotherapy (n=21); and cryo-chemo-immunotherapy (n=33). A combination of cryotherapy with either chemotherapy or immunotherapy lead to significantly longer OS (18 months and 17 months, respectively) compared to chemotherapy and chemo-immunotherapy (8.5 months and 12 months, respectively; P<0.001); however, the median OS of patients who underwent cryo-chemo-immunotherapy was significantly longer (27 months) compared to the other treatment programs (P<0.001). In conclusion, a combination of cryotherapy, chemotherapy and DC-CIK immunotherapy proved the best treatment option for metastatic NSCLC in this group of patients.

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**TÍTULO / TITLE:** - Exercise in Patients with Non-Small-Cell Lung Cancer (NSCLC).

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Kuehr L; Wiskemann J; Abel U; Ulrich CM; Hummler S; Thomas M

**INSTITUCIÓN / INSTITUTION:** - 1National Center for Tumor Diseases and German Cancer Research Center, Division of Preventive Oncology, Heidelberg, Germany 2 Thoraxklinik, Dept. Thoracic Oncology, University of Heidelberg, Heidelberg, Germany 3 National Center for Tumor Diseases and University Clinic Heidelberg, Division of Medical Oncology, Heidelberg, Germany 4 National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany * Both authors contributed equally

**RESUMEN / SUMMARY:** - PURPOSE: This study aimed to evaluate safety, feasibility and effects of an eight-week combined resistance and endurance exercise program in patients with advanced NSCLC during in- and outpatient care. METHODS: In this intervention study, 40 patients with predominantly advanced NSCLC receiving simultaneous or sequential radio-chemotherapy or chemotherapy alone were enrolled. Over a period of eight weeks, patients were instructed to exercise at least 5x/week during the inpatient setting, and at least 3x/week in the outpatient setting.
Physical performance status (endurance capacity: 6 minute-walk-test; strength capacity: handheld dynamometry), quality-of-life (FACT-L), fatigue (MFI) and depression (PHQ-9) were assessed at baseline (T0), after the exercise intervention (T1) and at a follow-up time point eight weeks later (T2). The primary endpoint was adequate adherence (feasibility) defined as completing at least two training sessions/week during a minimum of six weeks. RESULTS: 31/40 (77.5%) patients completed the post-exercise assessment (T1) and 22/40, the (55%) follow-up (T2). Stages were IIA 5%; IIIA 8%; IIIB 20%; IV 67%, and the median age was 63 years (range 22-75). Overall, adherence was 82% for those patients who completed T1, and 55% of the 40 patients participating, fulfilled the adequate adherence criterion. Those who completed the intervention showed a significant improvement in 6 minute-walk distance and in knee-, elbow- and hip-muscle strength after the intervention (T1). Quality of life, fatigue and depression scores remained stable or declined slightly. Significant improvements in knee-muscle strength were also observed at T2.

CONCLUSION: Exercise training is feasible in advanced and metastatic NSCLC patients during anticancer treatment. In this pilot study, endurance and strength capacity improved over time, indicating the rehabilitative importance of the applied intervention. To investigate the potential impact of exercise training in this patient group, a larger randomized trial is warranted.

[129]

TÍTULO / TITLE: - Fibulin-3-mediated inhibition of epithelial-to-mesenchymal transition and self-renewal of ALDH+ lung cancer stem cells through IGF1R signaling.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Kim IG; Kim SY; Choi SI; Lee JH; Kim KC; Cho EW


RESUMEN / SUMMARY: - Fibulins (FBLNs), a family of extracellular matrix proteins, have recently been shown to act as tumor suppressors or activators in different cancers, and the underlying molecular mechanisms of their action in cancer remain unclear. We have previously shown that the expression of FBLN3 is suppressed by promoter hypermethylation and is associated with invasiveness in aggressive non-small cell lung cancer. In this study, we evaluated the roles and signaling mechanism of FBLN3 in lung cancer stem cells (CSCs). Forced expression of FBLN3 suppressed invasion and migration of lung adenocarcinoma cells and decreased the expression of epithelial-to-mesenchymal transition (EMT) activators, including N-cadherin and Snail. Stemness
activities of lung adenocarcinoma cells were also suppressed by FBLN3 as indicated by a decrease in spheroid formation and the levels of stemness markers such as Sox2 and beta-catenin. These effects of FBLN3 were mediated by the glycogen synthase kinase-3beta, GSK3beta/beta-catenin pathway, and the upstream regulators of GSK3beta, including phosphoinositide 3-kinase (PI3K)/AKT and insulin-like growth factor-1 receptor (IGF1R), were inactivated by FBLN3. Moreover, IGF1R was shown to be a direct target of FBLN3, which competitively inhibited insulin-like growth factor (IGF) action. To confirm the effect of FBLN3 on lung CSCs, aldehyde dehydrogenase-positive (ALDH+) A549 lung CSCs were sorted and treated with recombinant FBLN3 protein. FBLN3 clearly suppressed EMT, stemness activity and the over-activated IGF1R/PI3K/AKT/GSK3beta pathway of the ALDH+ CSC subpopulation. In addition, injection of recombinant FBLN3 protein around subcutaneous xenografts established with ALDH+ CSCs in athymic nude mice significantly suppressed tumor growth and progression. Overall, our results show that FBLN3 suppresses both EMT and self-renewal of the lung CSCs by modulating the IGF1R/PI3K/AKT/GSK3beta pathway and that FBLN3 would be useful as an alternative CSC therapy.

Oncogene advance online publication, 9 September 2013; doi:10.1038/onc.2013.373.

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[130]

TÍTULO / TITLE: - Challenge and Opportunity of Targeted Lung Cancer Chemoprevention.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1200/JCO.2013.51.2400
AUTORES / AUTHORS: - Dubinett SM; Spira A
INSTITUCIÓN / INSTITUTION: - David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA.

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[131]

TÍTULO / TITLE: - Mutationally Activated PIK3CAH1047R Cooperates With BRAFV600E In Lung Cancer Progression.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1158/0008-5472.CAN-13-0681
AUTORES / AUTHORS: - Trejo CL; Green S; Marsh V; Collisson EA; Iezza G; Phillips WA; McMahon M
INSTITUCIÓN / INSTITUTION: - Gene Expression Laboratory, Salk Institute for Biological Studies.
RESUMEN / SUMMARY: - Adenocarcinoma of the lung, a leading cause of cancer death, frequently displays mutational activation of the KRAS proto-oncogene but, unlike lung
cancers expressing mutated EGFR, ROS1 or ALK, there is no pathway-targeted therapy for patients with KRAS mutated lung cancer. In pre-clinical models, expression of oncogenic KRASG12D in the lung epithelium of adult mice initiates development of lung adenocarcinoma through activation of downstream signaling pathways. By contrast, mutationaly activated BRAFV600E, a KRAS effector, fails to initiate lung carcinogenesis despite highly efficient induction of benign lung tumorigenesis. To test if PI3' -kinase-alpha (PIK3CA), another KRAS effector, might cooperate with oncogenic BRAFV600E to promote lung cancer progression, we employed mice carrying a conditional allele of Pik3ca that allows conversion of the wild-type catalytic subunit of PIK3CA to mutationaly activated PIK3CAH1047R. Whereas expression of PIK3CAH1047R in the lung epithelium, either alone or in combination with PTEN silencing, was without phenotype, concomitant expression of BRAFV600E and PIK3CAH1047R led to dramatically decreased tumor latency and increased tumor burden compared to BRAFV600E alone. Most notably, co-expression of BRAFV600E and PIK3CAH1047R elicited lung adenocarcinomas in a manner reminiscent of the effects of KRASG12D. These data emphasize a role for PI3'-kinase signaling, not in lung tumor initiation per se, but in both the rate of tumor growth and the propensity of benign lung tumors to progress to a malignant phenotype. Finally, biological and biochemical analysis of BRAFV600E/PIK3CAH1047R expressing mouse lung cancer cells revealed mechanistic clues as to cooperative regulation of the cell division cycle and apoptosis by these oncogenes.
Interleukin 17 (IL-17) has been found to be increased in some human cancers; however, the possible implication of IL-17 in regulating antitumor responses in lung cancer patients with malignant pleural effusions (MPE) remains to be elucidated. This study aimed to investigate the diagnostic value of pleural IL-17 and carcinoembryonic antigen (CEA) in MPE and benign pleural effusions (BPE). Pleural effusion samples from 108 patients were classified on the basis of diagnosis as MPE (n = 56) and BPE (n = 52). The concentration of IL-17 was determined by enzyme-linked immunosorbent assay (ELISA). The CEA levels were also determined in all patients. A significant difference was observed in the levels of CEA (P < 0.01) between MPE and BPE. The concentration of IL-17 in MPE was significantly higher compared to that in BPE (P < 0.01). With a cutoff point of 15.7 pg/ml, IL-17 had a sensitivity of 76.8 % and a specificity of 80.8 % for differential diagnosis. The combined detection of IL-17 and CEA had a sensitivity of 96.4 % and a specificity of 92.3 % to distinguish MPE from BPE. The combined detection of IL-17 and CEA may be more valuable in the differential diagnosis between MPE and BPE.

**TÍTULO / TITLE:** - Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain.

**RESUMEN / SUMMARY:** - Abstract Objective: This phase 3 study evaluated the efficacy and safety of tapentadol extended release (ER) compared with oxycodone controlled release (CR) for the management of moderate to severe, chronic malignant tumor-related cancer pain. Research design and methods: This randomized, double-blind, active-controlled study included Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. Patients were randomized (1:1) to receive oral tapentadol ER (25-200 mg bid) or oral oxycodone HCl CR (5-40 mg bid) for 4 weeks of double-blind treatment. ClinicalTrials.gov identifier: NCT01165281. Main outcome measures: This study was designed to evaluate the non-inferiority of the efficacy provided by tapentadol ER versus oxycodone CR, based on the mean change in average pain intensity (11 point numerical rating scale) from baseline to the last 3 days of study drug administration. Treatment-emergent adverse events (TEAEs) were
recorded throughout the study. Results: Of the 374 patients who were screened, 343 were randomized and 236 completed treatment. The least-squares mean difference in the change in pain intensity from baseline to the last 3 days of study treatment between tapentadol ER and oxycodone CR was -0.06 (95% confidence interval [CI], -0.506 to 0.383). The upper limit of the 95% CI was <1 (the predefined threshold value for non-inferiority), indicating that tapentadol ER provided analgesic efficacy that was non-inferior to that of oxycodone CR. The percentage of patients reporting at least one TEAE was similar in the tapentadol ER (87.5% [147/168]) and oxycodone CR (90.1% [155/172]) treatment groups, but the incidence of gastrointestinal TEAEs was lower in the tapentadol ER group (55.4% [93/168]) than in the oxycodone CR group (67.4% [116/172]). Conclusions: Tapentadol ER (25-200 mg bid) provides analgesic efficacy that is non-inferior to that provided by oxycodone HCl CR (5-40 mg bid) for the management of moderate to severe, chronic malignant tumor-related pain, and is well tolerated overall, with a better gastrointestinal tolerability profile than oxycodone CR.

[135]

**TÍTULO / TITLE:** Enhanced autophagy is required for survival in EGFR-independent EGFR-mutant lung adenocarcinoma cells.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Sakuma Y; Matsukuma S; Nakamura Y; Yoshihara M; Koizume S; Sekiguchi H; Saito H; Nakayama H; Kameda Y; Yokose T; Oguni S; Niki T; Miyagi Y

**INSTITUCIÓN / INSTITUTION:** 1] Molecular Pathology and Genetics Division, Kanagawa Cancer Center Research Institute, Yokohama, Japan [2] Laboratory for Molecular Diagnostics, Kanagawa Cancer Center Hospital, Yokohama, Japan [3] Department of Pathology, Jichi Medical University, Tochigi, Japan.

**RESUMEN / SUMMARY:** Lung cancers harboring epidermal growth factor receptor (EGFR) mutations depend on constitutive activation of the kinase for survival. Although most EGFR-mutant lung cancers are sensitive to EGFR tyrosine kinase inhibitors (TKIs) and shrink in response to treatment, acquired resistance to TKI therapy is common. We demonstrate here that two EGFR-mutated lung adenocarcinoma cell lines, HCC827 and HCC4006, contain a subpopulation of cells that have undergone epithelial-to-mesenchymal transition and survive independent of activated EGFR. These EGFR-independent cancer cells, herein termed gefitinib-resistant (GR) cells, demonstrate higher levels of basal autophagy than their parental cells and thrive under hypoxic, reduced-serum conditions in vitro; this somewhat simulates the hypoxic environment common to cancerous tissues. We show that depletion of the essential autophagy gene, ATG5, by small interfering RNA (siRNA) or chloroquine, an autophagy inhibitor,
markedly reduces GR cell viability under hypoxic conditions. Moreover, we show a significant elevation in caspase activity in GR cells following knockdown of ATG5. These results suggest that GR cells can evade apoptosis and survive in hostile, hypoxic environments with constant autophagic flux. We also show the presence of autophagosomes in some cancer cells from patient samples, even in untreated EGFR-mutant lung cancer tissue samples. Together, our results indicate that autophagy inhibitors alone or in combination with EGFR TKIs may be an effective approach for the treatment of EGFR-mutant lung cancers, where basal autophagy of some cancer cells is upregulated.

[136]

TÍTULO / TITLE: - Frequency and type of epidermal growth factor receptor mutations in moroccan patients with lung adenocarcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Errihani H; Inrhaoun H; Boukir A; Gamra L; Mestari A; Jabri L; Bensouda Y; Mrabti H; Elghissassi I

INSTITUCIÓN / INSTITUTION: - *Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco; daggerDepartment of Pathology, Nations-Unies Pathology Center, Rabat, Morocco; double daggerDepartment of Pathology, Hassan Pathology Center, Rabat, Morocco; section signDepartment of Pathology, Agdal Pathology Center, Rabat, Morocco; and ||Department of Pathology, Casapath Pathology Center, Casablanca, Morocco.

RESUMEN / SUMMARY: - INTRODUCTION: Epidermal growth factor receptor (EGFR) mutations in non-small-cell lung cancer predict response to tyrosine kinase inhibitors. The frequency of EGFR mutations is ethnicity-dependent, with a higher proportion in Asian populations than in whites. The prevalence of these mutations among North African patients is unknown. The objective of this study was to report the frequency and spectrum of EGFR mutations in a group of Moroccan patients with lung adenocarcinoma (AC). METHODS: Tumor specimens from 137 Moroccan patients with lung AC were selected to determine frequency and spectrum of EGFR mutations. Mutation detection techniques were polymerase chain reaction amplification and sequencing of exons 18, 19, 20, and 21. RESULTS: The overall frequency of the EGFR mutation was 21%. Mutations were mainly detected in the exon 19 (69%), followed by exon 21 (21%) and exon 20 (7%), whereas mutations in the exon 18 were rare (3%). EGFR mutation rate was significantly higher in women and in never smokers. CONCLUSION: Some one fifth of lung AC tumors in Moroccan patients harbor EGFR mutations. This mutation frequency is higher than that found in whites but lower than
in Asian population. Further studies, in larger numbers of patients, are needed to confirm these findings.

[137]
TÍTULO / TITLE: - Human papillomavirus 16/18 infections in lung cancer patients in Mexico.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Badillo-Almaraz I; Zapata-Benavides P; Saavedra-Alonso S; Zamora-Avila D; Resendez-Perez D; Tamez-Guerra R; Herrera-Esparza R; Rodriguez-Padilla C
INSTITUCIÓN / INSTITUTION: - Universidad Autonoma de Nuevo Leon (UANL), Facultad de Ciencias Biologicas, Departamento de Microbiologia e Inmunologia, Ciudad Universitaria, San Nicolas de los Garza, Mexico.
RESUMEN / SUMMARY: - Background/Aims: Human papillomavirus (HPV) is an epitheliotropic, double-stranded DNA virus, and its high-risk genotypes are associated with human cancer. HPV genome has been detected in lung carcinomas in certain places around the world, including Mexico; however, the prevalence of this is unclear. In this study, we examine the frequency of high-risk HPV 16/18 in lung cancer tissues from a Mexican population. Methods: 39 lung cancer specimens were analyzed by polymerase chain reaction (PCR) using HPV GP5+/GP6+ primers and then were genotyped using specific primers to HPV 16/18. Additionally, in situ hybridization (ISH) was performed using BIO-labeled oligonucleotide probes. Results: Our results identified 15 positive cases (38.46%) for HPV 16 and 1 positive case (2.56%) for HPV 18 by PCR. ISH showed the presence of HPV DNA in 13 of 16 (81%) samples, in agreement with the PCR results. Conclusions: In this study, we detected HPV 16/18 gene sequences in lung cancer samples obtained from Mexican patients by PCR and ISH. We found the highest prevalence of HPV 16 infection in lung adenocarcinomas, suggesting that HPV infection may be associated with lung cancer. However, further studies are needed to elucidate the role of HPV in lung carcinogenesis.

[138]
TÍTULO / TITLE: - Analysis of EGFR, EML4-ALK, KRAS, and c-MET mutations in Chinese lung adenocarcinoma patients.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
ABSTRACT Introduction: Mutation analysis of cancer driver genes is helpful for determining an optimal treatment strategy. We evaluated mutations in four driver genes, namely epidermal growth factor receptor (EGFR), Kirsten ras oncogene (KRAS), c-MET, and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), in Chinese lung adenocarcinoma patients from Hunan Province. Methods: We enrolled 110 lung adenocarcinoma patients in a single institution. EGFR and KRAS mutations were examined by direct sequencing, the EML4-ALK fusion gene was analyzed by fluorescence in situ hybridization, and c-MET amplification and c-Met protein expression were detected by quantitative PCR and immunohistochemistry, respectively. Results: EGFR and KRAS mutations were observed in 52.7% (58/110) and 3.6% (4/106) of patients, respectively. c-MET amplification was detected in 5.5% (6/110) of patients. In addition, 30% (33/110) of the cases expressed c-Met protein, including all of the patients harboring c-MET amplification. Ten percent (11/110) of patients harbored the EML4-ALK fusion gene, and the frequency of ALK rearrangement was higher than that of other cohort analyses involving patients from other regions in China. Almost all of these gene mutations were exclusive except that in two female non-smoking patients, who harbored an EGFR mutation and EML4-ALK rearrangement simultaneously. In total, 70% of patients in the study harbored one of the four gene mutations. Conclusions: Most Chinese lung adenocarcinoma patients harbor driver gene mutations, among which ALK rearrangements were more common in Hunan patients than in previously reported populations. Future clinical trials should be conducted to determine the safety and efficacy of drug combination targeting different driver mutations.

[139]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhong R; Liu L; Zou L; Zhu Y; Chen W; Zhu B; Shen N; Rui R; Long L; Ke J; Lu X; Zhang T; Zhang Y; Wang Z; Liu L; Sun Y; Cheng L; Miao X

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology and Biostatistics and the Ministry of Education Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
RESUMEN / SUMMARY: - Recent genome-wide association studies (GWAS) have reported multiple genetic variations at 5p15.33 (TERT-CLPTM1L) associated with risk of lung cancer. However, most of the associated variations identified by GWAS thus far are unlikely to be the actual causal variants, but may be mostly marker-single nucleotide polymorphisms tagging functional variations that influence gene expression. This study aimed to explore the function-validated and potentially functional variations in TERT-CLPTM1L locus conferring susceptibility to lung cancer. A case-control study including 502 cases and 502 controls in Chinese Han population was firstly conducted. Bioinformatic approaches are applied to prioritize genetic variations based on their potential functionality. In the logistic regression analysis, TERT-rs2853669, rs2736108, and CLPTM1L-rs31490 were significant associated with increased risk of lung cancer (OR = 1.46, 95% CI = 1.22-1.75; OR = 1.22, 95% CI = 1.00-1.49 and OR = 1.74, 95% CI = 1.35-2.23 under additive model, respectively). The significant associations were observed in non-small-cell lung cancer but not-in-small-cell lung cancer, and more prominent in adenocarcinoma. Haplotype analysis presented a significant allele-dose effect of haplotypes in increasing risk of lung cancer (P for trend = 1.894 x 10^-6). Moreover, significant multiplicative interactions were observed between smoking and these three polymorphisms of TERT-rs2853669, rs2736108, and CLPTM1L-rs31490, even after bonferroni correction for multiple comparisons (Pinteraction = 1.316 x 10^-9, 3.912 x 10^-4, and 2.483 x 10^-5, respectively). These findings indicated that the function-validated and potentially functional variations in TERT-CLPTM1L locus, modified by smoking, may play a substantial role in the susceptibility to lung cancer. © 2013 Wiley Periodicals, Inc.

[140]

TÍTULO / TITLE: - Rhamnetin and Cirsiliol Induce Radiosensitization and Inhibition of Epithelial-Mesenchymal Transition (EMT) by miR-34b-mediated Suppression of Notch-1 Expression in Non-small Cell Lung Cancer Cell Lines.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Kang J; Kim E; Kim W; Seong KM; Youn H; Kim JW; Kim J; Youn B

INSTITUCIÓN / INSTITUTION: - From the Department of Biological Sciences, Pusan National University, Busan 609-735.

RESUMEN / SUMMARY: - Radioresistance is a major cause of decreasing the efficiency of radiotherapy for non-small cell lung cancer (NSCLC). To understand the radioresistance mechanisms in NSCLC, we focused on the radiation-induced Notch-1 signaling pathway involved in critical cell fate decisions by modulating cell proliferation. In this study, we investigated the use of Notch-1-regulating flavonoid compounds as novel
therapeutic drugs to regulate radiosensitivity in NSCLC cells, NCI-H1299 and NCI-H460, with different levels of radioresistance. Rhamnetin and cirsiliol were selected as candidate Notch-1-regulating radiosensitizers based on the results of assay screening for activity and pharmacological properties. Treatment with rhamnetin or cirsiliol reduced the proliferation of NSCLC cells through the suppression of radiation-induced Notch-1 expression. Indeed, rhamnetin and cirsiliol increased the expression of tumor-suppressive microRNA, miR-34, in a p53-dependent manner, leading to inhibition of Notch-1 expression. Consequently, reduced Notch-1 expression promoted apoptosis through significant down-regulation of the nuclear factor-kappaB pathway, resulting in a radiosensitizing effect on NSCLC cells. Irradiation-induced epithelial-mesenchymal transition was also notably attenuated in the presence of rhamnetin and cirsiliol. Moreover, an in vivo xenograft mouse model confirmed the radiosensitizing and epithelial-mesenchymal transition inhibition effects of rhamnetin and cirsiliol we observed in vitro. In these mice, tumor volume was significantly reduced by combinational treatment with irradiation and rhamnetin or cirsiliol compared with irradiation alone. Taken together, our findings provided evidence that rhamnetin and cirsiliol can act as promising radiosensitizers that enhance the radiotherapeutic efficacy by inhibiting radiation-induced Notch-1 signaling associated with radioresistance possibly via miR-34-mediated pathways.

[141]

- miRNA-214 is related to invasiveness of human non-small cell lung cancer and directly regulates alpha protein kinase 2 expression.

- TÍTULO / TITLE: miRNA-214 is related to invasiveness of human non-small cell lung cancer and directly regulates alpha protein kinase 2 expression.

- RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


- AUTORES / AUTHORS: Salim H; Arvanitis A; de Petris L; Kanter L; Haag P; Zovko A; Ozata DM; Lui WO; Lundholm L; Zhivotovsky B; Lewensohn R; Viktorsson K

- INSTITUCIÓN / INSTITUTION: Department of Oncology-Pathology, Karolinska Biomics Center, Karolinska Institutet, SE-171 76, Stockholm, Sweden.

- RESUMEN / SUMMARY: The prognosis of non-small cell lung cancer (NSCLC) is poor, since it has often metastasized to distant organs by the time of diagnosis. Therefore, biomarkers predicting metastasis are crucial. miRNAs play important roles in the regulation of different tumor cell processes, including metastasis. We recently showed that miRNA-214 is linked to a radioresistant phenotype of NSCLC. miRNA-214 has been linked to metastasis in other tumor types. Therefore, we examined the role of miRNA-214 in the metastatic potential of NSCLC. We showed that downregulation of miRNA-214 increased invasive potential, and conversely, overexpression of miRNA-214 decreased invasiveness of NSCLC cells in vitro. Gene expression and bioinformatic
analyses of NSCLC cells with ablated miRNA-214, identified a number of metastasis-related target genes, including pregnancy-associated plasma protein A (PAPP-A), alpha protein kinase 2 (ALPK2), cyclin-dependent kinase 6 (CDK6) and tumor necrosis-factor alpha-induced protein 3 (TNFAIP3). These were validated on mRNA and protein level to be regulated by miRNA-214. Through immunoprecipitation we showed that only ALPK2 is directly regulated by miRNA-214. We also examined the protein expression of these four genes in NSCLC tumors with respect to metastatic potential. These results showed that NSCLC tumors express these proteins at moderate-high levels in the nucleus, cytoplasm and/or plasma membrane although with no significant correlation to the overall survival or the metastatic potential of the patients. However, we also showed that the membrane-localized PAPP-A had a higher expression level compared to the cytoplasm-localized. In conclusion, we show that low miRNA-214 expression is linked to a higher invasive potential of NSCLC cells. © 2013 Wiley Periodicals, Inc.

[142]  
TÍTULO / TITLE: Combined epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor and chemotherapy in non-small-cell lung cancer: Chemo-refractoriness of cells harboring sensitizing-EGFR mutations in the presence of gefitinib.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Tsai CM; Chen JT; Chiu CH; Lai CL; Hsiao SY; Chang KT

INSTITUCIÓN / INSTITUTION: Division of Thoracic Oncology, Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan. Electronic address: doc3006a@gmail.com.

RESUMEN / SUMMARY: BACKGROUND: Combined epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) with chemotherapy is believed to be more effective in treating non-small-cell lung cancer (NSCLC) with sensitizing-EGFR mutation (SEM). This hypothesis failed to be realized clinically and needs to be examined in vitro. MATERIALS AND METHODS: Using the tetrazolium colorimetric assay and classical isobole method, we investigated the combination effects of 6 gefitinib-chemotherapeutic doublets (gefitinib/cisplatin, gemcitabine, pemetrexed, paclitaxel, docetaxel, or vinorelbine) in a panel of 15 NSCLC cell lines. RESULTS: Upon treatment with the 6 gefitinib-chemotherapeutic doublets, the 12 cell lines that did not harbor SEM displayed a broad spectrum of group results, from obvious synergism to robust antagonism. The values of group mean combination index (mCIs) ranged from 0.769 to 1.201. In contrast, the 3 cell lines with SEM showed a tendency toward consistent antagonism to the tested doublets, impressively, with a narrow range of higher group
mCi (0.993-1.141). In the presence of gefitinib, the SEM or gefitinib-sensitive group was more chemo-refractory than the non-SEM (index of chemo-refractoriness (RI): 69.33 versus 42.67; P=0.036) or gefitinib-resistant group (68.25 versus 40.64, P=0.0108), respectively. The results of using the gefitinib/drug combinations with the gefitinib-sensitive non-SEM cell line H322 and the gefitinib-resistant EGFR mutant H820 shared patterns similar to those with the SEM and non-SEM cell lines, respectively. CONCLUSION: Gefitinib-treated EGFR-TKI-sensitive NSCLC cells showed a wide spectrum of chemo-refractoriness, suggesting that concomitantly combined EGFR-TKI-chemotherapy might not be a good treatment strategy for NSCLC harboring SEM.

[143]
TÍTULO / TITLE: - Lung cancer in never smokers: Disease characteristics and risk factors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

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RESUMEN / SUMMARY: - It is estimated that approximately 25% of all lung cancer cases are observed in never-smokers and its incidence is expected to increase due to smoking prevention programs. Risk factors for the development of lung cancer described include second-hand smoking, radon exposure, occupational exposure to carcinogens and to cooking oil fumes and indoor coal burning. Other factors reported are infections (HPV and Mycobacterium tuberculosis), hormonal and dietary factors and diabetes mellitus. Having an affected relative also increases the risk for lung cancer while recent studies have identified several single nucleotide polymorphisms associated with increased risk for lung cancer development in never smokers. Distinct clinical, pathology and molecular characteristics are observed in lung cancer in never smokers; more frequently is observed in females and adenocarcinoma is the predominant histology while it has a different pattern of molecular alterations. The purpose of this review is to summarize our current knowledge of this disease.

[144]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
INTRODUCTION: A Simplified Comorbidity Score (SCS) provided additional prognostic information to the established factors in patients with non-small cell lung cancer. We undertook this analysis to test the prognostic value of the SCS in a population-based study. PATIENTS AND METHODS: Retrospective survey of all Victorians diagnosed with lung cancer in January-June 2003, identified from the Victorian Cancer Registry. RESULTS: There were 921 patients, with data available for 841 (91.3%). Median age was 72 years (range 30-94) and 63.1% were male. A tissue diagnosis was made for 89.9%, of which 86.6% were non-small cell (NSCLC), and 13.4% small cell carcinoma (SCLC). Comorbidities on which the SCS is based were distributed: cardiovascular 54.6%; respiratory 38.9%; neoplastic 19.9%; renal 4.6%; diabetes 11.7%; alcoholism 5.5%; and tobacco 83.1%. In patients with NSCLC, higher SCS score (>9) was associated with increasing stage, ECOG performance status, male sex, increasing age, tobacco consumption and not receiving treatment. Using Cox regression, survival was analysed by SCS score after adjusting for the effect of age, sex, cell type (NSCLC, SCLC, no histology), ECOG performance status and stage for all patients and then restricted to NSCLC. As a continuous or dichotomous (<= or >9) variable, SCS was not a significant prognostic factor for all patients or when restricted to NSCLC. CONCLUSION: In this retrospective analysis of population based registry patients, SCS did not provide additional prognostic information in patients with lung cancer. ECOG performance status may be a substitute for the effect of comorbidity.
INSTITUCIÓN / INSTITUTION: - Department of Radiology (E010), German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research, Heidelberg, Germany; Clinic of Radiology and Nuclear Medicine, University of Basel Hospital, Petersgraben 4, 4031 Basel, Switzerland. Electronic address: gregor.sommer@usb.ch.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate non-contrast-enhanced Fourier decomposition MRI (FD MRI) for assessment of regional lung perfusion in patients with Non-Small-Cell Lung Cancer (NSCLC) in comparison to dynamic contrast-enhanced MRI (DCE MRI). METHODS: Time-resolved non-contrast-enhanced images of the lungs were acquired prospectively in 15 patients using a 2D balanced steady-state free precession (b-SSFP) sequence. After non-rigid registration of the native image data, perfusion-weighted images were calculated by separating periodic changes of lung proton density at the cardiac frequency using FD. DCE MRI subtraction datasets were acquired as standard of reference. Both datasets were analyzed visually for perfusion defects. Then segmentation analyses were performed to describe perfusion of pulmonary lobes semi-quantitatively as percentages of total lung perfusion. Overall FD MRI perfusion signal was compared to velocity-encoded flow measurements in the pulmonary trunk as an additional fully quantitative reference. RESULTS: Image quality ratings of FD MRI were significantly inferior to those of DCE MRI (P<0.0001). Sensitivity, specificity, and accuracy of FD MRI for visual detection of perfusion defects were 84%, 92%, and 91%. Semi-quantitative evaluation of lobar perfusion provided high agreement between FD MRI and DCE MRI for both entire lungs and upper lobes, but less agreement in the lower parts of both lungs. FD perfusion signal showed high linear correlation with pulmonary arterial blood flow. CONCLUSION: FD MRI is a promising technique that allows for assessing regional lung perfusion in NSCLC patients without contrast media or ionizing radiation. However, for being applied in clinical routine, image quality and robustness of the technique need to be further improved.

[146] TÍTULO / TITLE: - A retrospective comparison of proton therapy and carbon ion therapy for stage I non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Fujii O; Demizu Y; Hashimoto N; Araya M; Takagi M; Terashima K; Mima M; Iwata H; Niwa Y; Jin D; Daimon T; Sasaki R; Hishikawa Y; Abe M; Murakami M; Fuwa N
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Japan. Electronic address: osfujii@aa.cyberhome.ne.jp.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: This retrospective study aimed to compare the clinical outcomes and late toxicities of proton therapy (PT) with those of carbon ion therapy (CIT) for stage I non-small cell lung cancer (NSCLC). MATERIAL AND METHODS: A total of 111 patients who underwent particle therapy for stage I NSCLC between April 2003 and December 2009 were enrolled in this study. PT (n=70) and CIT (n=41) were delivered to total doses of 52.8-80GyE in 4-26 fractions and 52.8-70.2GyE in 4-26 fractions, respectively. The median follow-up time was 41 months. RESULTS: Differences in outcome between the PT and CIT groups regarding 3-year overall survival (72% and 76%, respectively), progression-free survival (44% and 53%, respectively), and local control (81% and 78%, respectively) were not statistically significant. In multivariate analysis, the type of treatment beam did not correlate with overall survival. The severity of late toxicities was comparable between the two groups. CONCLUSIONS: Clinical results in the PT group were comparable to those in the CIT group. However, this study was a retrospective analysis of a highly heterogeneous population. Consequently, more homogeneous prospective data, large multicentric databases and, ideally, randomized trials are warranted.

[147]

TÍTULO / TITLE: - Segmentectomy Versus Wedge Resection for Non-Small Cell Lung Cancer in High-Risk Operable Patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Kent M; Landreneau R; Mandrekar S; Hillman S; Nichols F; Jones D; Starnes S; Tan A; Putnam J; Meyers B; Daly B; Fernando HC

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts. Electronic address: mkent@bidmc.harvard.edu.

RESUMEN / SUMMARY: - BACKGROUND: Patients with early-stage lung cancer and limited pulmonary reserve may not be appropriate candidates for lobectomy. In these situations, sublobar resection (wedge or segmentectomy) is generally performed. Many physicians believe that segmentectomy is superior because it allows for an improved parenchymal margin and nodal sampling. METHODS: We performed an analysis using operative and pathology reports collected as part of planned data collection for American College of Surgeons Surgical Oncology Group (ACOSG) Z4032. This was a prospective trial in which patients with clinical stage I lung cancer and limited pulmonary function were randomized to sublobar resection with or without...
brachytherapy. The operative approach (video-assisted thoracic surgery [VATS] vs thoracotomy), extent of resection, and degree of lymph node evaluation were at the discretion of the individual surgeon. The primary aim of this analysis was to compare the parenchymal margin achieved between segmentectomy and wedge resection. Secondary aims included the extent of nodal staging and whether the operative approach (VATS vs open) had an effect on margin status and nodal evaluation.

RESULTS: Among 210 patients, 135 (64%) underwent a VATS approach and 75 (36%) a thoracotomy. A segmentectomy was performed in 57 patients (27%) and a wedge resection in 153 patients (73%). There were no significant differences in the degree of nodal upstaging, stations sampled, or parenchymal margin obtained between VATS and thoracotomy. However, significant differences were observed between patients who underwent a segmentectomy and those who underwent a wedge resection with regard to parenchymal margin (1.5 cm vs 0.8 cm, \( p = 0.0001 \)), nodal upstaging (9% vs 1%, \( p = 0.006 \)), and nodal stations sampled (3 vs 1, \( p < 0.0001 \)). Notably, 41% of patients treated by wedge resection had no nodes sampled at the time of operation compared with 2% of those who underwent segmentectomy (\( p < 0.0001 \)).

CONCLUSIONS: In ACOSG Z4032, wedge resection, regardless of the approach, was associated with a smaller parenchymal margin and a lower yield of lymph nodes and rate of nodal upstaging when compared with segmentectomy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hubers AJ; Heideman DA; Yatabe Y; Wood MD; Tull J; Taron M; Molina MA; Mayo C; Bertran-Alamillo J; Herder GJ; Koning R; Sie D; Ylstra B; Meijer GA; Snijders PJ; Witte BI; Postmus PE; Smit EF; Thunnissen E
INSTITUCIÓN / INSTITUTION: - Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands.
RESUMEN / SUMMARY: - OBJECTIVES: Epidermal growth factor receptor (EGFR) mutations have been identified in lung adenocarcinomas and are associated with high response chance to EGFR tyrosine kinase inhibitors. EGFR mutations can be detected in tumour tissue, cytology specimens and blood from lung cancer patients. Thus far, EGFR mutation analysis has not been systematically demonstrated for sputum samples. The aim of the present study was to determine whether EGFR mutation analysis is attainable on sputum samples, employing different assays in a multicenter study.
MATERIALS AND METHODS: Sputum DNA from 10 lung cancer patients with confirmed
EGFR mutation in their tumour tissue, 10 lung cancer patients without evidence of an EGFR mutation, and 10 patients with chronic obstructive pulmonary disease (COPD) was used for mutation analysis by Cycleave PCR, COLD-PCR, PangaeaBiotech SL Technology (PST), and High Resolution Melting, respectively. Targeted resequencing (TruSeq Amplicon Cancer Panel) and droplet digital PCR were additionally performed on the 10 samples with EGFR mutation. RESULTS: Dependent on the assay, EGFR mutations could be detected in 30-50% of the sputum samples of patients with EGFR mutations. The different techniques revealed consistent results, with slightly higher sensitivity for PST. Neither the lung cancer patients without EGFR mutation nor the COPD controls tested positive for EGFR mutations in their sputum samples, indicating high clinical specificity of all assays. CONCLUSION: EGFR mutations can be detected in sputum samples from patients with EGFR-mutated non-small cell lung cancer, which may replace biopsy procedure for some patients.

[149]

TÍTULO / TITLE: - EGFR Mutations in US Hispanic Versus Non-Hispanic White Patients With Lung Adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 5858/arpa.2013-0311-OA
AUTORES / AUTHORS: - Zhang W; McQuitty EB; Olsen R; Fan H; Hendrickson H; Tio FO; Newton K; Cagle P; Jagirdar J
RESUMEN / SUMMARY: - Context.-Lung cancer is the leading cause of cancer deaths worldwide. First-generation tyrosine kinase inhibitors improve progression-free survival in lung cancers with epidermal growth factor receptor (EGFR) mutations. EGFR mutations occur predominantly in exons 19 and 21 in lung adenocarcinomas of Asians (approximately 30%), whites (approximately 15%), and African Americans (approximately 19%). However, minimal information exists on the prevalence or type of genetic changes that occur in lung cancers in US Hispanic patients. We investigated the EGFR mutation frequency in primary lung adenocarcinomas in US Hispanics compared with non-Hispanic whites. Objective.-To evaluate EGFR mutations in lung adenocarcinomas from US Hispanic patients compared with those from non-Hispanic white patients. Design.-DNA samples were extracted from paraffin-embedded tissue of consecutive lung adenocarcinomas from 83 patients. Samples were collected from 40 Hispanics and 43 non-Hispanic whites. Mutations in EGFR were analyzed using a custom assay. Results.-Fourteen of 83 patients (16.9%) had EGFR mutations in their tumor DNA, including 6 of 40 Hispanics (15.0%) and 8 of 43 non-Hispanic whites (18.6%). No association with age, sex, or tumor stage was identified. Smoking history could not be obtained for most of the 83 patients, although 8 of the 11 patients with EGFR mutations for whom smoking history was obtained were nonsmokers. Most of
the tumors with EGFR mutations (12 of 14; 85.7%) were acinar with lepidic or papillary subtypes. EGFR mutations occurred in exon 19 (42.8%), exon 18 (28.6%), exon 20 (28.6%), and exon 21 (14.3%). Two cases had 2 mutations identified in different exons. Conclusion.-The frequency of EGFR mutations is similar in US Hispanics compared with non-Hispanic whites.
AUTORES / AUTHORS: Abazeed ME; Adams DJ; Hurov KE; Tamayo P; Creighton CJ; Sonkin D; Giacomelli AO; Du C; Fries DF; Wong KK; Mesirov JP; Loeffler JS; Schreiber SL; Hammerman PS; Meyerson M

INSTITUCIÓN / INSTITUTION: Radiation Oncology, Harvard Radiation Oncology Program.

RESUMEN / SUMMARY: Radiation therapy is one of the mainstays of anti-cancer treatment, but the relationship between the radiosensitivity of cancer cells and their genomic characteristics is still not well-defined. Here we report the development of a high-throughput platform for measuring radiation survival in vitro and its validation by comparison to conventional clonogenic radiation survival analysis. We combined results from this high-throughput assay with genomic parameters in cell lines from squamous cell lung carcinoma, which is standardly treated by radiation therapy, to identify parameters that predict radiation sensitivity. We showed that activation of NFE2L2, a frequent event in lung squamous cancers, confers radiation resistance. An expression-based, in silico screen nominated inhibitors of PI3K as NFE2L2 antagonists. We showed that the selective PI3K inhibitor, NVP-BKM120, both decreased NRF2 protein levels and sensitized NFE2L2 or KEAP1 mutant cells to radiation. We then combined results from this high-throughput assay with single-sample gene set enrichment analysis (ssGSEA) of gene expression data. The resulting analysis identified pathways implicated in cell survival, genotoxic stress, detoxification, and innate and adaptive immunity as key correlates of radiation sensitivity. The integrative, high-throughput methods shown here for large-scale profiling of radiation survival and genomic features of solid-tumor derived cell lines should facilitate tumor radiogenomics and the discovery of genotype-selective radiation sensitizers and protective agents.

PTPTPTP - JOURNAL ARTICLE ----------------------------------------------- [152]

TÍTULO / TITLE: Prognostic significance of the number of removed lymph nodes at lobectomy in patients with positron emission tomography-computed tomography-negative N2 non-small cell lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Tsai YM; Huang TW; Hsu HH; Cheng CY; Lin YC; Cheng YL; Chang H; Lee SC

INSTITUCIÓN / INSTITUTION: Division of Thoracic Surgery, Department of Surgery, National Defence Medical Centre, Taiwan, ROC.

RESUMEN / SUMMARY: Background: We assessed the relation between the extent of lymph node (LN) dissection and the prognosis for positron emission tomography-computed tomography (PET-CT)-negative patients with clinical early-stage non-small cell lung cancer (NSCLC), undergoing lobectomy and mediastinal LN dissection.
Methods: 277 patients with clinical stage I/II NSCLC who had undergone a preoperative PET-CT scan followed by lobectomy were analysed retrospectively. The prognostic value of age, maximum standardized uptake value (SUVmax) of the tumour, tumour size, carcinoembryonic antigen and number of dissected LNs was assessed to determine any association with overall survival and disease-free survival. Results: 31 patients developed postoperative relapse, and multiple logistic regression revealed that the number of dissected LNs was an independent factor predicting relapse. Patients were categorized into groups according to the number of LNs dissected (group I, < 10; group II, >/= 10). There were no statistical differences between 2 groups but group II patients had a lower relapse rate (6.3%, p = 0.003) and better disease-free survival (74.95 months, p = 0.045). Conclusions: Mediastinal LN dissection is still important for clinical early-stage NSCLC patients undergoing lobectomy even when the preoperative PET-CT is negative, and results in fewer relapses and improved disease-free survival. © 2013 S. Karger GmbH, Freiburg.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Xie M; He CS; Wei SH; Zhang L
INSTITUCIÓN / INSTITUTION: - China State Key Laboratory of Respiratory Disease and Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Road, Guangzhou 510120, China. Electronic address: mianxie@gird.cn.
RESUMEN / SUMMARY: - Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) occurs in non-small cell lung cancer (NSCLC) patients who initially respond to TKI treatment but whose cancer then progresses. Recent studies have shown that Notch signal is associated with drug resistance. However, the exact mechanism of Notch during acquisition of resistance to EGFR-TKI in human lung cancer remains unclear. In the present study, we showed that the expression of Notch-1 was highly upregulated in EGFR-TKI acquired resistant lung cancer cells. More importantly, Notch-1 contributed to the acquisition of the epithelial-mesenchymal transition (EMT) phenotype, which was critically associated with acquired resistance to EGFR-TKI. Silencing of Notch-1 using siRNA resulted in mesenchymal-epithelial transition (MET), which was associated with impaired invasion and anchorage-independent growth of lung cancer and resensitisation to gefitinib in acquired resistant NSCLC cells. Finally, gefitinib treatment of Balb/c nu/nu with
acquired resistant lung cancer xenografts in combination with Notch inhibitor N-[N-(3,5-difluorophenacetyl)-l-alanyl]-(S)-phenylglycine t-butyl ester (DAPT) resulted in effective tumour growth retardation, with decreased proliferative activity and increased apoptotic activity. Collectively, these data suggest that Notch-1 might play a novel role in acquired resistance to gefitinib, which could be reversed by inhibiting Notch-1.

[154]
TÍTULO / TITLE: - Vitamin D intake and lung cancer risk in the Women’s Health Initiative.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Cheng TY; Lacroix AZ; Beresford SA; Goodman GE; Thornquist MD; Zheng Y; Chlebowski RT; Ho GY; Neuhouser ML
INSTITUCIÓN / INSTITUTION: - Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA and Biostatistics, University of Washington, Seattle, WA; Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA.

RESUMEN / SUMMARY: - BACKGROUND: Prior research suggests that vitamin D protects against lung cancer only among certain subgroups. OBJECTIVES: We investigated whether vitamin D intake was associated with lung cancer and explored whether vitamin A intake modified the association. DESIGN: Prospective cohort data from 128,779 postmenopausal women, including 1771 incident lung cancers in the Women’s Health Initiative (Clinical Trials and Observational Study) 1993-2010, were analyzed. Twelve percent of women received active intervention (1 g Ca + 400 IU vitamin D3/d) in the Calcium/Vitamin D Trial. Baseline total intake included both dietary intake (from food-frequency questionnaires) and supplement intake (from bottle labels). HRs were estimated by Cox proportional hazard models. RESULTS: No significant association was observed overall. Among never smokers, a total vitamin D intake >/=400 IU/d was significantly associated with lower risks of lung cancer (HR: 0.37; 95% CI: 0.18, 0.77 for >/=800 compared with <100 IU/d; P-trend = 0.01). No significant effect modification of total vitamin A intake on the association between total vitamin D intake and lung cancer was found. However, the Calcium/Vitamin D Trial active intervention was significantly associated with a lower lung cancer risk only among women with a vitamin A intake <1000 mug/d retinol activity equivalents (HR: 0.69; 95% CI: 0.50, 0.96; P-interaction = 0.09). CONCLUSIONS: Vitamin D intake was associated with a lower lung cancer risk in never-smoking, postmenopausal women. Lower vitamin A intake may be important for a beneficial association of 1 g Ca + 400 IU
vitamin D3 supplementation with lung cancer. This trial was registered at clinicaltrials.gov as NCT00000611.

[155]
TÍTULO / TITLE: Persistent unilateral facial pain in lung cancer patients with mediastinal nodal involvement.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Pembroke CA; Byrne A; Lester JF; Button M
INSTITUCIÓN / INSTITUTION: Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff CF14 2TL, UK. Electronic address: Catherine.a.pembroke@wales.nhs.uk.

RESUMEN / SUMMARY: Persistent idiopathic facial pain associated with mediastinal involvement in non-small cell lung cancer (NSCLC) may occur at presentation or at relapse. It is often under-recognised, leading to prolonged symptoms, distress and sometimes inappropriate interventions. We present three case histories and a review of the published literature to highlight this important symptom.

[156]
TÍTULO / TITLE: A high-throughput screen identifies PARP1/2 inhibitors as a potential therapy for ERCC1-deficient non-small cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Postel-Vinay S; Bajrami I; Fribulet L; Elliott R; Fontebasso Y; Dorvault N; Olaussen KA; Andre F; Soria JC; Lord CJ; Ashworth A

RESUMEN / SUMMARY: Excision repair cross-complementation group 1 (ERCC1) is a DNA repair enzyme that is frequently defective in non-small cell lung cancer (NSCLC). Although low ERCC1 expression correlates with platinum sensitivity, the clinical effectiveness of platinum therapy is limited, highlighting the need for alternative treatment strategies. To discover new mechanism-based therapeutic strategies for ERCC1-defective tumours, we performed high-throughput drug screens in an isogenic NSCLC model of ERCC1 deficiency and dissected the mechanism underlying ERCC1-
selective effects by studying molecular biomarkers of tumour cell response. The high-throughput screens identified multiple clinical poly (ADP-ribose) polymerase 1 and 2 (PARP1/2) inhibitors, such as olaparib (AZD-2281), niraparib (MK-4827) and BMN 673, as being selective for ERCC1 deficiency. We observed that ERCC1-deficient cells displayed a significant delay in double-strand break repair associated with a profound and prolonged G2/M arrest following PARP1/2 inhibitor treatment. Importantly, we found that ERCC1 isoform 202, which has recently been shown to mediate platinum sensitivity, also modulated PARP1/2 sensitivity. A PARP1/2 inhibitor-synthetic lethal siRNA screen revealed that ERCC1 deficiency was epistatic with homologous recombination deficiency. However, ERCC1-deficient cells did not display a defect in RAD51 foci formation, suggesting that ERCC1 might be required to process PARP1/2 inhibitor-induced DNA lesions before DNA strand invasion. PARP1 silencing restored PARP1/2 inhibitor resistance in ERCC1-deficient cells but had no effect in ERCC1-proficient cells, supporting the hypothesis that PARP1 might be required for the ERCC1 selectivity of PARP1/2 inhibitors. This study suggests that PARP1/2 inhibitors as a monotherapy could represent a novel therapeutic strategy for NSCLC patients with ERCC1-deficient tumours. Oncogene advance online publication, 12 August 2013; doi:10.1038/onc.2013.311.

[157]
TÍTULO / TITLE: - Phase II study of pemetrexed plus intermittent erlotinib combination therapy for pretreated advanced non-squamous non-small cell lung cancer with documentation of epidermal growth factor receptor mutation status.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Minami S; Kijima T; Hamaguchi M; Nakatani T; Koba T; Takeuchi Y; Kida H; Nagatomo I; Yamamoto S; Tachibana I; Komuta K; Kawase I
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka 543-0035, Japan.
RESUMEN / SUMMARY: - INTRODUCTION: Erlotinib and pemetrexed have been approved for the second-line and maintenance treatment of non-small cell lung cancer (NSCLC). With the recommended doses determined by our previous phase I study, we conducted a phase II study to evaluate the efficacy and safety of combination of the two agents in pretreated non-squamous NSCLC patients. METHODS: This study was performed in patients with stage IIIIB/IV or post-surgically recurrent non-squamous NSCLC whose disease had progressed on or after receiving first-line chemotherapy. Patients received 500mg/m2 of intravenous pemetrexed every 21 days and 150mg of oral erlotinib on days 2-16 until disease progression, unacceptable toxicity,
withdrawal of consent. The expected response rate and threshold were defined as 33.5% and 10%, respectively. Assuming a one-sided alpha of 5%, a power of 80%, the possible deviation from assessment, 26 patients were necessary. RESULTS: A total of 27 patients, 16 males and 11 females were recruited. Patients had the median age of 70 years (range, 48-80 years) and included 21 stage IV diseases, 22 adenocarcinomas. Epidermal growth factor receptor (EGFR) mutations were examined in all patients. One patient had positive EGFR mutation, but the other 26 patients had wild-type EGFR. The median number of treatment courses was 3 (range, 1 to over 19). The best overall response rate and disease control rate were 11.1% and 63.0%, respectively. The median progression-free survival and overall survival were 2.8 months (95% confidence interval (CI); 1.9-7.5 months) and 15.8 months (95% CI; 9.3 months to not available), respectively. Dermal, hepatic, gastrointestinal and hematological disorders were the frequently observed adverse events. One patient experienced grade 3 drug-induced interstitial lung disease. CONCLUSIONS: We could not demonstrate the add-on effect of intermittent erlotinib on pemetrexed in a second-line setting for patients with non-squamous NSCLC without EGFR mutations.
TT, OR = 0.55, 95% CI, 0.36-0.84). Besides, the CC + TC carriers in the smokers were at a significantly reduced risk of lung cancer (CC + TC vs. TT, OR = 0.48, 95% CI, 0.16-1.44). The study supports that the polymorphisms of VDR BsmI and TaqI play protective roles in the lung carcinogenesis, particularly among the smokers. The association of VDR ApaI polymorphism with the lung cancer risk needs to be further elucidated.

[159]

TÍTULO / TITLE: - Pain Intensity and Pain Interference in Patients With Lung Cancer: A Pilot Study of Biopsychosocial Predictors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dalton JA; Higgins MK; Miller AH; Keefe FJ; Khuri FR
INSTITUCIÓN / INSTITUTION: - *Nell Hodgson Woodruff School of Nursing Departments of Psychiatry section signHematology and Medical Oncology, School of Medicine, Winship Cancer Institute, Emory University, Atlanta, GA double daggerDepartment of Psychiatry, Division of Behavioral Medicine, Duke University Medical Center, Durham, NC.
RESUMEN / SUMMARY: - OBJECTIVE:: To explore biopsychosocial factors (beliefs, depression, catastrophizing cytokines) in individuals newly diagnosed with lung cancer and no pain to determine their relationship at diagnosis and across time and to determine whether these factors contribute to pain intensity or pain interference with function at pain onset. MATERIALS AND METHODS:: A longitudinal, exploratory, pilot study was implemented in a private medical center and a VA medical center in the southeast. Twelve subjects not experiencing pain related to cancer of the lung or its treatment were recruited. A Karnofsky status of 40% and hemoglobin of 8 g were required. Five questionnaires were completed and 10 mL of blood was drawn at baseline; 4 questionnaires and blood draws were repeated monthly for 5 months. One baseline questionnaire and a pain assessment were added at final. Demographic, clinical, and questionnaire data were summarized; standardized scale scores were calculated. RESULTS:: Biopsychosocial scores that were low at baseline increased from T1-T4 but decreased slightly T5-T6. Individuals with higher pain intensity and higher pain interference at final had higher psychosocial scores at baseline than individuals with lower pain intensity and lower pain interference at final. CONCLUSIONS:: Unrelated to disease stage, metastasis, or treatment, unique levels of biopsychosocial factors are observed in patients newly diagnosed with lung cancer who report higher levels of pain intensity and higher levels of pain interference at the time pain occurs. Replication studies are needed to validate this response pattern and determine the value of repeated individual assessments.
TÍTULO / TITLE: - Deep inspiration breath hold radiotherapy for locally advanced lung cancer: Comparison of different treatment techniques on target coverage, lung dose and treatment delivery time.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Josipovic M; Persson GF; Hakansson K; Damkjaer SM; Bangsgaard JP; Westman G; Riisgaard S; Specht L; Aznar MC

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Rigshospitalet, Copenhagen, Denmark.

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TÍTULO / TITLE: - Overexpression and promoter mutation of the TERT gene in malignant pleural mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Tallet A; Nault JC; Renier A; Hysi I; Galateau-Salle F; Cazes A; Copin MC; Hofman P; Andujar P; Le Pimpec-Barthes F; Zucman-Rossi J; Jaurand MC; Jean D


RESUMEN / SUMMARY: - Malignant pleural mesothelioma (MPM) is a very aggressive tumor with no known curative treatment. Better knowledge of the molecular mechanisms of mesothelial carcinogenesis is required to develop new therapeutic strategies. MPM, like all cancer cells, needs to maintain telomere length to prevent senescence. Previous studies suggested that the telomere lengthening mechanism in MPM is based mainly on telomerase activity. For this reason, we focused on the key catalytic enzyme, TERT (telomerase reverse transcriptase), by analyzing its gene expression in MPM and by studying the mechanism underlying its upregulation. We used our large collection of MPM composed of 61 MPM in culture and 71 frozen MPM tumor samples. Evaluation of TERT mRNA expression by quantitative RT-PCR showed overexpression in MPM in culture compared with normal mesothelial cells, and in MPM tumor samples compared with normal pleura. We identified a ‘hot spot’ of mutations in the TERT gene core promoter in both MPM in culture and in MPM tumor
samples with an overall frequency of 15%. Furthermore, data clearly identified mutation in the TERT promoter as a mechanism of TERT mRNA upregulation in MPM. In contrast, gene copy number amplification was not associated with TERT overexpression. Then, we analyzed the clinicopathological, etiological and genetic characteristics of MPM with mutations in the TERT promoter. TERT promoter mutations were more frequent in MPM with sarcomatoid histologic subtype (P<0.01), and they were frequently associated with CDKN2A gene inactivation (P=0.03). In conclusion, a subgroup of MPM presents TERT promoter mutations, which lead to TERT mRNA upregulation. This is the first recurrent gain-of-function oncogenic mutations identified in MPM. Oncogene advance online publication, 26 August 2013; doi:10.1038/onc.2013.351.

[162]

TÍTULO / TITLE: Raman micro spectroscopy study of the interaction of vincristine with A549 cells supported by expression analysis of bcl-2 protein.
RESUMEN / SUMMARY: Understanding the interaction of anticancer drugs with model cell lines is important to elucidate the mode of action of these drugs as well as to develop cost effective and rapid screening methods. Raman spectroscopy has been demonstrated to be a valuable technique for high throughput, noninvasive analysis. The interaction of vincristine with a human lung adenocarcinoma cell line (A549) was investigated using Raman micro spectroscopy. The results were correlated with parallel measurements from the MTT cytotoxicity assay, which yielded an IC50 value of 0.10 +/- 0.03 μM. The Raman spectral data acquired from vincristine treated A549 cells was analysed to understand its interaction with the nucleus in the cell and elucidate DNA intercalation. The dose dependent spectral changes in the nucleus are analysed by PLS-Jack knifing for the identification of the more significant changes associated with the mode of action of the drug. Results are correlated with a similar dose dependent expression analysis of the bcl-2 protein, an anti-apoptotic protein associated with DNA damage, in the vincristine treated A549 cells using flow cytometry. The results indicate the co-existence of two modes of action, microtubule binding at low doses and DNA intercalation at high doses.
TÍTULO / TITLE: Expression profile and function of Wnt signaling mechanisms in malignant mesothelioma cells.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Fox SA; Richards AK; Kusumah I; Perumal V; Bolitho EM; Mutsaers SE; Dharmarajan AM

INSTITUCIÓN / INSTITUTION: Molecular Pharmacology Laboratory, School of Pharmacy, Curtin Health Innovation Research Institute, Curtin University, Bentley, WA, Australia. Electronic address: s.fox@curtin.edu.au.

RESUMEN / SUMMARY: Malignant mesothelioma (MM) is an uncommon and particularly aggressive cancer associated with asbestos exposure, which currently presents an intractable clinical challenge. Wnt signaling has been reported to play a role in the neoplastic properties of mesothelioma cells but has not been investigated in detail in this cancer. We surveyed expression of Wnts, their receptors, and other key molecules in this pathway in well established in vitro mesothelioma models in comparison with primary mesothelial cultures. We also tested the biological response of MM cell lines to exogenous Wnt and secreted regulators, as well as targeting beta-catenin. We detected frequent expression of Wnt3 and Wnt5a, as well as Fzd 2, 4 and 6. The mRNA of Wnt4, Fzd3, sFRP4, APC and axin2 were downregulated in MM relative to mesothelial cells while LEF1 was overexpressed in MM. Functionally, we observed that Wnt3a stimulated MM proliferation while sFRP4 was inhibitory. Furthermore, directly targeting beta-catenin expression could sensitise MM cells to cytotoxic drugs. These results provide evidence for altered expression of a number of Wnt/Fzd signaling molecules in MM. Modulation of Wnt signaling in MM may prove a means of targeting proliferation and drug resistance in this cancer.

VALIDATION OF A PROLIFERATION-BASED EXPRESSION SIGNATURE AS PROGNOSTIC MARKER IN EARLY STAGE LUNG ADENOCARCINOMA.

TÍTULO / TITLE: Validation of a Proliferation-based Expression Signature as Prognostic Marker in Early Stage Lung Adenocarcinoma.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Wistuba II; Behrens C; Lombardi F; Fujimoto J; Raso MG; Spaggiari L; Galetta D; Riley R; Hughes E; Reed J; Sangale Z; Swisher SG; Kahlor N; Moran C; Gutin A; Barberis M; Kim ES

Enlace al texto completo (gratuito o de pago) 1158/1078-0432.CCR-13-0596
PURPOSE: New prognostic markers to guide treatment decisions in early stage non-small cell lung cancer are necessary to improve patient outcomes. In this report, we assess the utility of a pre-defined mRNA expression signature of cell cycle progression genes (CCP score) to define 5-year risk of lung cancer related death in patients with early stage lung adenocarcinoma. EXPERIMENTAL DESIGN: A CCP score was calculated from the mRNA expression levels of 31 proliferation genes in stage I and II tumors from two public microarray data sets (Director’s Consortium (DC) and GSE31210). The same gene set was tested by quantitative PCR in 381 formalin-fixed paraffin-embedded (FFPE) primary tumors. Association of the CCP score with outcome was assessed by Cox proportional hazards analysis. RESULTS: In univariate analysis the CCP score was a strong predictor of cancer-specific survival in both the DC cohort (p=0.00014, HR 2.08, 95%CI 1.43-3.02) and GSE31210 (p=0.0010, HR 2.25, 95%CI 1.42-3.56). In multivariate analysis the CCP score remained the dominant prognostic marker in the presence of clinical variables (p=0.0022, HR 2.02, 95%CI 1.29-3.17 in DC, p=0.0026, HR 2.16, 95%CI 1.32-3.53 in GSE31210). On a quantitative PCR platform the CCP score maintained highly significant prognostic value in FFPE derived mRNA from clinical samples in both univariate (p=0.00033, HR 2.10, 95%CI 1.39-3.17) and multivariate analyses (p=0.0071, HR 1.92, 95%CI 1.18-3.10). CONCLUSIONS: The CCP score is a significant predictor of lung cancer death in early stage lung adenocarcinoma treated with surgery and may be a valuable tool in selecting patients for adjuvant treatment.

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TÍTULO / TITLE: Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


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TÍTULO / TITLE: Significance of the serum carcinoembryonic antigen level during the follow-up of patients with completely resected non-small-cell lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


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OBJECTIVES: The purpose of this study was to elucidate the detectability of recurrence and the prognostic significance of the serum carcinoembryonic antigen (CEA) levels in patients with completely resected non-small-cell lung cancer (NSCLC). METHODS: Five hundred and eighteen NSCLC patients who underwent complete resection at Aichi Cancer Center between April 2001 and March 2006 were enrolled in this study. The patient characteristics were as follows: the median age was 63 years; 331 tumours were classified as pathological stage I, 88 tumours were pathological stage II and 99 tumours were pathological stage III; 140 tumours were adenocarcinomas with epidermal growth factor receptor (EGFR) mutations, 268 tumours were adenocarcinomas with EGFR wild-type mutations and 110 tumours were other NSCLCs. The patients were divided into three groups: those with a normal CEA level before and 1-3 months after surgery (N group, n = 380), those with an elevated CEA level before surgery and a normal CEA level 1-3 months after surgery (HN group, n = 105) and those with an elevated CEA level 1-3 months after surgery regardless of the preoperative CEA level (H group, n = 33). The correlations between the changes in the serum CEA levels and the clinical outcomes were analysed.

RESULTS: Recurrence developed in 122 patients (32%) in the N group, 49 patients (47%) in the HN group and 19 patients (58%) in the H group (P = 0.001). The sensitivity and specificity of an elevated serum CEA level during the follow-up period for detecting recurrence were 30 and 98% in the N group and 82 and 73% in the HN group, respectively. Twenty-seven asymptomatic recurrent tumours combined with an elevated serum CEA level were detected in the HN group. In the multivariate Cox regression analysis, the serum CEA level 1-3 months after surgery had prognostic value for overall survival. CONCLUSIONS: In completely resected NSCLC patients, measuring the serum CEA level during the follow-up period is useful in patients in whom an elevated level normalizes after surgery, and the serum CEA level 1-3 months after surgery is considered to have prognostic significance regarding survival.

[167]
INSTITUCIÓN / INSTITUTION: - Departments of *Pathology daggerUrology double daggerOncology, The Johns Hopkins Hospital, Baltimore, MD.

RESUMEN / SUMMARY: - The tunica vaginalis is an embryologically derived mesothelium-lined outpouching of the peritoneal cavity, which may develop neoplastic mesothelial proliferations similar to, although much less commonly than, pleural or peritoneal surfaces. We herein report our experience with 12 cases of florid paratesticular mesothelial hyperplasia, highlighting the spectrum of morphologic changes seen and the utility of fluorescence in situ hybridization analysis of homozygous deletion of 9p21 as an adjunct diagnostic tool. All cases were referred because of concern regarding the nature of the mesothelial proliferation. The median age of patients at presentation was 44.5 years (range, 16 to 71 y). Ten of 12 patients clinically presented with hydroceles (2 of which were complicated by infection or hemorrhage), 1 with “paraepididymal cyst” and 1 patient with an epididymal cyst. In contrast to the normal tunica consisting of a thin fibrous wall lined by a monolayer of flattened bland mesothelium and no significant inflammation, all of our cases were characterized by background changes of fibroblastic organization and stromal chronic inflammation. In all cases, the mesothelial proliferation within the fibrous and inflamed stroma was sparse and consisted of linear arrays of widely spaced horizontally orientated simple nonbranching elongated tubules and small solid nests and cords that were well spaced apart. There was an abrupt linear demarcation of tubules at the deep aspect of the fibrous tissue, with no evidence of definite invasion into the submesothelial tissue. Fluorescence in situ hybridization for 9p21 was negative in all 5 cases in which tissue was available for analysis. Nine patients with extended follow-up were alive (median 8 y; range, 1 to 13 y). In summary, the proliferative changes seen in reactive mesothelial hyperplasia associated with hydroceles may be florid and mimic malignant mesothelioma. In particular, the entrapment of isolated mesothelial clusters within deep fibrous tissue may be the cause of significant diagnostic difficulty. There are, however, morphologic clues such as linear arraying of widely spaced architecturally simple cell clusters that may aid in the correct identification of the benignity of these proliferations.

[168]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 1007/s00428-013-1472-7

AUTORES / AUTHORS: - Han XH; Zhang NN; Ma L; Lin DM; Hao XZ; Liu YT; Wang L; Liu P; Yuan Z; Li D; Lin H; Sun Y; Shi YK
RESUMEN / SUMMARY: Accurate determination of anaplastic lymphoma kinase (ALK) rearrangements is critical in identifying ALK-positive patients for targeted therapy in non-small-cell lung cancer (NSCLC). Fluorescence in situ hybridization (FISH) is the current standard method to detect ALK rearrangements but is technically challenging and costly. We compared optimised immunohistochemistry (IHC), quantitative real-time polymerase chain reaction (qRT-PCR) and fluorescence in situ hybridization techniques in this study of 139 samples of advanced NSCLC with non-squamous histology. ALK alteration was found in 32.6 % (43/132) of patients by FISH, 32.9 % (45/137) of patients by IHC and 27.9 % (34/122) of samples by qRT-PCR (concordance rate of 96.9 % between FISH and IHC, 95.7 % between FISH and qRT-PCR, P < 0.001). IHC sensitivity and specificity were 97.7 % and 96.6 %, respectively, while the sensitivity and specificity of qRT-PCR were 89.2 % and 98.7 %, respectively. ALK rearrangements were more common in young patients (P = 0.007), non-smokers or light smokers (P = 0.008) and adenocarcinoma histology, especially with signet ring cell features (P < 0.001). Optimised IHC could be a useful method in screening ALK rearrangements in clinical practice with qRT-PCR as an alternative diagnostic tool to clarify specific ALK variants.

[169]

TÍTULO / TITLE: High specific detection and near-infrared photothermal therapy of lung cancer cells with high SERS active aptamer-silver-gold shell-core nanostructures.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Wu P; Gao Y; Lu Y; Zhang H; Cai C

AUTORES / AUTHORS: Wu P; Gao Y; Lu Y; Zhang H; Cai C
INSTITUCIÓN / INSTITUTION: Jiangsu Key Laboratory of New Power Batteries, College of Chemistry and Materials Science, Nanjing Normal University, Nanjing 210097, P.R. China. cxcai@njnu.edu.cn.
RESUMEN / SUMMARY: Lung cancer is the leading cause of cancer death worldwide. Its early detection is of paramount importance for diagnosis, classification, treatment, and improvement of survivorship. However, current methods are not sensitive enough to detect lung cancer in its nascent stage. We reported an aptamer-Ag-Au shell-core nanostructure-based surface-enhanced Raman scattering (SERS) assay for sensitive and specific detection, and near-infrared (NIR) photothermal therapy of lung adenocarcinoma cells (A549 cells). The nanostructures target the cells with high affinity and specificity via the specific interaction between the aptamer (a 45-base
oligonucleotide) and the cell, and distinguish A549 cells from other types of cancer cells (HeLa and MCF-7 cells) and subtypes of lung cancer cells (NCI-H157, NCI-H520, NCI-H1299, and NCI-H446 cells). The nanostructures have a high capability to absorb NIR irradiation and are able to perform photothermal therapy of the cells at a very low irradiation power density (0.20 W cm\(^{-2}\)) without destroying the healthy cells and the surrounding normal tissues. In addition, the nanostructures exhibit a high SERS activity. Based on the SERS signal of the labeled Raman reporter (Rh6G molecules), we can specifically detect A549 cells at a very low abundance (approximately 10 cells per mL) and monitor the therapy process of the cancer cells. Therefore, this nanostructure-based SERS assay has great potential in specific recognition, sensitive detection, and effective photothermal therapy of lung cancer.

[170]

**TÍTULO / TITLE:** - Inter-observer reproducibility of semi-automatic tumor diameter measurement and volumetric analysis in patients with lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Dinkel J; Khalilzadeh O; Hintze C; Fabel M; Puderbach M; Eichinger M; Schlemmer HP; Thorn M; Heussel CP; Thomas M; Kauczor HU; Biederer J

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology, University Hospital Heidelberg, Heidelberg, Germany; Department of Radiology, German Cancer Research Center, Heidelberg, Germany; Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany. Electronic address: julien.dinkel@med.uni-heidelberg.de.

**RESUMEN / SUMMARY:** - OBJECTIVES: Therapy monitoring in oncologic patient requires precise measurement methods. In order to improve the precision of measurements, we used a semi-automated generic segmentation algorithm to measure the size of large lung cancer tumors. The reproducibility of computer-assisted measurements were assessed and compared with manual measurements. METHODS: CT scans of 24 consecutive lung cancer patients who were referred to our hospital over a period of 6 months were analyzed. The tumor sizes were measured manually by 3 independent radiologists, according to World Health Organization (WHO) and the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. At least 10 months later, measurements were repeated semi-automatically on the same scans by the same radiologists. The inter-observer reproducibility of all measurements was assessed and compared between manual and semi-automated measurements. RESULTS: Manual measurements of the tumor longest diameter were significantly (p<0.05) smaller compared with the semi-automated measurements. The intra-rater correlations
coefficients were significantly higher for measurements of longest diameter (intra-class correlation coefficients: 0.998 vs. 0.986; p<0.001) and area (0.995 vs. 0.988; p=0.032) using semi-automated compared with manual method. The variation coefficient for manual measurement of the tumor area (WHO guideline, 15.7% vs. 7.3%) and the longest diameter (RECIST guideline, 7.7% vs. 2.7%) was 2-3 times that of semi-automated measurement. CONCLUSIONS: By using computer-assisted size assessment in primary lung tumor, interobserver-variability can be reduced to about half to one-third compared to standard manual measurements. This indicates a high potential value for therapy monitoring in lung cancer patients.

Increased lung cancer risks among hairdressers were observed in large registry-based cohort studies from Scandinavia, but these studies could not adjust for smoking. Our objective was to evaluate the lung cancer risk among hairdressers while adjusting for smoking and other confounders in a pooled database of 16 case-control studies conducted in Europe, Canada, China, and New Zealand between 1985 and 2010 (the Pooled Analysis of Case-Control Studies on the Joint Effects of Occupational Carcinogens in the Development of Lung Cancer). Lifetime occupational and smoking information was collected through interviews with 19,369 cases of lung cancer and 23,674 matched population or hospital controls. Overall, 170 cases and 167 controls had ever worked as hairdresser or barber. The odds ratios for lung cancer in women were 1.65 (95% confidence interval (CI): 1.16, 2.35) without adjustment for smoking and 1.12 (95% CI: 0.75, 1.68) with adjustment for smoking; however, women employed before 1954 also experienced an increased lung cancer risk after adjustment for smoking (odds ratio = 2.66, 95% CI: 1.09, 6.47). The odds ratios in male hairdressers/barbers were generally not elevated, except for an increased odds ratio for adenocarcinoma in long-term barbers (odds ratio = 2.20, 95% CI: 1.02, 4.77). Our results suggest that the increased lung cancer risks among hairdressers are due to their smoking behavior; single elevated risk estimates should be interpreted with caution and need replication in other studies.

AUTORES / AUTHORS:  - Ishigaki Y; Nakamura Y; Tatsuno T; Hashimoto M; Iwabuchi K; Tomosugi N

INSTITUCIÓN / INSTITUTION:  - Medical Research Institute, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku, 920-0293, Japan, ishigaki@kanazawa-med.ac.jp.

RESUMEN / SUMMARY:  - RBM8A (Y14) is carrying RNA-binding motif and forms the tight heterodimer with MAGOH. The heterodimer is known to be a member of exon junction complex on exporting mRNA and is required for mRNA metabolisms such as splicing, mRNA export and nonsense-mediated mRNA decay. Almost all RBM8A-MAGOH complexes localize in nucleoplasm and shuttle between nuclei and cytoplasm for RNA metabolism. Recently, the abnormality of G2/M transition and aberrant centrosome regulation in RBM8A- or MAGOH-deficient cells has been reported. These results prompt us to reevaluate the localization of RBM8A-MAGOH in human cells. Interestingly, our immunostaining experiments showed the localization of these proteins in centrosome in addition to nuclei. Furthermore, the transiently expressed eYFP-tagged RBM8A and Flag-tagged MAGOH also co-localized with centrosome signals. In addition, the proximity ligation in situ assay was performed to detect the complex formation in centrosome. Our experiments clearly showed that Myc-tagged RBM8A and Flag-tagged MAGOH formed a complex in centrosome. GFP-tagged PLK1 also co-localized with Myc-RBM8A. Our results show that RBM8A-MAGOH complex is required for M-phase progression via direct localization to centrosome rather than indirect effect.

[174]

TÍTULO / TITLE:  - Prospective validation of quantitative NSE mRNA in pleural fluid of non-small cell lung cancer patients.

RESUMEN / SUMMARY:  - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS:  - Tang D; Wang M; Sui A; Wang Y; Yang R; Wang Z; Zhao Y; Jiao W; Shen Y

INSTITUCIÓN / INSTITUTION:  - , Qingdao, China.

RESUMEN / SUMMARY:  - Although the survival of lung cancer patients has improved significantly due to the development of early detective tools, lung cancer remains a leading cause of cancer-related death after curative surgery. So it is extremely important for cancer patients to predict early metastasis, especially pleural dissemination, the most frequent type of recurrence in patients after surgery. Based
on a retrospective study of 86 curatively resected lung cancer patients (training set), we determined a cutoff value of NSE mRNA using receiver-operating characteristic curve. Then, we prospectively used this cutoff value to validate the risk of pleural recurrence in a new cohort of 81 lung cancer patients (validation set) between April 2009 and June 2010 by real-time reverse transcriptase-polymerase chain reaction. During the median 27 months of postoperative surveillance, 16 of the 81 patients died, and 9 of the 16 developed pleural metastases. Multivariate analysis with the Cox proportional hazards model showed that positive NSE mRNA was a significant independent risk factor with both overall survival and pleural recurrence-free survival (both P < 0.0001) as end points which were significantly worse in patients with positive NSE mRNA (P < 0.0001). These results indicate that quantitative NSE mRNA in pleural fluid is a reliable prognostic indicator of pleural recurrence in the clinical setting.
change in clinical staging (M0 to M1a) in 10 patients and a change in pathological staging (pleural fluid cytology positive) in 1 patient. The time required for PULC examination was 15 +/- 7 min. There were no complications related to the procedures. CONCLUSIONS: Preoperative pleural ultrasonography is a rapid and effective way to improve precision of staging in patients with lung cancer. More precise staging may allow for more appropriate testing, patient prognostication and operative planning.

[176]
TÍTULO / TITLE: - Exposure-Response Analysis and Risk Assessment for Lung Cancer in Relationship to Silica Exposure: A 44-Year Cohort Study of 34,018 Workers.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Liu Y; Steenland K; Rong Y; Hnizdo E; Huang X; Zhang H; Shi T; Sun Y; Wu T; Chen W
RESUMEN / SUMMARY: - Crystalline silica has been classified as a human carcinogen by the International Agency for Research on Cancer (Lyon, France); however, few previous studies have provided quantitative data on silica exposure, silicosis, and/or smoking. We investigated a cohort in China (in 1960-2003) of 34,018 workers without exposure to carcinogenic confounders. Cumulative silica exposure was estimated by linking a job-exposure matrix to work history. Cox proportional hazards model was used to conduct exposure-response analysis and risk assessment. During a mean 34.5-year follow-up, 546 lung cancer deaths were identified. Categorical analyses by quartiles of cumulative silica exposure (using a 25-year lag) yielded hazard ratios of 1.26, 1.54, 1.68, and 1.70, respectively, compared with the unexposed group. Monotonic exposure-response trends were observed among nonsilicotics (P for trend < 0.001). Analyses using splines showed similar trends. The joint effect of silica and smoking was more than additive and close to multiplicative. For workers exposed from ages 20 to 65 years at 0.1 mg/m3 of silica exposure, the estimated excess lifetime risk (through age 75 years) was 0.51%. These findings confirm silica as a human carcinogen and suggest that current exposure limits in many countries might be insufficient to protect workers from lung cancer. They also indicate that smoking cessation could help reduce lung cancer risk for silica-exposed individuals.

[177]
TÍTULO / TITLE: - FoxP3 genetic variants and risk of non-small cell lung cancer in the Chinese Han population.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
CD4+CD25+ regulatory T cell-mediated immunosuppression is one of the crucial mechanisms that tumor cells use to evade the immune system. The forkhead box P3 (FoxP3) gene regulates regulatory T-cell development and function and may modulate the susceptibility to non-small cell lung cancer (NSCLC). Because a single nucleotide polymorphism (SNP) within the FoxP3 gene (rs3761548 in the promoter region) is associated with susceptibility to Graves' disease, this study detected rs3761548 in a hospital-based case-control study. A total of 192 NSCLC patients and 259 healthy subjects were recruited for the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis of FoxP3 SNP. The data showed that the A allele of rs3761548 significantly increased NSCLC risk (P=0.000, OR=2.32, 95%CI=1.736-3.102). The AC genotype, AA genotype, and the combined A variant genotype (AA+AC) were also associated with a higher risk of NSCLC (OR [95%CI]=2.147[1.419-3.247], 4.413[2.359-8.255], and 2.563[1.746-3.761], respectively). Moreover, a significantly higher frequency of AA+AC genotype was observed in patients with stage II NSCLC (OR, 2.053; 95%CI, 1.033-4.078). In conclusion, the data from the current study demonstrated for the first time the association of the FoxP3 SNP with a risk of developing NSCLC in the Chinese Han population.

[178]

CK2 inhibitor CX4945 induces sequential inactivation of proteins in the signaling pathways related with cell migration and suppresses metastasis of A549 human lung cancer cells.
cancers including prostate cancer. Here we report that migration and invasion of A549 human lung cancer cells are suppressed by the inhibition of CK2 induced by CX4945. We found that CX4945 sequentially attenuates the proteins in PI3K/Akt and MAPK pathways, two signaling pathways related with cell migration. This sequential control of signal pathways inhibits the expression of membrane type 1-matrix metalloproteinase and this leads to the selective attenuation of one of the gelatinases, MMP-2, which can degrade components of extracellular matrix, and metastasis of A549 human lung cancer cell.

[179]

TÍTULO / TITLE: - The EDA-containing cellular fibronectin induces epithelial-mesenchymal transition in lung cancer cells through integrin alpha9beta1-mediated activation of PI3-K/AKT and Erk1/2.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


•• Enlace al texto completo (gratuito o de pago) 1093/carcin/bgt276

AUTORES / AUTHORS: - Sun X; Fa P; Cui Z; Xia Y; Sun L; Li Z; Tang A; Gui Y; Cai Z

INSTITUCIÓN / INSTITUTION: - Department of Biobank, Shenzhen Tumor Clinical Immune Gene Therapy Engineering Lab, Shenzhen Second People’s Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518035, China.

RESUMEN / SUMMARY: - Cellular fibronectin (cFN) is one of the main components of tissue extracellular matrices and is involved in multiple physiologic and pathologic processes such as embryogenesis, wound healing, inflammation and tumor progression. The function of fibronectin in regulating normal cell adhesion and migration is well documented, but its function in cancer progression is only partially unraveled. We have reported previously that fibronectin stimulates the proliferation and survival of non-small lung carcinoma cells through upregulation of pro-oncogenic signals related to cyclooxygenase-2/phosphatidylinositol-3-kinase/protein kinase B (COX-2/PI3-K/AKT)/mammalian target of rapamycin triggered by activation of the integrin alpha5beta1. Here, we extend these studies by showing that fibronectin promotes epithelial-mesenchymal transition (EMT) in lung cancer cells. We found that cFN, but not plasma fibronectin or type 1 collagen, induces lung carcinoma cell scattering in vitro, promotes cell migration and invasion of Matrigel and stimulates the expression of the mesenchymal marker alpha-smooth muscle actin while decreasing the expression of the epithelial marker E-cadherin through PI3-K and Erk pathways. Interestingly, the extra domain A (EDA) within cFN was found to be crucial for this process, as confirmed by testing cells overexpressing EDA or cells exposed to EDA-containing matrices. We found that the integrin alpha9, but not alpha5, mediated cFN-induced EMT as silencing integrin alpha9 neutralized cFN-induced EMT. Overall,
our findings show that the EDA domain within cFN induces EMT in lung carcinoma cells through integrin alpha9-mediated activation of PI3-K and Erk.

[180]

TÍTULO / TITLE: - The Integration of Multimodality Care for the Treatment of Small Cell Lung Cancer in a Rural Population and Its Impact on Survival.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago)
1097/COC.0b013e3182a5346d
AUTORES / AUTHORS: - Lee K; Kloecker G; Pan J; Rai S; Dunlap NE
INSTITUCIÓN / INSTITUTION: - Departments of *Radiation Oncology daggerMedical Oncology double daggerBiostatistics Shared Facility, James Graham Brown Cancer Center, University of Louisville, Louisville, KY.
RESUMEN / SUMMARY: - OBJECTIVES:: Many factors and disparities contribute to the multidisciplinary management of small cell lung cancer (SCLC). Our objective was to conduct a cancer registry analysis of patients with SCLC in Kentucky to identify factors affecting treatment choice and mortality. METHODS:: Database collection was done through the Kentucky Cancer Registry, which is part of the Surveillance, Epidemiology, and End Results program. Patients diagnosed between 1995 and 2008, diagnosed with SCLC, and AJCC stage I through IV were included. Statistical analyses were performed to identify variables affecting initial treatment choice and survival. RESULTS:: Analysis evaluated 4814 patients from the Kentucky Cancer Registry. For extensive stage, age (P<0.001) and urban versus rural county (P=0.03) were significantly associated with the type of treatment received. Age was the only variable impacting treatment choice in limited-stage patients. Limited stage patients were more likely to receive chemotherapy and radiation (chemoRT; 54.6% vs. 46.5%). On multivariate analysis, for extensive stage patients, age at diagnosis, male sex, and treatments other than chemoRT were variables associated for increased risk of death. In limited stage patients, increasing age, and treatments other than chemoRT were variables associated with increased risk of death. Survival was significantly improved in both limited stage and extensive stage patients that received chemoRT compared with chemotherapy only, radiation only, or no treatment. CONCLUSIONS:: Treatment with chemoRT was associated with improved survival in patients with limited and extensive stage SCLC. In these patients, socioeconomic, racial, or geographic factors did not impact the type of treatment received or survival.

[181]
Somatic mutation of KIT is rare in small cell lung cancer patients from Northeast China.

Studies have confirmed that protein overexpression or mutations of KIT are involved in growth and development of a variety of cancers, however, little is known about data of gene mutation and protein expression in small cell lung cancer (SCLC) patients from northeast China. The aim of study is to investigate gene mutation and protein expression in such patients with small cell lung cancer (SCLC) and analyse their clinical significance. The expression of c-Kit protein was analyzed by immunohistochemistry in 77 SCLC samples and 22 normal lung samples. KIT mutations were screened in exons 9, 11, 13, 14, 17 and 18 by DNA direct sequencing. The study showed that positive staining for c-Kit was observed in 28 of 77 SCLC patients. There was no correlations between expression of c-Kit and sex, ages, smoking status, stage. only 1 case was found to have known T801I mutation in exon 17. The median survival (13.9 months) of cases with c-Kit-positive was shorter than that (19.9 months) of cases with c-Kit-negative. The finding revealed that stages was identified as an independent predictive factor for SCLC patients. Our finding reveals that somatic mutation of KIT is rare in SCLC patients from the northeast China and there is no enough evidence confirming KIT inhibitors for treatment in SCLC.

[182]

Succinate dehydrogenase 5(SDH5) regulate (GSK)-3beta-beta-catenin-mediated lung cancer metastasis.

We demonstrate that loss of SDH5 expression initiates epithelial-mesenchymal transition (EMT), which is visualized by the repression of E-cadherin and up-regulation of vimentin in lung cancer cell lines and clinical lung cancer specimens. In SDH5 knockout mice, lung epithelial cells exhibited elevated mesenchymal markers, which is characteristic of EMT. Using a human lung xenograft-mouse model, we observed that knocking down endogenous SDH5 in human
carcinoma cells leads to the development of multiple lymph node metastases. Moreover, our data indicate that SDH5 functions as a critical protein in regulating EMT by modulating the (GSK)-3beta-beta-catenin signaling pathway. These results reveal a critical role for SDH5 in EMT and suggest that SDH5 may be a prognostic biomarker and potential therapeutic target for lung cancer metastasis.

[183]

TÍTULO / TITLE: - Comprehensive assessment of the association between DNA repair gene XRCC3 rs861539 C/T polymorphism and lung cancer risk.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Ding G; Xu W; Hua H; Huang Q; Liang H; Ni Y; Ding Z
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Chongming Branch of Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 202150, China.
RESUMEN / SUMMARY: - A few case-control studies were performed to assess the association between X-ray repair cross-complementing group 3 (XRCC3) rs861539 C/T polymorphism and lung cancer susceptibility, but no consistent finding was reported. In the present study, we performed a meta-analysis of 14 case-control studies with a total of 7,869 lung cancer cases and 10,778 controls to provide a comprehensive assessment of the association between XRCC3 rs861539 C/T polymorphism and lung cancer risk. Pooled odds ratios (ORs) and corresponding 95 % confidence intervals (95 % CIs) were calculated to assess the strength of the association. Overall, there was no significant association between XRCC3 rs861539 C/T polymorphism and lung cancer risk under all genetic models [OR (95 % CI) for T versus C, 1.00 (0.89-1.13), P = 0.99; OR (95 % CI) for TT versus CC, 1.07 (0.81-1.41), P = 0.62; OR (95 % CI) for TT/CT versus CC, 0.95 (0.84-1.07), P = 0.39; OR (95 % CI) for TT versus CT/CC, 1.10 (0.86-1.39), P = 0.62]. In the subgroup analyses of both Asians and Caucasians, there was still no significant association between XRCC3 rs861539 C/T polymorphism and lung cancer risk under all genetic models (All P values were more than 0.05). However, there was an obvious association between XRCC3 rs861539 C/T polymorphism and decreased risk of lung cancer in the subgroup analysis of the mixed population (All P values were less than 0.05). In addition, there was some risk of publication bias in the meta-analysis, and there was obvious discrepancy in the findings between studies with large sample size and studies with small sample size in the meta-analysis. The meta-analysis indicates that the association between XRCC3 rs861539 C/T polymorphism and lung cancer risk is still uncertain owing to the obvious discrepancy in the findings between studies with large sample size and studies with small sample size. More studies with large sample size are needed to further assess the association.
PURPOSE: To calculate the burden of lung cancer illness due to radon for all thirty-six health units in Ontario and determine the number of radon-attributable lung cancer deaths that could be prevented. METHODS: We calculated the population attributable risk percent, excess life-time risk ratio, life-years lost, the number of lung cancer deaths due to radon, and the number of deaths that could be prevented if all homes above various cut-points were effectively reduced to background levels. RESULTS: It is estimated that 13.6 % (95 % CI 11.0, 16.7) of lung cancer deaths in Ontario are attributable to radon, corresponding to 847 (95 % CI 686, 1,039) lung cancer deaths each year, approximately 84 % of these in ever-smokers. If all homes above 200 Bq/m3, the current Canadian guideline, were remediated to background levels, it is estimated that 91 lung cancer deaths could be prevented each year, 233 if remediation was performed at 100 Bq/m3. There was important variation across health units. CONCLUSIONS: Radon is an important contributor to lung cancer deaths in Ontario. A large portion of radon-attributable lung cancer deaths are from exposures below the current Canadian guideline, suggesting interventions that install effective radon-preventive measures into buildings at build may be a good alternative population prevention strategy to testing and remediation. For some health units, testing and remediation may also prevent a portion of radon-related lung cancer deaths. Regional attributable risk estimates can help with local public health resource allocation and decision making.

[185]
TITULO / TITLE: - Promoter methylation profiles between human lung adenocarcinoma multidrug resistant A549/cisplatin (A549/DDP) cells and its progenitor A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Guo R; Wu G; Li H; Qian P; Han J; Pan F; Li W; Li J; Ji F
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, 324th Hospital of the People’s Liberation Army, Chongqing 400020, China. fairy780308@163.com
RESUMEN / SUMMARY: - Although aberrant DNA methylation has been implicated in the pathophysiology of lung cancer, the role of methylation in multidrug resistance (MDR) of lung cancer has remained unclear. To investigate whether certain distinct DNA methylation pattern is associated with acquired MDR of lung adenocarcinoma, methylated-DNA immunoprecipitation-chromatin immunoprecipitation (MeDIP-ChIP) was utilised to compare the genome-wide promoter methylation of the human lung adenocarcinoma MDR A549/cisplatin (A549/DDP) cells with its progenitor A549 cells. The comparison identified 3617 genes with differentially methylated promoter, of which 1581 were hypermethylated and 2036 were hypomethylated. Then, bisulphite sequencing polymerase chain reaction (PCR) (BSP) and quantitative reverse transcription (RT)-PCR (Q-PCR) were used to validate the promoter methylation of five candidate genes and to determine whether the expression of genes was associated with the promoter methylation. BSP confirmed that the promoter methylation incidence of the hypermethylated genes, G protein-coupled receptor 56 isoform 3 (GPR56), metallothionein 1G (MT1G), and RAS association domain family gene 1 (RASSF1), was significantly higher in A549/DDP cells compared with A549 cells (p<0.001, p=0.0099, and p=0.0165), whereas no significant difference was found in that of the other two genes, CCNL2 and BAD (p=0.0594 and p=0.5546). Additionally, Q-PCR showed that the mRNA expression of the three hypermethylated genes was significantly lower in A549/DDP cells compared with A549 cells (all p<0.001). In conclusion, this study reported for the first time that a distinct promoter methylation pattern is associated with MDR of lung adenocarcinoma A549/DDP cells and suggested that GPR56, MT1G, and RASSF1 might be the potential methylation markers associated with acquired MDR of lung adenocarcinoma.

[186]

TÍTULO / TITLE: - 18F-FDG PET/CT in suspected recurrences of epithelial malignant pleural mesothelioma in asbestos-fibers-exposed patients (comparison to standard diagnostic follow-up).

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Niccoli-Asabella A; Notaristefano A; Rubini D; Altini C; Ferrari C; Merenda N; Fanelli M; Rubini G

INSTITUCIÓN / INSTITUTION: - Nuclear Medicine Unit-University of Bari “Aldo Moro,” Italy. Electronic address: artor.niccoliasabella@uniba.it.

RESUMEN / SUMMARY: - This retrospective study evaluated the role of 18-fluorine-labeled 2-deoxy-2-fluoro-d-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) in patients with previous occupational or
environmental exposure to asbestos, with histopathological diagnosis of epithelial malignant pleural mesothelioma and suspected recurrences, comparing the data from 18F-FDG PET/CT and computed tomography with contrast enhancement (CECT). 18F-FDG PET/CT has greater sensitivity than CECT in identifying local extent, lymph nodes, and metastasis. 18F-FDG PET/CT whole-body explorations are useful to monitor the follow-up and evaluate the metabolic response to chemo- and radiotherapy, modifying the scheduled treatment plan.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lee JK; Kim KC
INSTITUCIÓN / INSTITUTION: - Medical and Bio-Material Research Center, Department of Biological Sciences, College of Natural Sciences, Kangwon National University, Chuncheon 200-701, Republic of Korea.
RESUMEN / SUMMARY: - 3-Dezaeplanocin A (DZNep), an epigenetic anticancer drug, leads to the indirect suppression of S-adenosyl methionine-dependent cellular methylations by inhibiting S-adenosyl homocystein (AdoHcy) hydrolase. Although it is well known that DZNep targets the degradation of EZH2 protein, H3K27me3 HMTase, there are still uncertainties about the regulation of other types of HMTases during cell death. In this study, we describe that SETDB1 gene expression was regulated by DZNep treatment in human lung cancer cells. We confirm that DZNep induced growth inhibition and increased the dead cell population of lung cancer cells. DZNep treatment affected histone methylations, including H3K27me3 and H3K9me3, but not H3K4me3. Reduced levels of H3K27me3 and H3K9me3 were related with the decreased EZH2 and SETDB1 proteins. Real time PCR analysis showed that SETDB1 gene expression was decreased by DZNep treatment, but no effect was observed for EZH2 gene expression. We cloned the promoter region of SETDB1 and SUV39H1 genes, and performed luciferase assays. The promoter activity of SETDB1 gene was down regulated by DZNep treatment, whereas no effect on SUV39H1 promoter activity was observed. In conclusion, we suggest that DZNep regulates not only on H3K27me3 HMTase EZH2, but also H3K9 HMTase SETDB1 gene expression at the transcription level, implicating that the mechanism of action of DZNep targets multiple HMTases during the death of lung cancer cells.

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An exploration of pathways involved in lung carcinoid progression using gene expression profiling.

Pulmonary carcinoids comprise a well-differentiated subset of neuroendocrine tumors usually associated with a favorable prognosis, but mechanisms underlying disease progression are poorly understood. In an explorative approach to identify pathways associated with progression, we compared gene expression profiles of tumors from five patients with a favorable and five with a poor disease outcome. Differentially expressed genes were validated using quantitative real-time PCR on 65 carcinoid tumors, in combination with survival analysis. One of the identified pathways was further examined using immunohistochemistry. As compared with other chromosomal locations, a significantly higher number of genes downregulated in carcinoids with a poor prognosis were located at chromosome 11q (P = 0.00017), a region known to be frequently lost in carcinoids. In addition, a number of upregulated genes were found involved in the mitotic spindle checkpoint, the chromosomal passenger complex (CPC), mitotic kinase CDC2 activity and the BRCA-Fanconi anemia pathway. At the individual gene level, BIRC5 (survivin), BUB1, CD44, IL20RA, KLK12 and OTP were independent predictors of patient outcome. For survivin, the number of positive nuclei was also related to poor prognosis within the group of carcinoids. Aurora B kinase and survivin, major components of the CPC, were particularly upregulated in high-grade carcinomas and may therefore comprise therapeutic targets for these tumors. To our knowledge, this is the first expression profiling study focusing specifically on pulmonary carcinoids and progression. We have identified novel pathways underlying malignant progression and validated several genes as being strong prognostic indicators, some of which could serve as putative therapeutic targets.

Multiple Endocrine Disruption by the MET/ALK Inhibitor Crizotinib in Patients With Non-Small Cell Lung Cancer.

Pulmonary carcinoids comprise a well-differentiated subset of neuroendocrine tumors usually associated with a favorable prognosis, but mechanisms underlying disease progression are poorly understood. In an explorative approach to identify pathways associated with progression, we compared gene expression profiles of tumors from five patients with a favorable and five with a poor disease outcome. Differentially expressed genes were validated using quantitative real-time PCR on 65 carcinoid tumors, in combination with survival analysis. One of the identified pathways was further examined using immunohistochemistry. As compared with other chromosomal locations, a significantly higher number of genes downregulated in carcinoids with a poor prognosis were located at chromosome 11q (P = 0.00017), a region known to be frequently lost in carcinoids. In addition, a number of upregulated genes were found involved in the mitotic spindle checkpoint, the chromosomal passenger complex (CPC), mitotic kinase CDC2 activity and the BRCA-Fanconi anemia pathway. At the individual gene level, BIRC5 (survivin), BUB1, CD44, IL20RA, KLK12 and OTP were independent predictors of patient outcome. For survivin, the number of positive nuclei was also related to poor prognosis within the group of carcinoids. Aurora B kinase and survivin, major components of the CPC, were particularly upregulated in high-grade carcinomas and may therefore comprise therapeutic targets for these tumors. To our knowledge, this is the first expression profiling study focusing specifically on pulmonary carcinoids and progression. We have identified novel pathways underlying malignant progression and validated several genes as being strong prognostic indicators, some of which could serve as putative therapeutic targets.
OBJECTIVES: Non-small cell lung cancer (NSCLC) is a heterogenous group of disorders that can be subclassified based upon molecular characterization. Anaplastic lymphoma kinase translocation and MET aberrations occur in a subset of NSCLC. Anaplastic lymphoma kinase/MET have been shown to be inhibited by the small molecule tyrosine kinase inhibitor crizotinib. Recently, crizotinib was shown to decrease testosterone in males. Herein, we describe the effects of crizotinib on multiple hormonal axes.

MATERIALS AND METHODS: Seven consecutive patients with NSCLC who were receiving crizotinib as part of their standard care were evaluated for hormonal disruptions.

RESULTS: Primary hypogonadism was detected in 4/5 of males, whereas mildly elevated prolactin was observed in 4/7 patients. Hypocalcemia was observed in 3/7 patients. Interestingly, 5/7 patients had elevated levels of insulin-like growth factor-1 (IGF-1) levels, and the remaining 2 individuals had levels that were near the upper limits of the normal range.

CONCLUSIONS: Because of cellular cross-talk between MET and IGF-1 signaling, elevated IGF-1 levels induced by crizotinib treatment may have implications for long-term drug efficacy. Furthermore, this finding suggests a potential avenue of therapeutic synergy, namely coordinate inhibition of the MET and IGF-1 signaling pathways. Finally, as crizotinib has been recently approved, it is prudent to check hormone and calcium biomarkers and correct noted deficiencies for improved outcomes and quality of life.
Department of the Hospital Virgen de la Victoria (Malaga) during the same period.

Results: Of the 4721 HIV patients (83% men) followed-up during the study period, 61 (1.29%) developed LC; 82% men, mean age 48 years, all except two smokers, 47.5% with a prior lung infection, and median CD4 cells 237/mm3. Forty (65.5%) patients were on antiretroviral therapy at LC diagnosis (70% had an undetectable viral load). HIV-negative group was older at diagnosis, contained fewer active smokers, greater frequency of the squamous cell carcinoma histological subtype and fewer cases of adenocarcinoma. Presentation was advanced in both groups and the median survival of HIV patients was three months.

Conclusions: LC is a common tumour in HIV patients. It affects men and women equally, with a history of smoking and often a prior opportunistic lung disease. Affected patients are often immunosuppressed and have AIDS.

[191] RESUMEN / SUMMARY: - To determine whether the bleomycin (BLM)-induced bystander response occurs in human brain glioblastoma (BMG-1) cells, the BMG-1 cells were exposed to two different concentrations of BLM. The co-culture methodology was adopted to study the in vitro bystander effects. DNA damage was measured using the micronucleus (MN) and gamma-H2AX assays. Cytotoxicity was measured using the trypan blue assay. Cell cycle kinetics was analyzed using flow cytometry. The overall results did not show any significant increase in either genotoxicity or cytotoxicity or a delay in the cell cycle kinetics in BMG-1 bystander cells co-cultured with BLM-exposed cells, suggesting that BLM did not induce a bystander response in the BMG-1 cells. Furthermore, the MN results of the BLM-exposed BMG-1 cells co-cultured with unexposed bystander human lung adenocarcinoma (A549 and NCI-H460) cells and vice versa suggested that the BMG-1 cells do not secrete bystander signals but do respond to those signals. Analyzing the underlying mechanism and pathways involved in preventing the cells from secreting bystander signals will provide new insights that can be applied to inhibit these mechanisms in other cell types, thereby preventing and
controlling the bystander response and genomic instability and increasing the therapeutic gain in chemotherapy.

[192]

**TÍTULO / TITLE:** Can dogs smell lung cancer? First study using exhaled breath and urine screening in unselected patients with suspected lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Acta Oncol. 2013 Aug 19.

**AUTORES / AUTHORS:** Amundsen T; Sundstrom S; Buvik T; Gederaas OA; Haaverstad R

**INSTITUCIÓN / INSTITUTION:** Department of Thoracic Medicine, St. Olavs Hospital HF, Trondheim, Norway.

**RESUMEN / SUMMARY:** Background. On the basis of our own experience and literature search, we hypothesised that a canine olfactory test may be useful for detecting lung cancer in an unselected population of patients suspected to have lung cancer. Material and methods. We conducted a prospective study of 93 patients consecutively admitted to hospital with suspected lung cancer. Exhaled breath and urine were sampled before the patients underwent bronchoscopy. The canine olfactory test was performed in a double-blinded manner. Sensitivity and specificity were outcome measures. Results. With 99% sensitivity, the olfactory test demonstrated that dogs have the ability to distinguish cancer patients from healthy individuals. With an intensified training procedure, the exhaled breath and urine tests showed sensitivity rates of 56-76% and specificity rates of 8.3-33.3%, respectively, in our heterogeneous study population. Conclusion. Although the olfactory test appears to be a promising tool for the detection of cancer, the main challenge is to determine whether the test can sufficiently discriminate between patients at risk, patients with benign disease, and patients with malignant disease. We need to gain a deeper understanding of this test and further refine it before applying it as a screening tool for lung cancer in clinical settings.

[193]

**TÍTULO / TITLE:** Inter-tester reproducibility of tumour change in small cell lung cancer patients undergoing chemoradiotherapy.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Ellegaard MB; Knap MM; Hoffmann L
Resumen / Summary: Abstract Background. Tumour volume change during delivery of chemoradiotherapy is observed in small cell lung cancer (SCLC) patients. In this study, we have compared tumour volume and anatomical changes, e.g. atelectasis or pleural effusions determined by three different methods. Method. A total of 37 SCLC patients undergoing thoracic radiotherapy during 2010-2011 were included. The patients were treated based on a daily three-dimensional (3D) cone beam computed tomography (CBCT) bony anatomy registration. The CBCT scans were retrospectively reviewed visually by a radiation therapist (Visual-RTT) in order to register tumour volume changes. Furthermore, the tumour volume changes were obtained by either deformable image registration (DIR) or delineation by a radiation oncologist (RO). Kappa (kappa) statistics and paired t-tests were used for evaluation of the inter-tester agreement. Results. The tumour volume change between the Visual-RTT, the DIR and the RO assessments obtained 84-97% agreement (kappa = 0.68-0.95). Furthermore, there was no statistically significant difference between the tumour change assessment of the RO (mean 13.6 ml) and the DIR (mean 14.5 ml), p = 0.59. Tumour shrinkage was observed in 15 (41%) patients and anatomical changes in seven (19%) patients. Conclusion. The inter-tester reproducibility of tumour volume change between the three methods is excellent. Visual-RTT on-line inspection may be used to determine tumour shrinkage and anatomical changes as atelectasis or pleural effusions during the radiotherapy course by use of daily CBCT scans.

[194]
Título / Title: LKB1 loss by alteration of the NKX2-1/p53 pathway promotes tumor malignancy and predicts poor survival and relapse in lung adenocarcinomas.
Resumen / Summary: Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1038/onc.2013.353
Autores / Authors: Tsai LH; Chen PM; Cheng YW; Chen CY; Sheu GT; Wu TC; Lee H
Institución / Institution: [1] Institute of Medical and Molecular Toxicology, Taichung, Taiwan [2] Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan.
Resumen / Summary: LKB1 loss is a frequent homozygous deletion and/or gene mutation found in lung adenocarcinomas. However, few cases of LKB1 loss by either deletion or mutation are seen in Asian patients. Our preliminary data showed that LKB1 loss was associated with p53 mutation in lung tumors from Taiwanese adenocarcinoma patients and p53 transcription is directly regulated by NKX2-1. Therefore, we hypothesized that LKB1 loss could occur due to aberration of p53 regulation mediated by NKX2-1. In the present study, 16 lung adenocarcinoma cell lines were investigated to determine if LKB1 transcription could be deregulated by...
NKX2-1-mediated p53 aberration. Mechanistic studies indicated that LKB1 was directly upregulated by p53 and that NKX2-1-mediated p53 expression may positively regulate LKB1 expression in p53 wild-type cells. However, in p53-mutated cells, LKB1 transcription was deregulated by NKX2-1 via suppression of SP1 binding onto the LKB1 promoter. Therefore, the action of the NKX2-1/p53 pathway on LKB1 loss differed in p53 wild-type versus p53-mutated cells. As expected, soft-agar growth and invasion capability was significantly reduced by ectopic expression of NKX2-1 in p53 wild-type cells, but it was markedly elevated by silencing NKX2-1 in p53-mutated cells. Similar reciprocal observations were also seen in lung tumors from lung adenocarcinoma patients with either wild-type or mutated p53 tumors. Cox regression analysis showed that patients with low-LKB1 tumors had poorer overall survival (OS) and relapse-free survival (RFS) when compared with patients with high-LKB1 tumors. In p53 wild-type patients, shorter OS and RFS periods were predicted for low-NKX2-1/low-LKB1 tumors than for high-NKX2-1/high-LKB1 tumors. In patients with p53-mutated tumors, poorer OS and RFS were predicted for high-NKX2-1/low-LKB1 tumors than for low-NKX2-1/high-LKB1 tumors. In summary, losses of LKB1 at the transcriptional level by altered activity of the NKX2-1/p53 pathway may promote tumor malignancy and poor patient outcome. Oncogene advance online publication, 2 September 2013; doi:10.1038/onc.2013.353.

[195]

**TÍTULO / TITLE:** Paraneoplastic neurological syndrome in a patient with squamous cell lung cancer.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** Mori H; Yamada O; Ohno Y; Kaito D; Yanase K; Ito F; Endo J; Morishita M; Funaguchi N; Minatoguchi S
**INSTITUCIÓN / INSTITUTION:** Department of Respiratory Medicine, Hashima Community Medical Center, Japan.
**RESUMEN / SUMMARY:** A 78-year-old man presented with urinary retention and difficulty walking. Both legs showed muscle weakness, and he was experiencing lower body hypoesthesia. T2-weighted magnetic resonance imaging revealed lesions with high signal intensity and enhancement in the spinal cord and cerebrum. A cerebrospinal fluid specimen showed inflammatory changes, but negative cytology findings. Chest computed tomography revealed a tumor measuring 40 mm in diameter, and a lung biopsy revealed the presence of squamous cell carcinoma. We diagnosed the patient with paraneoplastic neurological syndrome related to lung cancer. The patient was treated with steroid pulse therapy and chemotherapy, which relieved the symptoms and enabled the patient to achieve an independent gait.
TÍTULO / TITLE: - Paraneoplastic focal segmental glomerulosclerosis in a patient with lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Tadokoro A; Ishii T; Takahama T; Watanabe N; Takano K; Kanaji N; Imataki O; Dobashi H; Bandoh S; Matsunaga T
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Japan.
RESUMEN / SUMMARY: - Focal segmental glomerulosclerosis (FSGS) is extremely rare among paraneoplastic nephrotic syndromes. We herein report a case of lung adenocarcinoma with nephrotic syndrome caused by paraneoplastic FSGS. A 68-year-old man visited our hospital for an evaluation of a right hilar mass on chest radiography and supraclavicular lymphadenopathy. Because an aspiration biopsy of the supraclavicular lymph node revealed adenocarcinoma, the patient was diagnosed with lung adenocarcinoma. He also had nephrotic syndrome, and the pathological findings of the renal biopsy demonstrated FSGS. Standard-dose carboplatin-containing chemotherapy led to a partial response for lung cancer and improved the patient’s nephrotic syndrome without causing any adverse renal effects.

TÍTULO / TITLE: - PPAPDC1B and WHSC1L1 Are Common Drivers of the 8p11-12 Amplicon, Not Only in Breast Tumors But also in Pancreatic Adenocarcinomas and Lung Tumors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mahmood SF; Gruel N; Nicolle R; Chapeaublanc E; Delattre O; Radvanyi F; Bernard-Pierrot I
INSTITUCIÓN / INSTITUTION: - Centre National de la Recherche Scientifique, UMR 144, Institut Curie, Paris, France; Research Center, Institut Curie, Paris, France.
RESUMEN / SUMMARY: - Amplification of the 8p11-12 chromosomal region is a common genetic event in many epithelial cancers. In breast cancer, several genes within this region have been shown to display oncogenic activity. Among these genes, the enzyme-encoding genes, PPAPDC1B and WHSC1L1, have been identified as potential therapeutic targets. We investigated whether PPAPDC1B and WHSC1L1 acted as general driver genes, thereby serving as therapeutic targets in other tumors with 8p11-
12 amplification. By using publicly available genomic data from a panel of 883 cell lines derived from different cancers, we identified the cell lines presenting amplification of both WHSC1L1 and PPAPDC1B. In particular, we focused on cell lines derived from lung cancer and pancreatic adenocarcinoma and found a correlation between the amplification of PPAPDC1B and WHSC1L1 with their overexpression. Loss-of-function studies based on the use of siRNA and shRNA demonstrated that PPAPDC1B and WHSC1L1 played a major role in regulating the survival of pancreatic adenocarcinoma and small-cell lung cancer-derived cell lines, both in anchorage-dependent and anchorage-independent conditions, displaying amplification and overexpression of these genes. We also demonstrated that PPAPDC1B and WHSC1L1 regulated xenograft growth in these cell lines. Finally, quantitative RT-PCR experiments after PPAPDC1B and WHSC1L1 knockdown revealed exclusive PPAPDC1B and WHSC1L1 gene targets in small-cell lung cancer and pancreatic adenocarcinoma-derived cell lines compared with breast cancer.

[198]
TÍTULO / TITLE: - Mst1 overexpression inhibited the growth of human non-small cell lung cancer in vitro and in vivo.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1038/cgt.2013.40
AUTORES / AUTHORS: - Xu CM; Liu WW; Liu CJ; Wen C; Lu HF; Wan FS
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Basic Medical College of Nanchang University, Nanchang, China.
RESUMEN / SUMMARY: - Mammalian STE20-like kinase 1 (Mst1) ubiquitously encodes serine threonine kinase, which is a 59-kDa class II GC kinase that shares 76% identity in amino-acid sequence with MST2, and is the closest mammalian homolog of Drosophila Hippo protein kinase, a major inhibitor of cell proliferation in Drosophila. Recent studies have shown that Mst1 and Mst2 perform tumor-suppressor function in a redundant manner and were originally identified as pro-apoptotic cytoplasmic kinases important for controlling cell growth, proliferation, apoptosis and organ size. We used recombinant eukaryotic expression vector containing human wild-type Mst1 gene to transfect human non-small cell lung cancer (NSCLC) A549 cells in vitro and in vivo. The results showed that Mst1 overexpression inhibited cell proliferation and induced apoptosis of A549 cells, promoted Yes-associated protein (YAP) (Ser127) phosphorylation and downregulated the transcriptional level of Cystein-rich protein connective tissue growth factor (CTGF), amphiregulin (AREG) and Survivin. In human NSCLC-cell-A549-xenograft models, Mst1 gene or cisplatin alone suppressed the growth of tumors and increased the cytoplasm-positive expression levels of YAP and
Phospho-YAP (Ser127) proteins; however, their combination had the strongest anticancer effects. Overall, Mst1 has an important role in inhibiting the growth of NSCLC in vitro and in vivo; its antiproliferative effect is associated with induction of apoptosis through promotion of the cytoplasmic localization and phosphorylation of YAP protein at Ser127 site, indicating that Mst1 may be developed as a promising therapeutic target for NSCLC.

[199]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Khakwani A; Rich AL; Powell HA; Tata LJ; Stanley RA; Baldwin DR; Duffy JP; Hubbard RB
INSTITUCIÓN / INSTITUTION: - Division of Epidemiology and Public Health, University of Nottingham, Nottingham NG5 1PB, UK.
RESUMEN / SUMMARY: - Background: In comparison with other European and North American countries, England has poor survival figures for lung cancer. Our aim was to evaluate the changes in survival since the introduction of the National Lung Cancer Audit (NLCA). Methods: We used data from the NLCA to identify people with non-small-cell lung cancer (NSCLC) and stratified people according to their performance status (PS) and clinical stage. Using Cox regression, we calculated hazard ratios (HRs) for death according to the year of diagnosis from 2004/2005 to 2010; adjusted for patient features including age, sex and co-morbidity. We also assessed whether any changes in survival were explained by the changes in surgical resection rates or histological subtype. Results: In this cohort of 120 745 patients, the overall median survival did not change; but there was a 1% annual improvement in survival over the study period (adjusted HR 0.99, 95% confidence interval (CI) 0.98-0.99). Survival improvement was only seen in patients with good PS and early stage (adjusted HR 0.97, 95% CI 0.95-0.99) and this was partly accounted for by changes in resection rates. Conclusion: Survival has only improved for a limited group of people with NSCLC and increasing surgical resection rates appeared to explain some of this improvement. British Journal of Cancer advance online publication, 19 September 2013; doi:10.1038/bjc.2013.572 www.bjcancer.com.

[200]
El riesgo de cáncer de pulmón entre trabajadores de turnos nocturnos es desconocido. Durante más de 20 años de seguimiento (1988-2008), documentamos 1,455 casos de cáncer de pulmón incidente entre 78,612 mujeres en el estudio de salud de las enfermeras. Para examinar la relación entre el trabajo de turnos nocturnos rotatorio y el riesgo de cáncer de pulmón, utilizamos modelos de riesgo de vida proporcional multivariante ajustados por detalles de características de fumado y otros factores de riesgo. Observamos un riesgo aumentado del 28% de cáncer de pulmón entre mujeres con 15 o más años trabajando turnos de noche rotatorios (riesgo relativo multivariante (RR) = 1.28, intervalo de confianza (IC) 95%: 1.07, 1.53; pr = 0.03) en comparación con mujeres que no trabajaban turnos de noche. Esta asociación fue más fuerte para los carcinomas de células pequeñas de pulmón (RR multivariante = 1.56, IC 95%: 0.99, 2.47; pr = 0.03) y no se observó para adenocarcinomas de pulmón (RR multivariante = 0.91, IC 95%: 0.67, 1.24; pr = 0.40). Además, el riesgo aumentado asociado con 15 o más años de trabajo de noche rotatorio se limitó a fumadores actuales (RR = 1.61, IC 95%: 1.21, 2.13; pr < 0.001), con no asociación observada en no fumadores (pr de interacción = 0.03). Estos resultados sugieren que hay aumentos modestos de riesgos de cáncer de pulmón asociados con períodos de trabajo de noche rotatorio prolongado entre fumadores, pero no entre no fumadores. Aunque es posible que esta observación esté confundida residualmente por el fumado, nuestros hallazgos también podrían proporcionar evidencia de un desorden circadiano como un “segundo golpe” en la etiología de los tumores de pulmón relacionados con el fumado.

[201]
**Título / Title:** Erlotinib Response in an NSCLC Patient with a Novel Compound G719D+L861R Mutation in EGFR.

**Resumen / Summary:** Enlace al Resumen / Link to its Summary

**Revista / Journal:** J Thorac Oncol. 2013 Sep;8(9):e83-4. doi:10.1097/JTO.0b013e31829ceb8d.

**Autores / Authors:** Berge EM; Aisner DL; Doebele RC

**Institución / Institution:** *Departments of Medicine, Division of Medical Oncology, daggerPathology, University of Colorado School of Medicine, Aurora, Colorado.

[202]
**Título / Title:** Outcomes following surgical treatment compared to radiation for stage I NSCLC: A SEER database analysis.

**Resumen / Summary:** Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 10.1016/j.lungcan.2013.06.021

AUTORES / AUTHORS: Monirul Islam KM; Shostrom V; Kessinger A; Ganti AK

INSTITUCIÓN / INSTITUTION: Department of Epidemiology, University of Nebraska Medical Center, Omaha, NE, United States.

RESUMEN / SUMMARY: INTRODUCTION: Outcomes following surgery are better than following radiation therapy (RT), for stage I NSCLC. Whether this is due to selection of healthier patients for surgery is unclear. This study was undertaken to compare outcomes between surgical patients and patients who were surgical candidates but did not receive surgery. METHODS: Data of patients with stage I NSCLC between 1988 and 2007, included in the SEER database were analyzed. Overall survival (OS) was examined by treatment type (surgery only, radiation only, surgery and radiation, and no treatment). OS was compared between RT patients who refused surgery and those not fit for surgery. Cox proportional hazards model was used to compare outcomes by treatment type. RESULTS: Data from 8579 patients with stage I NSCLC during 1988-2007 were analyzed. Use of RT alone increased during the study period. An increasing proportion of patients with stage I lung cancer chose to have no treatment. On multivariate analysis, OS was better among patients who had surgery. There was a 56% improvement in survival among patients who had surgery compared to fit patients who refused surgery (HR 0.437, 95% CI 0.301-0.632). Patients who refused surgery had a better OS than those who were not fit for surgery (log-rank p=0.01). Patients who received RT alone or no treatment had a significant improvement in five-year OS during the latter part of the study period (1998-2002 vs. 1988-1992). CONCLUSIONS: In medically fit patients, outcomes following surgery are better than those following conventional radiation. Hence surgery should be chosen over conventional radiation, whenever possible. Outcomes following RT show an improvement over time reflecting improvement in radiation techniques.

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RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Maniwa T; Endo M; Isaka M; Nakagawa K; Ohde Y; Okumura T; Kondo H

INSTITUCIÓN / INSTITUTION: Division of Thoracic Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, Japan, to.maniwa@scchr.jp.
RESUMEN / SUMMARY: - PURPOSE: Interstitial lung disease (ILD) has been associated with primary lung cancer and an increased risk of postoperative acute exacerbation (AE). The effectiveness of 2-[18]-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) for staging lung cancer is well established. This study investigates the association of FDG uptake on PET in patients with AE of ILD. METHODS: The subjects of this retrospective study were 1309 patients with lung cancer, who underwent pulmonary resection at Shizuoka Cancer Center between September, 2002 and January, 2011. ILD was diagnosed with chest computed tomography in 95 patients, 81 of whom underwent 18F-FDG PET before surgery. Six patients suffered from AE after surgery (AE group), while the remaining 75 (non-AE group) did not. We investigated the clinico-pathological findings and the results of FDG uptake on PET using the value of the I/M ratio, which is the ratio of the peak of standardized uptake value (SUV) of the ILD area to the mean SUV of the mediastinum. RESULTS: There was no significant difference in clinico-pathological findings, but a significance difference in the I/M ratio (P  = 0.0102). CONCLUSION: The FDG uptake in PET may be a predictive factor for AE of ILD in patients who have undergone lung cancer surgery.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - He F; Chang SC; Wallar GM; Zhang ZF; Cai L

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology, School of Public Health, Fujian Medical University, Fuzhou, China.

RESUMEN / SUMMARY: - Single-nucleotide polymorphisms (SNPs) of DNA repair genes have been reported to modify cancer risk. This study aimed to determine SNPs of the DNA repair genes X-ray repair cross-complementing group 3 (XRCC3) and X-ray cross-complementing group 4 (XRCC4) and their association with non-small-cell lung cancer (NSCLC) susceptibility in a Chinese population. A total of 507 NSCLC patients and 662 healthy controls were recruited for genotyping. Epidemiological and clinical data were also collected for association studies. The data showed that the rs1799794 G allele in the XRCC3 gene and minor allele carriers of XRCC4, including rs1056503 and rs9293337, were inversely associated with NSCLC risk (GG vs homozygote AA), whereas the rs861537 AG or AA genotype and XRCC4 rs6869366 had a significantly increased NSCLC risk. Furthermore, tobacco smoking over 26 pack-years, a family history of lung cancer, exposure to environmental tobacco smoke (ETS) and negative mental status were risk factors for developing NSCLC. This study suggests that SNPs of XRCC3 and
XRCC4 and other environmental factors are risk factors for developing NSCLC in this Chinese Han population. Journal of Human Genetics advance online publication, 8 August 2013; doi:10.1038/jhg.2013.78.

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[205]

TÍTULO / TITLE - Pemetrexed downregulates ERCC1 expression and enhances cytotoxicity effected by resveratrol in human nonsmall cell lung cancer cells.

RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS - Chen RS; Ko JC; Chiu HC; Wo TY; Huang YJ; Tseng SC; Chen HJ; Huang YC; Jian YJ; Lee WT; Lin YW

INSTITUCIÓN / INSTITUTION - Department of Biochemical Science and Technology, National Chiayi University, 300 Syuefu Road, Chiayi, 600, Taiwan.

RESUMEN / SUMMARY - The multitargeted antifolate pemetrexed has demonstrated certain clinical activities against nonsmall cell lung cancer (NSCLC). Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a polyphenol found in grapes and other plants and has great potential as a preventative and therapeutic agent due to its anticarcinogenic activity. The efficacy of adding resveratrol to pemetrexed to prolong the survival of patients with NSCLC still remains unclear. The excision repair cross-complementation 1 (ERCC1) is a DNA repair gene coding 5’ endonuclease in nucleotide excision repair and is overexpressed in chemo- or radioresistant carcinomas. In this study, resveratrol (10-50 μM) inhibited cell survival in two NSCLC cells, H520 and H1975. Treatment with resveratrol increased ERCC1 messenger RNA and protein levels in a MKK3/6-p38 MAPK signal activation-dependent manner. Furthermore, blocking p38 MAPK activation by SB202190 or knocking down ERCC1 expression by transfection with small interfering RNA of ERCC1 enhanced the cytotoxicity of resveratrol. Combining resveratrol with pemetrexed resulted in a synergistic cytotoxic effect, accompanied with the reduction of phospho-p38 MAPK and ERCC1 protein levels, and a DNA repair capacity. Expression of constitutively active MKK6 (MKK6E) or HA-p38 MAPK vectors significantly rescued the decreased p38 MAPK activity, and restored ERCC1 protein levels and cell survival in resveratrol and pemetrexed cotreated NSCLC cells. In this study, for the first time, we have demonstrated the synergistic effect of combined treatment with resveratrol and pemetrexed in human NSCLC cells through downregulation of the MKK3/6-p38 MAPK-ERCC1 signal, suggesting a potential benefit of combining resveratrol and pemetrexed to treat lung cancer in the future.

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[206]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Ciuleanu T; Tsai CM; Tsao CJ; Milanowski J; Amoroso D; Heo DS; Groen HJ; Szczesna A; Chung CY; Chao TY; Middleton G; Zeaiter A; Klingelschmitt G; Klughammer B; Thatcher N

INSTITUCIÓN / INSTITUTION: - Institute of Oncology Ion Chiricuta, Cluj-Napoca, Romania; University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, 400015, Romania. Electronic address: tudor@iocn.ro.

RESUMEN / SUMMARY: - BACKGROUND: Molecularly targeted agents for non-small cell lung cancer (NSCLC) can provide similar efficacy to chemotherapy without chemotherapy-associated toxicities. Combining two agents with different modes of action could further increase the efficacy of these therapies. The TASK study evaluated the efficacy and safety of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in combination with the anti-angiogenic agent bevacizumab as first-line therapy in unselected, advanced non-squamous NSCLC patients. METHODS: Patients were recruited from December 2007 to September 2008. Planned sample size was 200 patients, a total of 124 patients were randomized. Patients were randomized using a minimization algorithm 1:1 to receive bevacizumab (iv 15mg/kg day 1 of each 21-day cycle) plus chemotherapy (gemcitabine/cisplatin or carboplatin/paclitaxel standard doses, 4-6 cycles) (BC arm) or bevacizumab plus erlotinib (p.o. 150mg/day; BE arm) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). If the hazard ratio (HR) of PFS for BE relative to BC was above 1.25 at the pre-planned interim analysis in favor of BC, the study would be re-evaluated. Secondary endpoints included overall survival, response rate and safety. RESULTS: All randomized patients (n=63 BE; n=61 BC) were evaluated for the efficacy analyses. At the updated interim analysis, median PFS was 18.4 weeks (95% confidence interval [CI] 17.0-25.1) versus 25.0 weeks (95% CI 20.6-25.1) for BE versus BC, respectively (HR for death or disease progression, BE relative to BC, 2.05, p=0.0183). The incidence of death was 19% for BE treatment compared with 11.5% for BC treatment. The HR for PFS at the updated interim analysis was above 1.25, therefore patients on the BE arm were permitted to change arms or switch to another drug and the study was terminated. Adverse events reported were as expected. CONCLUSIONS: The TASK study did not show a benefit in terms of PFS for the combination of erlotinib with bevacizumab in unselected first-line advanced non-squamous NSCLC compared with chemotherapy plus bevacizumab.
TÍTULO / TITLE: - Expression of HAb18G in non-small lung cancer and characterization of activation, migration, proliferation, and apoptosis in A549 cells following siRNA-induced downregulation of HAb18G.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Xu X; Liu S; Lei B; Li W; Lin N; Sheng W; Huang A; Shen H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

RESUMEN / SUMMARY: - HAb18G, a novel cancer biomarker, has been shown to be involved in the progression of malignancy by regulating expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). The goal of this study was to evaluate the role of HAb18G in the biology of NSCLC and to determine its potential as a therapeutic target. HAb18G protein expression was detected by immunohistochemistry in 150 NSCLC tissues. The results showed that HAb18G protein expression was associated with tumor diameter, lymph node status, tumor stage, and poor prognosis (P < 0.05). Multivariate analysis showed that HAb18G overexpression was an independent prognostic factor (HR, 3.713; 95 % CI, 1.114-12.373; P = 0.033). Transient infection of A549 lung cancer cells with small interfering RNA (SiRNA) against HAb18G efficiently inhibited the expression of HAb18G in A549 lung cancer cells at both mRNA and protein levels. Downregulation of HAb18G not only reduced MMP-2, MMP-9, and VEGF at mRNA and protein levels in A549 cells, but also inhibited fibroblasts to secrete MMP-2 and MMP-9 at mRNA level. Additionally, downregulation of HAb18G mRNA resulted in decreased migration, proliferation, and increased apoptosis of A549 in vitro. Our findings suggest that HAb18G overexpression plays an important role in progression of NSCLC and HAb18G may be a potential target of NSCLC therapy.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Xu X; Liu S; Lei B; Li W; Lin N; Sheng W; Huang A; Shen H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

RESUMEN / SUMMARY: - microRNAs (miRNAs) play a significant role in the regulation of transcription and translation of cancer-related genes. We have identified a miRNA-based signature for response and survival of NSCLC patients treated with cisplatin-vinorelbine A ELCWP prospective study. A total of 263 primary non-small cell lung cancer tissues were examined. miRNA expression in tumor tissues was profiled by microarray analysis. A total of 228 miRNAs were significantly differentially expressed between the responders and non-responders. A 32 miRNA signature was identified distinguishing the responders and non-responders. This signature was validated in an independent set of 84 patients. The miRNA signature was found to be an independent prognostic factor in NSCLC patients treated with cisplatin-vinorelbine A ELCWP prospective study.
RESUMEN / SUMMARY: - Clinical variables, like stage and performance status (PS), have predictive and prognostic values in advanced non-small cell lung cancer (NSCLC) patients treated with chemotherapy, not allowing adequate individual prediction. MicroRNA (miRNA) are non-coding RNAs regulating gene expression. In a prospective study, we assessed the predictive value for response and survival of tumour miRNA in NSCLC patients treated by 1st line cisplatin and vinorelbine. miRNA expression was analysed on a biopsy obtained during the diagnostic bronchoscopy, using TaqMan Low Density Arrays. The signature for response was derived using logistic regression with stepwise variable selection. The associations between overall survival and miRNA expression levels were estimated by using the Kaplan-Meier method, log-rank test, and Cox proportional hazard regression models to estimate the hazard ratios. In total, 38 patients with adequate tumour biopsies, treated with cisplatin-vinorelbine were included: male (n=27), 80-100 Karnofsky PS (n=27), adenocarcinoma (n=20), stage IV (n=30). One patient was considered not assessable for response but remained included in the survival analyses. Out of the 37 patients assessable for response, 16 partial responses (43%) were observed. A two miRNA signature (miR-149 and miR-375) was found predictive for response and was also associated to progression-free survival (p=0.05). Using a linear combination of the miR CT values with Cox’s regression coefficients as weights, we constructed a prognostic score for overall survival including four miRNA (miR-200c, miR-424, miR-29c and miR-124). The signature distinguished patients with good (n=18) and poor (n=20) prognosis with respective median survival times of 47.3 months (95% CI 29.8-52.4) and 15.5 months (95% CI 9.1-22.8) (p<0.001; hazard ratio 21.1, 95% CI 4.7-94.9). CONCLUSIONS: miRNA signature allows predicting response and is of prognostic value for survival in patients with NSCLC treated with first line cisplatin and vinorelbine.
INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural Medicines, Department of Pharmaceutics, China Pharmaceutical University, Nanjing, 210009, People’s Republic of China.

RESUMEN / SUMMARY: - The clinical success of gene therapy critically depends upon the safety and efficiency of delivery system used. Although polyethylenimine (PEI) has been commonly used as an efficient cationic polymeric gene carrier due to its high transfection efficiency, its cytotoxicity and nondegradability limit the polymer’s therapeutic applications in clinical trials. In this study, biocompatible polyspermine based on spermine (SPE) and poly(ethylene glycol) (PEG) diacrylate (SPE-alt-PEG) was synthesized using a Michael-type addition reaction, and its ability as an alternative gene carrier for lung cancer therapy was evaluated. SPE-alt-PEG polyspermine was complexed with plasmid DNA, and the resulting complexes were characterized by particle size and surface charge by dynamic light scattering, complex formation and DNA protection ability by gel retardation, and complex shape by energy-filtering transmission electron microscopy. The SPE-alt-PEG copolymer showed low cytotoxicity, and SPE-alt-PEG/DNA complexes showed efficacious transfection efficiency compared with 25 kDa PEI (PEI 25K). Also SPE-alt-PEG/GFP complexes were efficiently transferred into the lungs after aerosol administration without toxicity, and delivery of Pdcd4 gene as a therapeutic gene with SPE-alt-PEG polyspermine greatly reduced tumor size as well as tumor numbers in K-rasLA1 lung cancer model mice compared relative to the effect observed for PEI 25K. These results suggest that SPE-alt-PEG has potential as a gene carrier for lung cancer gene therapy. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part A, 2013.

[210]

TÍTULO / TITLE: - Prognostic Role of Positron Emission Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

REVISTA / JOURNAL: - Enlace al texto completo (gratuito o de pago)

AUTORES / AUTHORS: - Uehara H; Tsutani Y; Okumura S; Nakayama H; Adachi S; Yoshimura M; Miyata Y; Okada M

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Cancer Institute Hospital, Tokyo, Japan.

RESUMEN / SUMMARY: - BACKGROUND: This multicenter study aimed to validate the ability of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) plus high-resolution computed tomography (HR-CT) to predict the malignant behavior and prognosis of early adenocarcinomas of the lung.
METHODS: We calculated maximum standardized uptake values (maxSUV) from PET/CT images and ground-glass opacity (GGO) ratios on HR-CT images before complete surgical intervention in 610 patients with clinical stage IA lung adenocarcinoma. Pathologic invasiveness and survival were compared with clinical factors and radiographic findings including the maxSUV, which was revised to correct for interinstitutional discrepancies that confer limitations upon multicenter PET studies. RESULTS: Analyses of receiver-operating characteristic curves revealed optimal maxSUV and GGO ratio cutoffs to predict recurrence of 2.9 and 25%, respectively. Both the maxSUV and GGO ratio reflected tumor invasiveness, nodal metastasis, recurrence, and patient survivals, and were significant prognostic factors for recurrence-free and cancer-specific survivals on multivariate Cox analysis (all, p < 0.001). The combination of maxSUV and GGO ratio is a better predictor of malignant tumor grade than either alone. CONCLUSIONS: The combination of maxSUV and GGO ratio as well as each alone are important predictors of prognosis in patients with clinical stage IA adenocarcinoma of the lung and should be considered before selecting therapeutic strategies.

[211]
TÍTULO / TITLE: - The error-prone DNA polymerase iota provides quantitative resistance to lung tumorigenesis and mutagenesis in mice.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Iguchi M; Osanai M; Hayashi Y; Koentgen F; Lee GH
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Kochi University School of Medicine, Kochi, Japan.
RESUMEN / SUMMARY: - Opposite undamaged nucleotide T, DNA polymerase iota (Poliota) preferentially incorporates G rather than A, violating the Watson-Crick rule. Although the actual biological role of Poliota remains enigmatic, we have identified its coding gene as a candidate for pulmonary adenoma resistance 2 (Par2), a mouse quantitative trait locus modulating chemically induced lung tumor susceptibility. Notably, the most tumor-sensitive Par2 allele possessed by the 129X1/SvJ mouse is associated with a loss-of-function mutation in Poliota. To determine whether the nonfunctional Poliota is responsible for the 129X1/SvJ-specific Par2 phenotype, we knocked out Poliota in a C57BL/6J mouse carrying a less tumor-sensitive Par2 allele. Disruption of the C57BL/6J Poliota conferred 129X1/SvJ-like sensitivity on the C57BL/6J Par2 locus and increased the in vivo mutation frequency in the lung, providing definitive proof that Poliota causes the Par2 effect and inhibits tumorigenesis and mutagenesis, despite its extreme replication infidelity. Oncogene advance online publication, 19 August 2013; doi:10.1038/onc.2013.331.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Zeybek A; Toru S; Ozbudak IH; Sarper A; Oz N; Bozcuk H; Ozbilim G; Demircan A

**INSTITUCIÓN / INSTITUTION:** 1 Department of Thoracic Surgery, School of Medicine, Mugla Sitki Kocman University, Mugla, Turkey.

**RESUMEN / SUMMARY:** Abstract Therapeutic approaches to lung adenocarcinomas differ because of their heterogeneous morphologies, prognoses, and clinical features. For this reason, new histopathologic classifications for lung adenocarcinomas were done by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society to form subtypes with homogeneous prognoses. There are limited clinical data in the literature on the prognosis of the subgroups formed according to the new classification. A total of 86 patients with adenocarcinoma who had undergone pathologic stages I and II curative resection and mediastinal lymph node dissection were retrospectively analyzed according to the seventh TNM staging system revised by the Union for International Cancer Control/American Joint Committee on Cancer. Histologic subtyping was reassessed according to the dominant histopathologic morphology. When survival rates of lung adenocarcinomas were compared according to their localizations, it was observed that adenocarcinomas localized to the right hemithorax had a longer survival than the ones with left hemithorax localization (P = 0.026). When necrosis was taken into account, it was seen that necrosis rate was higher in solid predominant type compared with other types, whereas it was lower in acinary type (P = 0.046). When peritumoral lymphovascular invasion data were assessed, it was observed that disease-free survival was influenced in a negative fashion (P = 0.018). New histopathologic classification of adenocarcinomas has been a step forward to attaining homogeneous groups, but when the biologic heterogeneity of the adenocarcinomas is taken into account, the authors believe that considering the peritumoral lymphatic vascular invasion, left hemithorax localization, and tumoral necrosis entities in the upcoming TNM classification will contribute to evaluating the prognosis.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1016/j.ijrobp.2013.04.013

AUTORES / AUTHORS: - Chang JY

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- Native and rearranged ALK copy number and rearranged cell count in non-small cell lung cancer: Implications for ALK inhibitor therapy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1002/cncr.28311

AUTORES / AUTHORS: - Camidge DR; Skokan M; Kiatsimkul P; Helfrich B; Lu X; Baron AE; Schulte N; Maxson D; Aisner DL; Franklin WA; Doebele RC; Varella-Garcia M

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Medical Oncology, University of Colorado, Denver, Colorado.

RESUMEN / SUMMARY: - BACKGROUND: Patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) respond to ALK inhibitors. Clinically, the presence of >/=15% cells with rearrangements identified on break-apart fluorescence in situ hybridization (FISH) classifies tumors as positive. Increases in native and rearranged ALK copy number also occur. METHODS: In total, 1426 NSCLC clinical specimens (174 ALK-positive specimens and 1252 ALK-negative specimens) and 24 ALK-negative NSCLC cell lines were investigated. ALK copy number and genomic status were assessed by FISH. RESULTS: Clinical specimens with 0% to 9%, 10% to 15%, 16% to 30%, 31% to 50%, and >50% ALK-positive cells were identified in 79.3%, 8.5%, 1.4%, 2.7%, and 8.1%, respectively. An increased native ALK copy number (>=/=3 copies per cell in >/=40% of cells) was detected in 19% of ALK-positive tumors and in 62% of ALK-negative tumors. In ALK-negative tumors, abundant, focal amplification of native ALK was rare (0.8%). Other atypical patterns occurred in approximately 6% of tumors. The mean native ALK copy number ranged from 2.1 to 6.9 copies in cell lines and was not correlated with crizotinib sensitivity (50% inhibitory concentration, 0.34-2.8 muM; r = 0.279; P = .1764). Neither native or rearranged ALK copy number nor the percentage of positive cells correlated with extra-central nervous system progression-free survival in ALK-positive patients who were receiving crizotinib. CONCLUSIONS: Overall, 8.5% of tumors fell below the established positivity threshold by <</=5%. Further investigation of ALK by other diagnostic techniques in such cases may be warranted. Native ALK copy number increases alone were not associated with sensitivity to ALK inhibition in vitro. However, rare, complex patterns of increased native ALK in patients should be
studied further; because, otherwise, atypical rearrangements contained within these may be missed. Cancer 2013. © 2013 American Cancer Society.

[215]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Yuan Z; Li WT; Ye XD; Dong S; Peng WJ
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Shanghai Cancer Hospital, Fudan University, 270 Dong An Rd., Shanghai 200032, People’s Republic of China; Department of Radiology, Nanjing Jinling Hospital, Clinical School of Medical College, Nanjing University, Nanjing, People’s Republic of China. Electronic address: yuanzheng0404@163.com.

RESUMEN / SUMMARY: - PURPOSE: To investigate the effectiveness and toxicity of intra-arterial infusion chemotherapy as a therapeutic modality for advanced non-small-cell lung cancer (NSCLC). MATERIALS AND METHODS: In a retrospective study, 40 patients with stage III NSCLC received intra-arterial infusion chemotherapy with gemcitabine and cisplatin. Tumor staining was graded based on angiography, and the number of NSCLC feeding arteries detected was recorded. Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events. The response to treatment was evaluated per Response Evaluation Criteria In Solid Tumors (RECIST). Efficacy was assessed based on time to tumor progression (TTP), and survival was estimated by Kaplan-Meier analysis. Prognostic factors influencing TTP and overall survival rate were evaluated by Cox regression analysis. RESULTS: The most frequent drug-related adverse events were cough (n = 17; 42.5%), anorexia (n = 14; 35%), and pain (n = 9; 22.5%). Evaluated per RECIST, a total of 47.5% of patients (n = 19) exhibited response to therapy after completion of the first three cycles of intra-arterial infusion chemotherapy. The median TTP was 5 months. Patients had a median life expectancy of 9 months. By Cox regression analysis, tumor staining was shown to be an independent prognostic factor for TTP (relative risk, 0.405; 95% confidence interval, 0.216-0.760) and overall survival (relative risk, 0.348; 95% confidence interval, 0.185-0.656). CONCLUSIONS: Intra-arterial infusion chemotherapy for advanced lung cancer has the potential to reduce the size of tumors and has no severe adverse effects.
Should patients with extrapulmonary small-cell carcinoma receive prophylactic cranial irradiation?

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** J Thorac Oncol. 2013 Sep;8(9):1215-21. doi: 10.1097/JTO.0b013e31829f6b03.

**AUTORES / AUTHORS:** Naidoo J; Teo MY; Deady S; Comber H; Calvert P

**INSTITUCIÓN / INSTITUTION:** * Department of Medical Oncology, Waterford Regional Hospital, Waterford, Ireland; daggerDepartment of Medical Oncology, The Adelaide and Meath Hospital Tallaght, Dublin, Ireland; and double daggerDepartment of Research and Data Analysis, National Cancer Registry of Ireland, Cork, Ireland.

**RESUMEN / SUMMARY:** INTRODUCTION: Extrapulmonary small-cell carcinoma (EPSCC) is a rare disease. Management is based on small-cell lung carcinoma. Prophylactic cranial irradiation (PCI) is not routinely administered in EPSCC. This study investigates the role of PCI in EPSCC, by analyzing the incidence, treatment, and survival of patients with brain metastases in a national cohort. Disease biology and epidemiology are also investigated. METHODS: Patients diagnosed with primary EPSCC from the National Cancer Registry of Ireland from 1995 to 2007 were identified. The number of patients who developed brain metastases, their survival, and treatment data were documented. Patients who received PCI were investigated. Patient and disease characteristics, treatment, and survival data were stratified by stage and primary site. RESULTS: Two hundred eighty patients were identified; 141 (50.4%) were men and 139 (49.6%) were women. One hundred eighty six patients (66.4%) had extensive-stage disease, 65 (23.2%) had limited-stage disease, and in 29 patients (10.3%) the stage was unknown. Eighteen patients (6.4%) developed brain metastases, with a median overall survival of 10.1 months. Eleven (61%) received cranial irradiation, and 12 (67%) received palliative chemotherapy. Two patients in the entire cohort (0.17%) received PCI. The most common primary sites included the esophagus (n = 43; 15.4%), cervix uteri (n = 17; 6.0%), bladder (n = 13; 4.6%), and prostate (n = 10; 3.6%). Median overall survival was 15.2 months (10.2-20.6) for limited-stage disease, 2.3 months (1.7-3.1) for extensive-stage EPSCC, and 3.7 months (1.3-8.3) for disease of unknown stage. CONCLUSION: Brain metastases were uncommon in EPSCC compared with small-cell lung carcinoma. PCI is thus probably not warranted in this disease.

The role of epithelial-mesenchymal transition and IGF-1R expression in prediction of gefitinib activity as the second-line treatment for advanced nonsmall-cell lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

[217]
**RESUMEN / SUMMARY:**

**OBJECTIVE:** Except for EGFR gene mutation, there is still lack of predictive factors for gefitinib activity as the second-line treatments for advanced NSCLC with wild-type (WT) EGFR or patients with mutant EGFR but showed poor response. Our purpose was to assess the predictive value of epithelial-mesenchymal transition (EMT) and IGF-1R for gefitinib efficacy as the second-line treatment for NSCLC.

**METHODS:** 53 advanced NSCLC patients who accepted gefitinib as the second-line treatment were enrolled in this study. Expression of E-cadherin, vimentin, and IGF-1R was determined by immunohistochemistry. EGFR gene mutation was determined by liquidchip technique.

**RESULTS:** The positive rate of EMT, IGF-1R, and EGFR gene mutation was 54.7%, 58.5%, and 39.6%, respectively. EMT (-) was positively correlated with EGFR gene mutation (p = .034) and EMT (+) was associated with IGF-1R (+) (p = .000). EMT (-) was associated with a significantly higher objective response rate (ORR) for all the 53 patients (41.7% vs. 6.9%, p = .024) and showed a higher ORR tendency than EMT (+) in EGFR mutation patients (50.0% vs. 28.6%) and WT EGFR patients (20.0% vs. 4.5%) (p > .05). EMT (-) showed a significant longer median survival time (MST) than EMT (+) for all 53 patients (8 months vs. 4 months) and WT EGFR patients (6 months vs. 3 months) (p < .05). IGF-1R (-) showed a higher ORR tendency than IGF-1R (+) in EGFR mutation patients (54% vs. 30%) and WT EGFR patients (18.2% vs. 4.8%) (p > .05). CONCLUSION: EMT is correlated with efficacy of gefitinib as the second-line treatment for NSCLC, and combined detection of EMT and IGF-1R may be used as new predictors besides EGFR mutation, especially for patients with WT EGFR.

[218]
RESUMEN / SUMMARY: - Depression is common among lung cancer patients. Increasing evidence has suggested that hypothalamic-pituitary-adrenal (HPA) axis and pro-inflammatory cytokines may play a key role in the pathophysiology of depression as well as cancer. This pilot study investigated the efficacy of sputum interleukin (IL)-6, tumor necrosis factor (TNF)-alpha and salivary cortisol as new markers to support the diagnosis of depression in lung cancer patients. The diurnal rhythms of sputum IL-6, sputum TNF-alpha and salivary cortisol were measured in lung cancer patients with and without depression as well as depressed controls and healthy controls. The area under the diurnal variation curves (AUC) over the 24h time course and relative diurnal variation (VAR) were calculated. Receiver operating characteristic (ROC) analysis was performed. Patients with co-morbid depression and lung cancer showed highest level of sputum IL-6 AUC, sputum TNF-alpha AUC and lowest level of cortisol VAR (P<0.001). As a biomarker for depression, salivary cortisol VAR demonstrated an optimal cutoff point at 77.8% (AUC=0.94; 95% CI, 0.85-0.98), which is associated with a sensitivity of 82.1% and a specificity of 96.0%. Sputum IL-6 AUC demonstrated a sensitivity of 74.4% and a specificity of 92.0% (AUC=0.81; 95% CI, 0.69-0.90). These findings suggested that higher 24h overall levels of sputum IL-6, TNF-alpha and flattened diurnal salivary cortisol slopes were associated with depression in lung cancer patients. Sputum IL-6 AUC and salivary cortisol VAR performed best as biomarkers in the diagnosis of depression in lung cancer patients.

[219]

TÍTULO / TITLE: - Co-expression of receptors of the HER family correlates with clinical outcome in non-small cell lung cancer (NSCLC).

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 10.1007/s00428-013-1445-x

AUTORES / AUTHORS: - Bellezza G; Del Sordo R; Colella R; Ludovini V; Ragusa M; Bianconi F; Ferri I; Borri F; Chiari R; Puma F; Crino L; Sidoni A

INSTITUCIÓN / INSTITUTION: - Institute of Pathological Anatomy and Histology, Perugia University, Perugia, Italy, guidobellezza@virgilio.it.

RESUMEN / SUMMARY: - HER family receptors play a critical role in lung carcinogenesis. There is a growing body of evidence showing that cooperation between them contributes to a more aggressive tumor phenotype and impacts on their response to targeted therapy. We explored immunohistochemical co-expression of HER family receptors (HER1, HER2, HER3, HER4) and its potential role as prognostic factor in resected non-small cell lung cancer (NSCLC). Expression of HER family receptors was assessed by immunohistochemistry on 125 surgically resected NSCLC. Kaplan-Meier estimates of overall survival (OS), disease-free survival (DFS), and time to recurrence were calculated for clinical variables and HER expression, using the Cox model for
multivariate analysis. HER1 and HER3 expression was detected more frequently in squamous cell carcinoma (p = 0.002 and p < 0.001, respectively). HER4 was more often expressed in patients older than 60 years (p = 0.02) and in tumors of low histological grade (p = 0.04). Cases which expressed only HER1 had a worse DFS (p = 0.01) and OS (p = 0.01) compared to cases expressing HER1 and one or more of the other family members and to cases which did not express HER1 but one of the other HERs. By multivariate analysis, stage was an independent prognostic factor for DFS and OS. Furthermore, different patterns of co-expression of HER family receptors showed a statistically significant correlation with a shorter DFS (p = 0.03) and OS (p = 0.02). Our findings suggest that expression of HER1 only is correlated with worse DFS and OS. A better understanding of the functional relationships between these receptors may lead to a useful predictive indicator of response to targeted therapy.

TÍTULO / TITLE: Silibinin meglumine, a water-soluble form of milk thistle silymarin, is an orally active anti-cancer agent that impedes the epithelial-to-mesenchymal transition (EMT) in EGFR-mutant non-small-cell lung carcinoma cells.

RESUMEN / SUMMARY: Silibinin is the primary active constituent of a crude extract (silymarin) from milk thistle plant (Silybum marianum) seeds. We explored the ability of an oral milk thistle extract formulation that was enriched with a water-soluble form of silibinin complexed with the amino-sugar meglumine to inhibit the growth of non-small-cell lung carcinoma (NSCLC) mouse xenografts. As a single agent, oral silibinin meglumine notably decreased the overall volumes of NSCLC tumors as efficiently as did the EGFR tyrosine kinase inhibitor (TKI) gefitinib. Concurrent treatment with silibinin meglumine impeded the regrowth of gefitinib-unresponsive tumors, resulting in drastic tumor growth prevention. Because the epithelial-to-mesenchymal transition (EMT) is required by a multiplicity of mechanisms of resistance to EGFR TKIs, we evaluated the ability of silibinin meglumine to impede the EMT in vitro and in vivo. Silibinin-meglumine efficiently prevented the loss of markers associated with a polarized epithelial phenotype as well as the de novo synthesis of proteins associated
with the mesenchymal morphology of transitioning cells. Our current findings with this non-toxic, orally active, and water-soluble silibinin formulation might facilitate the design of clinical trials to test the administration of silibinin meglumine-containing injections, granules, or beverages in combination with EGFR TKIs in patients with EGFR-mutated NSCLC.

[221] TÍTULO / TITLE - E2F1-mediated DNA damage is implicated in 8-Cl-adenosine-induced chromosome missegregation and apoptosis in human lung cancer H1299 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Han YY; Zhou Z; Cao JX; Jin YQ; Li SY; Ni JH; An GS; Zhang YX; Jia HT
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Capital Medical University, You An Men 8, Beijing, 100069, People’s Republic of China.
RESUMEN / SUMMARY: - Although E2F1-mediated DNA double-stranded breaks (DSBs) and tetraploid have been extensively studied, the role of E2F1 in mitotic catastrophe is still unknown. We have previously shown that 8-chloro-adenosine (8-Cl-Ado) induces DNA DSBs and aberrant mitosis in human lung cancer cells, followed by delayed apoptosis. Here, we demonstrate that E2F1-mediated DNA damage is implicated in 8-Cl-Ado-induced chromosome missegregation and apoptosis in lung cancer H1299 cells. We showed that E2F1 was accumulated upon 8-Cl-Ado-induced DNA DSBs. Induction of E2F1 by 8-Cl-Ado caused DNA damage in cycling cells including M cells. In contrast, silencing of E2F1 expression decreased 8-Cl-Ado-induced DNA DSBs, particularly eliminated E2F1-mediated mitotic DNA damage. Over-expression of E2F1 and/or 8-Cl-Ado exposure resulted in aberrant mitotic spindles and chromosome segregation errors. Furthermore, over-expression of E2F1 expression enhanced 8-Cl-Ado-induced apoptosis. Together, our data indicate that E2F1-mediated DNA damage, in particular mitotic DNA damage, is an important fraction of 8-Cl-Ado-induced DNA damage, which is implicated in 8-Cl-Ado-induced mitotic catastrophe and delayed apoptosis. Induction of E2F1 by 8-Cl-Ado may contribute at least partly to the drug-inhibited proliferation of cancer cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 1038/onc.2013.336

AUTORES / AUTHORS: Chen CH; Thai P; Yoneda K; Adler KB; Yang PC; Wu R

INSTITUCIÓN / INSTITUTION: Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine and Center for Comparative Respiratory Biology and Medicine, University of California Davis, Davis, CA, USA.

RESUMEN / SUMMARY: Myristoylated Alanine-Rich C Kinase Substrate (MARCKS), a substrate of protein kinase C, is a key regulatory molecule controlling mucus granule secretion by airway epithelial cells as well as directed migration of leukocytes, stem cells and fibroblasts. Phosphorylation of MARCKS may be involved in these responses. However, the functionality of MARCKS and its related phosphorylation in lung cancer malignancy have not been characterized. This study demonstrated elevated levels of MARCKS and phospho-MARCKS in highly invasive lung cancer cell lines and lung cancer specimens from non-small-cell lung cancer patients. siRNA knockdown of MARCKS expression in these highly invasive lung cancer cell lines reduced cell migration and suppressed PI3K (phosphatidylinositol 3'-kinase)/Akt phosphorylation and Slug level. Interestingly, treatment with a peptide identical to the MARCKS N-terminus sequence (the MANS peptide) impaired cell migration in vitro and also the metastatic potential of invasive lung cancer cells in vivo. Mechanistically, MANS peptide treatment resulted in a coordination of increase of E-cadherin expression, suppression of MARCKS phosphorylation and AKT/Slug signalling pathway but not the expression of total MARCKS. These results indicate a crucial role for MARCKS, specifically its phosphorylated form, in potentiating lung cancer cell migration/metastasis and suggest a potential use of MARCKS-related peptides in the treatment of lung cancer metastasis. Oncogene advance online publication, 19 August 2013; doi:10.1038/onc.2013.336.

[223]

TÍTULO / TITLE: Distinct outcome of stage I lung adenocarcinoma with ACTN4 cell motility gene amplification.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Noro R; Honda K; Tsuta K; Ishii G; Maeshima AM; Miura N; Furuta K; Shibata T; Tsuda H; Ochiai A; Sakuma T; Nishijima N; Gemma A; Asamura H; Nagai K; Yamada T

INSTITUCIÓN / INSTITUTION: Division of Chemotherapy and Clinical Research, National Cancer Center Research Institute, Tokyo.

RESUMEN / SUMMARY: BACKGROUND: Even if detected at an early stage, a substantial number of lung cancers relapse after curative surgery. However, no method for
distinguishing such tumors has yet been established. PATIENTS AND METHODS: The copy number of the actinin-4 (ACTN4) gene was determined by fluorescence in situ hybridization on tissue microarrays comprising 543 surgically resected adenocarcinomas of the lung. RESULTS: Amplification (an increase in the copy number by \( \geq 2.0 \) fold) of the ACTN4 gene was detected in two of seven lung adenocarcinoma cell lines and 79 (15%) of 543 cases of pathological stage I-IV lung adenocarcinoma. Multivariate analysis revealed that ACTN4 gene amplification was the most significant independent factor associated with an extremely high risk of death (hazard ratio, 6.78; \( P = 9.48 \times 10^{-5} \), Cox regression analysis) among 290 patients with stage I lung adenocarcinoma. The prognostic significance of ACTN4 gene amplification was further validated in three independent cohorts totaling 1033 patients. CONCLUSIONS: Amplification of the ACTN4 gene defines a small but substantial subset of patients with stage I lung adenocarcinoma showing a distinct outcome. Such patients require intensive medical attention and might benefit from postoperative adjuvant chemotherapy.
patients received no further treatment after surgery, but two relapsed. All type II/III PPB had chemotherapy (CT) and their 5-year PFS was 42.9% (27.7-57.2). On univariate analysis, favourable prognostic factors were: complete tumour resection at diagnosis (p=0.008); and absence of invasiveness (p=0.02); for type II/III tumours, type of CT was also a significant factor (patients given doxorubicin fared better, with a 5-year PFS of 70% versus 31.3% [p=0.01]). INTERPRETATIONS: Type I PPB patients’ outcome was satisfactory. Complete resection at diagnosis seems important but rarely feasible for type II/III tumours, who benefited from doxorubicin-containing CT regimens. These results will inform the EXPERT group’s PPB treatment guidelines.

[225]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Gaga M; Powell CA; Schraufnagel DE; Schonfeld N; Rabe K; Hill NS; Sculier JP

RESUMEN / SUMMARY: - Background: Lung cancer is a common problem seen by pulmonologists. The American Thoracic Society (ATS) and European Respiratory Society (ERS) are professional organizations whose memberships are composed of large numbers of pulmonologists. Purpose: This document describes the key role of pulmonologists in the prevention, early diagnosis, and management of lung cancer. Methods: A committee of ATS and ERS leaders and their oncology groups discussed the activities of pulmonologists in relation to lung cancer in various settings and reviewed available literature on the topic. The content of this statement was approved by the board of directors of both the ATS and ERS. Results: Optimal lung cancer care requires a multidisciplinary team of specialists who care for a significant number of patients on a regular basis. Pulmonologists are responsible for and involved with patients from their initial diagnosis and staging through treatment and restaging. They are often involved with complications, palliative care, and end-of-life care, and thus have an important role in team leadership. Conclusions: Lung cancer is a disease with high mortality, profound effects on the quality of the lives of patients and their families, and an enormous cost and impact on society. To treat lung cancer optimally, care must be prompt, multidisciplinary, and patient-centered. In the entire process, pulmonologists have a key role. Pulmonologists and their professional societies should also enhance lung cancer research and education to provide better treatment options and patient care.
Genetic alterations defining NSCLC subtypes and their therapeutic implications.

Lung cancer is the leading cause of cancer death worldwide, accounting for more deaths than breast, prostate and colon cancer combined. While treatment decisions are determined primarily by stage, therapeutically non small cell lung cancer (NSCLC) has traditionally been treated as a single disease. However, recent findings have led to the recognition of histology and molecular subtypes as important determinants in treatment selection. Identifying the genetic differences that define these molecular and histological subtypes has the potential to impact treatment and as such is currently the focus of much research. Microarray and genomic sequencing efforts have provided unparalleled insight into the genomes of lung cancer subtypes, specifically adenocarcinoma (AC) and squamous cell carcinoma (SqCC), revealing subtype specific genomic alterations and molecular subtypes as well as differences in cell signaling pathways. In this review, we discuss the recurrent genomic alterations characteristic of AC and SqCC (including molecular subtypes), their therapeutic implications and emerging clinical practices aimed at tailoring treatments based on a tumor’s molecular alterations with the hope of improving patient response and survival.

Downregulation of miR-16 promotes growth and motility by targeting HDGF in non-small cell lung cancer cells.

Lung cancer is the leading cause of cancer death worldwide, accounting for more deaths than breast, prostate and colon cancer combined. While treatment decisions are determined primarily by stage, therapeutically non small cell lung cancer (NSCLC) has traditionally been treated as a single disease. However, recent findings have led to the recognition of histology and molecular subtypes as important determinants in treatment selection. Identifying the genetic differences that define these molecular and histological subtypes has the potential to impact treatment and as such is currently the focus of much research. Microarray and genomic sequencing efforts have provided unparalleled insight into the genomes of lung cancer subtypes, specifically adenocarcinoma (AC) and squamous cell carcinoma (SqCC), revealing subtype specific genomic alterations and molecular subtypes as well as differences in cell signaling pathways. In this review, we discuss the recurrent genomic alterations characteristic of AC and SqCC (including molecular subtypes), their therapeutic implications and emerging clinical practices aimed at tailoring treatments based on a tumor’s molecular alterations with the hope of improving patient response and survival.
MicroRNAs play important roles in the development and progression of non-small cell lung cancer (NSCLC). miR-16 functions as a tumor-suppressor and is inhibited in several malignancies. Herein, we validated that miR-16 is downregulated in NSCLC tissue samples and cell lines. Ectopic expression of miR-16 significantly inhibited cell proliferation and colony formation. Moreover, miR-16 suppressed cell migration and invasion in NSCLC cells. Hepatoma-derived growth factor (HDGF) was found to be a direct target of miR-16 in NSCLC cell lines. Rescue experiments showed that the suppressive effect of miR-16 on cell proliferation, colony formation, migration, and invasion is partially mediated by inhibiting HDGF expression. This study indicates that miR-16 might be associated with NSCLC progression, and suggests an essential role for miR-16 in NSCLC.
increasing pack-year cohorts; while the frequencies of KRAS mutations increased. Interestingly, in Asian patients the frequencies of EGFR mutations were similar in never smokers and in the cohorts with less than 45 pack-year histories of smoking and only decreased in the 45 pack-year plus cohort. CONCLUSIONS: The frequencies of somatic EGFR, KRAS, and ALK gene abnormalities using routine lung cancer tissue samples from our United States-based academic medical practice reflect the diverse ethnicity (with a higher frequency of EGFR mutations in Asian patients) and smoking patterns (with an inverse correlation between EGFR mutation and ALK rearrangement) of our tested population. These results may help other medical practices appreciate the expected results from introduction of routine tumor genotyping techniques into their day-to-day care of NSCLC.

[229]

TÍTULO / TITLE: Selective modulation of MHC class II chaperons by a novel IFN-gamma-inducible class II transactivator variant in lung adenocarcinoma A549 cells.

RESUMEN / SUMMARY: Class II transactivator (CIITA) plays a critical role in controlling major histocompatibility complex (MHC) class II gene expression. In this study, two novel alternatively spliced variants of human interferon (IFN)-gamma-inducible CIITA, one missing exon 7 (CIITADeltaE7), the other with TAG inserted at exon 4/5 junction (CIITA-TAG), were identified and characterized. Both variants are naturally occurring since they are present in primary cells. Unlike CIITA-TAG, CIITADeltaE7 is expressed more abundantly in lung adenocarcinoma A549 cells than in the non-transformed counterpart BEAS-2B cells following IFN-gamma stimulation. Transfection experiments showed that CIITADeltaE7 induced a markedly lower level of surface HLA-DR, -DP, -DQ expression than CIITA-TAG in A549 cells but not in BEAS-2B cells, although both variants elicited similar amounts of total DR, DP, and DQ proteins. This differential effect was correlated with, in A549 cells, decreased expression of Ii and HLA-DM genes, along with increased expression of HLA-DO genes. Ii and HLA-DM are chaperons assisting in HLA class II assembly, while HLA-DO functions to inhibit endosomal peptide loading and HLA class II membrane transport. These findings raise the possibility that CIITADeltaE7 interacts with unknown cancer-associated factors to selectively modulate genes involved in the assembly and transport of HLA class II molecules.
**Título / Title:** - Induction of senescence by adenosine suppressing the growth of lung cancer cells.

**Resumen / Summary:** - Enlace al Resumen / Link to its Summary


**Autores / Authors:** - Yang D; Song J; Wu L; Ma Y; Song C; Dovat S; Nishizaki T; Liu J

**Institución / Institution:** - Department of Digestive Diseases, Huashan Hospital, Fudan University, Shanghai 200040, China.

**Resumen / Summary:** - Extracellular adenosine is well reported to suppress tumor growth by induction of apoptosis. However, in this study we found that adenosine treatment results in cellular senescence in A549 lung cancer cells both in vitro and in vivo; adenosine induces cell cycle arrest and senescence in a p53/p21 dependent manner; adenosine elevates the level of phosphor-gammaH2AX, pCHK2 and pBRCA1, the markers for prolonged DNA damage response which are likely responsible for initiating the cellular senescence. Our study first demonstrates that adenosine suppresses growth of cancer cells by inducing senescence and provides additional evidence that adenosine could act as an effective anticancer agent for targeted cancer therapy.

**Título / Title:** - Properties and Inflammatory Effects of Various Size Fractions of Ambient Particulate Matter from Beijing on A549 and J774A.1 Cells.

**Resumen / Summary:** - Enlace al Resumen / Link to its Summary


**Autores / Authors:** - Wang B; Li K; Jin W; Lu Y; Zhang Y; Shen G; Wang R; Shen H; Li W; Huang Y; Zhang Y; Wang X; Li X; Liu W; Cao H; Tao S

**Institución / Institution:** - Laboratory for Earth Surface Processes, College of Urban and Environmental Sciences, Peking University, Beijing 100871, P.R. China.

**Resumen / Summary:** - Particulate matter (PM) is a major ambient air pollutant causing millions of premature deaths each year in China. The toxicity of PM is property and size dependent. In this study, ambient PM samples collected in Beijing were divided into five size fractions with nominal aerodynamic ranges of <0.40, 0.40-1.1, 1.1-3.3, 3.3-5.8, and 5.8-10 µm. Individual size fractions were characterized for a number of properties including particle size distribution, specific surface area, zeta potential, dithiothreitol (DTT)-based redox ability, and contents of water-soluble organic carbon.
(WSOC), polycyclic aromatic hydrocarbons (PAHs), selected metals, and endotoxin. Human adenocarcinomic alveolar epithelial cell line A549 and small mouse monocyte-macrophage cell line J774A.1 were tested for their relative viabilities and inflammatory effects (interleukine-8 for A549 and tumor necrosis factor-alpha for J774A.1) after exposure to PM of various sizes. It was found that PM specific area was positively correlated with WSOC, high molecular weight PAHs, DTT-based redox ability, negatively correlated with surface zeta potential and lithophile metals. Several trace metals from combustion sources were enriched in intermediate size fractions. For both endotoxin concentrations of the PM and PM induced inflammatory cytokine expressions by the two cell lines, there were general increasing trends as PM size increased with an exception of the finest fraction, which induced the highest inflammatory effects. It seems that the size dependence of cytokine expression was associated with a number of properties including endotoxin content, zeta potential, settling velocity, metal content, and DTT-based redox ability.

[232]

TÍTULO / TITLE: - IGF-1R and Bmi-1 expressions in lung adenocarcinoma and their clinicopathologic and prognostic significance.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhang X; Sun J; Wang H; Lou Y; Zhang Y; Sha H; Feng J; Han B

INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiaotong University, No. 241, West Huaihai Rd, 200030, Shanghai, China.

RESUMEN / SUMMARY: - IGF-1R and Bmi-1 play a critical role in cancer growth and survival. We explored the correlation between IGF-1R and Bmi-1, as well as their relationship with clinicopathological parameters and their impacts on outcomes in patients with lung adenocarcinoma resected. Tumors from 178 surgical lung adenocarcinoma patients were evaluated for IGF-1R and Bmi-1 expression by means of immunohistochemistry. The clinicopathological implications of these molecules were analyzed statistically. There was a significant correlation between the expression of IGF-1R and Bmi-1 (p = 0.011). The 5-year survival rate of patients with Bmi-1 positive was only 31.2 %, but patients with Bmi-1 negative had a survival rate of 50.7 % (p = 0.004). The pattern of survival curves showed that Bmi-1 was a significant prognostic factor of poor overall survival in lung adenocarcinoma patients. However, there was no obvious correlation between IGF-1R expression and patient survival. The results of multivariate Cox analysis revealed that the pathological stages and Bmi-1 expression were independent prognostic factors. Therefore, Bmi-1 may be a good biomarker to predict the prognosis of patients with completely resected lung adenocarcinoma.
Are erlotinib and gefitinib interchangeable, opposite or complementary for non-small cell lung cancer treatment? Biological, pharmacological and clinical aspects.

Gefitinib and erlotinib are the two anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of advanced NSCLC patients. These drugs target one of the most important pathways in lung carcinogenesis and are able to exploit the phenomenon of ‘oncogene addiction’, with different efficacy according to EGFR gene mutational status in tumor samples. Gefitinib has been approved only for EGFR mutation bearing patients regardless the line of treatment, while erlotinib is also indicated in patients without EGFR mutation who undergo second- or third-line treatment. Some studies evaluated the main differences between these drugs both for direct comparison and to improve their sequential use. In particular, toxicity profile resulted partially different, and these observations may be explained by several molecular and pharmacokinetic features. Therefore, this review integrates preclinical data with clinical evidences of TKIs to guide the optimization of currently available treatments in advanced NSCLC patients.


Gefitinib and erlotinib are the two anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of advanced NSCLC patients. These drugs target one of the most important pathways in lung carcinogenesis and are able to exploit the phenomenon of ‘oncogene addiction’, with different efficacy according to EGFR gene mutational status in tumor samples. Gefitinib has been approved only for EGFR mutation bearing patients regardless the line of treatment, while erlotinib is also indicated in patients without EGFR mutation who undergo second- or third-line treatment. Some studies evaluated the main differences between these drugs both for direct comparison and to improve their sequential use. In particular, toxicity profile resulted partially different, and these observations may be explained by several molecular and pharmacokinetic features. Therefore, this review integrates preclinical data with clinical evidences of TKIs to guide the optimization of currently available treatments in advanced NSCLC patients.
PURPOSE: To determine which parameters allow for CyberKnife fiducial-less tumor tracking in stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer. METHODS AND MATERIALS: A total of 133 lung SBRT patients were preselected for direct soft-tissue tracking based on manufacturer recommendations (peripherally located tumors ≥1.5 cm with a dense appearance) and staff experience. Patients underwent a tumor visualization test to verify adequate detection by the tracking system (orthogonal radiographs). An analysis of potential predictors of successful tumor tracking was conducted looking at: tumor stage, size, histology, tumor projection on the vertebral column or mediastinum, distance to the diaphragm, lung-to-soft tissue ratio, and patient body mass index. RESULTS: Tumor visualization was satisfactory for 88 patients (66%) and unsatisfactory for 45 patients (34%). Median time to treatment start was 6 days in the success group (range, 2-18 days) and 15 days (range, 3-63 days) in the failure group. A stage T2 (P=.04), larger tumor size (volume of 15.3 cm³ vs 6.5 cm³ in success and failure group, respectively) (P<.0001), and higher tumor density (0.86 g/cm³ vs 0.79 g/cm³) were predictive of adequate detection. There was a 63% decrease in failure risk with every 1-cm increase in maximum tumor dimension (relative risk for failure = 0.37, CI=0.23-0.60, P=.001). A diameter of 3.6 cm predicted a success probability of 80%. Histology, lung-to-soft tissue ratio, distance to diaphragm, patient’s body mass index, and tumor projection on vertebral column and mediastinum were not found to be predictive of success. CONCLUSIONS: Tumor size, volume, and density were the most predictive factors of a successful XSight Lung tumor tracking. Tumors >3.5 cm have ≥80% chance of being adequately visualized and therefore should all be considered for direct tumor tracking.
target group (n = 16) according to the RTOG 0236 guidelines. Each group was further divided into the large and small target subgroups. After the computation of treatment plans using RAT, a MC plan was generated using the same patient data and treatment parameters. Apart from the target reference point dose measurements, various dose parameters for the planning target volume (PTV) and organs at risk (OARs) were assessed. In addition, the “Fractional Deviation” (FDev) was also calculated for comparison, which was defined as the ratio of the RAT and MC values. For peripheral lung cases, RAT produced significantly higher dose values in all the reference points than MC. The FDev of all reference point doses and dose parameters was greater in the small target than the large target subgroup. For central lung cases, there was no significant reference point and OAR dose differences between RAT and MC. When comparing between the small target and large target subgroups, the FDev values of all the dose parameters and reference point doses did not show significant difference. Despite the shorter computation time, RAT was inferior to MC, in which the target dose was usually overestimated. RAT would not be recommended for SBRT of peripheral lung tumors regardless of the target size. However, it could be considered for large central lung tumors because its performance was comparable to MC.

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TÍTULO / TITLE: Histones and lung cancer: are the histone deacetylases a promising therapeutic target?

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Petta V; Gkiozos I; Strimpakos A; Syrigos K

INSTITUCIÓN / INSTITUTION: Oncology Unit, Third Department of Internal Medicine, Sotiria General Hospital, Athens University School of Medicine, 152 Mesogeion Av., 11527, Athens, Greece.

RESUMEN / SUMMARY: PURPOSE: Deoxyribonucleic acid is wrapped around an octamer of core histone proteins to form a nucleosome, the basic structure of chromatin. Two main families of enzymes maintain the equilibrium of acetyl groups added to or removed from lysine residues. Histone deacetylases (HDACs) catalyze the removal of acetyl groups from lysine residues in histone amino termini and non-histone proteins also, leading to chromatin condensation and transcriptional repression. HDAC overexpression, resulting in tumor suppressor genes silencing, has been found in several human cancer tissues, indicating that aberrant epigenetic activity is associated with cancer development. Therefore, inhibitors of these enzymes are emerging anticancer agents and there is evidence supporting their role in hematological malignancies. The minimal efficacy of conventional chemotherapy has prompted a renewed focus on targeted therapy based on pathways altered during the pathogenesis of lung cancer. We identify the pleiotropic antitumor effects of HDAC inhibitors in lung cancer, focusing on the result caused by their use individually, as well
as in combination with other chemotherapeutic agents, in lung cancer cell lines and in clinical trials. METHOD: We searched reviews and original papers in Pubmed over the last 10 years. RESULTS: We identified 76 original papers on this topic. CONCLUSIONS: Numerous preclinical studies have shown that HDAC inhibitors exhibit impressive antitumor activity in lung cancer cell lines. Nevertheless, Phase III randomized studies do not support HDAC inhibitors use in lung cancer patients in everyday practice. Ongoing and future studies would help determine their role in lung cancer treatment.
TÍTULO / TITLE: - Linobiflavonoid inhibits human lung adenocarcinoma A549 cells: effect on tubulin protein.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhao D; Yang G; Meng Q; Liu J; Yang S

INSTITUCIÓN / INSTITUTION: - The Second Affiliated Hospital, Harbin Medical University, Harbin, 150086, China, zdbzh@126.com.

RESUMEN / SUMMARY: - The antitumor bioactivities of linobiflavonoid were studied through evaluating its in vitro cytotoxicity against several cell lines (A549, H1975, SMMC-7721, HEP-2 and Vero cells), with the aid of 3-(4,5)-dimethylthiazoly1)-3,5-diphenytetrazolium bromide (MTT) assay. It was found that linobiflavonoid shows more notable inhibiting activity against A549 cells, with IC50 value of 4.67 μM. Furthermore, western blot analysis revealed that linobiflavonoid is able to increase the expression of beta-tubulin, whereas not alpha-tubulin. In virtual simulations indicated that linobiflavonoid specifically interacts with the binding pocket which is located at the top of beta-tubulin, due to the presence of strong hydrophobic effects between the core templates and the hydrophobic surface of the tubulin protein (TB) binding site. The binding energy (E inter ) was calculated to be -140.47 kcal/mol. Results above suggest that linobiflavonoid possesses anti-A549 properties relating to beta-tubulin depolymerization inhibition.

[238]

TÍTULO / TITLE: - SIRT3 regulates cell proliferation and apoptosis related to energy metabolism in non-small cell lung cancer cells through deacetylation of NMNAT2.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Li H; Feng Z; Wu W; Li J; Zhang J; Xia T

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Air Force General Hospital, Beijing 100142, P.R. China.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of death worldwide and associated with dismal prognoses. As a major mitochondrial deacetylase, SIRT3 regulates the activity of enzymes to coordinate global shifts in cellular metabolism and has important implications for tumor growth. Its role as a tumor suppressor or an oncogene in lung cancer is unclear, especially in non-small cell lung carcinoma (NSCLC). To identify the mechanism of SIRT3-interacting proteins, we performed a yeast two-hybrid screen using a human lung cDNA library. One of the positive clones encoded the full-length cDNA of the nicotinamide mononucleotide adenyllytransferase 2 (NMNAT2)
gene and the interaction between SIRT3 and NMNAT2 was identified. The interaction on growth, proliferation, apoptosis of NSCLC cell lines, and energy metabolism related to SIRT3 were investigated. Screening from the library resulted in NMNAT2 gene. We found that NMNAT2 interacts with SIRT3 both in vitro and in vivo; SIRT3 binds to NMNAT2 deacetylating it. Downregulation of SIRT3 inhibited acetylation of NMNAT2 and NAD+ synthesis activity of the enzyme. Low expression of SIRT3 significantly inhibited mitotic entry, growth and proliferation of NSCLC cell lines and promoted apoptosis, which was related to energy metabolism involving in the interaction between SIRT3 and NMNAT2. Taken together, our results strongly suggest that the binding of SIRT3 with NMNAT2 is a novel regulator of cell proliferation and apoptosis in NSCLC cell lines, implicating the interaction between SIRT3 and NMNAT2, energy metabolism associated with SIRT3.

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[239]

TÍTULO / TITLE: Antitumor Impact of Interferon-gamma Producing CD1d-restricted NKT Cells in Murine Malignant Mesothelioma.

RESUMEN / SUMMARY: CD1d-restricted natural killer T (iNKT) cells have been shown to provide adjuvant activity against cancer by producing interferon (IFN)-gamma. However, the role of invariant NKT (iNKT) cells in the tumor microenvironment has not yet been fully addressed. Our aim is to elucidate the antitumor effect of iNKT cells in the tumor microenvironment by using an intrathoracic murine malignant pleural mesothelioma model that we had previously developed and to provide pleural effusion as a good surrogate of the tumor microenvironment. We found that the number of iNKT cells increased dramatically in the pleural effusion after intrathoracic tumor cell injection at an earlier phase compared with accumulation of CD8 T cells. These iNKT cells showed increased expression of CD25 and increased ratio of cells positive for IFN-gamma intracellular staining. iNKT cells sorted from pleural effusion of tumor burden mice produced larger amount of IFN-gamma compared with naive mice. Mice pretreated in vivo with anti-CD1d-blocking Ab showed increased amount of pleural effusion and decreased ratio of total and effector-type CD8 T cells as well as decreased intracellular IFN-gamma expression of CD8T-cell in the pleural effusion. In vivo
administration of alpha-galactosylceramide (alpha-GalCer) showed prolonged survival associated with less pleural effusion and increased ratio of IFN-gamma-positive iNKT cells and CD8 T cells in the pleural effusion. Therefore, this study suggests that iNKT cells accumulating in the tumor microenvironment play an antitumor effect by producing IFN-gamma and enhancing subsequent CD8 T-cell response. Furthermore, in vivo administration of alpha-GalCer could suppress mesothelioma growth by activating iNKT cells.

[240]

MiR-495 enhances the sensitivity of non-small cell lung cancer cells to platinum by modulation of copper-transporting P-type adenosine triphosphatase A (ATP7A).

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Enlace al texto completo (gratuito o de pago)

Song L; Li Y; Li W; Wu S; Li Z

Department of Respiratory Medicine, Xijing Hospital, Fourth Military Medical University, Xi’an, 710032, China.

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules that regulate gene expression at post-transcriptional level. In this study, the aim is to explore which miRNAs might participate in the platinum resistance by targeting ATP7A in NSCLC. Using real time PCR-based miRNA expression profiling and bioinformatics, we selected miR-495 as a candidate miRNA. EGFP reporter assay, real time PCR and western blot validated that ATP7A was a direct target for miR-495. The drug sensitivity assay indicated that miR-495 enhanced the cell response to cisplatin (CDDP) in NSCLC cells, while inhibition of miR-495 led to the opposite effects. Importantly, either overexpression or knockdown of ATP7A could override the effect of miR-495 on chemosensitivity. We also demonstrated that miR-495 increased the intracellular CDDP accumulation and overexpression of ATP7A can reduce the increased drug concentration induced by miR-495. Finally, we discovered that there was a converse relationship between miR-495 and ATP7A levels in NSCLC tissues sensitive or resistant to CDDP. In conclusion, our data demonstrate that miR-495 regulates the multi-drug resistance by modulation of ATP7A expression in NSCLC and suggest that miR-495 may serve as a potential biomarker for the treatment of multi-drug resistant NSCLC patients with high ATP7A levels. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Wang JP; Lin KH; Liu CY; Yu YC; Wu PT; Chiu CC; Su CL; Chen KM; Fang K

INSTITUCIÓN / INSTITUTION: Department of Life Science, National Taiwan Normal University, Taipei, Taiwan.

RESUMEN / SUMMARY: In this work, we demonstrated that the growth of human non-small-cell-lung-cancer cells H460 and A549 cells can be inhibited by low concentrations of an epoxide derivative, teroxirone, in both in vitro and in vivo models. The cytotoxicity was mediated by apoptotic cell death through DNA damage. The onset of ultimate apoptosis is dependent on the status of p53. Teroxirone caused transient elevation of p53 that activates downstream p21 and procaspase-3 cleavage. The presence of caspase-3 inhibitor reverted apoptotic phenotype. Furthermore, we showed the cytotoxicity of teroxirone in H1299 cells with stable ectopic expression of p53, but not those of mutant p53. A siRNA-mediated knockdown of p53 expression attenuated drug sensitivity. The in vivo experiments demonstrated that teroxirone suppressed growth of xenograft tumors in nude mice. Being a potential therapeutic agent by restraining cell growth through apoptotic death at low concentrations, teroxirone provides a feasible perspective in reversing tumorigenic phenotype of human lung cancer cells.

[242]

TÍTULO / TITLE: Socioeconomic Status and Lung Cancer: Unraveling the Contribution of Genetic Admixture.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Aldrich MC; Selvin S; Wrensch MR; Sison JD; Hansen HM; Quesenberry CP Jr; Seldin MF; Barcellos LF; Buffler PA; Wiencke JK

INSTITUCIÓN / INSTITUTION: At the time of the study, Melinda C. Aldrich was with the Division of Epidemiology, School of Public Health, University of California, Berkeley. Steve Selvin is with the Division of Biostatistics, School of Public Health, University of California, Berkeley. Margaret R. Wrensch, Helen M. Hansen, and John K. Wiencke are with the Department of Neurologic Surgery, University of California, San Francisco. Jennette D. Sison was with the Department of Neurologic Surgery, University of California, San Francisco. Charles P. Quesenberry Jr, is with the Division of Research,
Kaiser Permanente, Oakland, CA. Michael F. Seldin is with the Departments of Biological Chemistry and Medicine, University of California, Davis. Lisa F. Barcellos and Patricia A. Buffler are with the Division of Epidemiology, School of Public Health, University of California, Berkeley.

RESUMEN / SUMMARY: Objectives. We examined the relationship between genetic ancestry, socioeconomic status (SES), and lung cancer among African Americans and Latinos. Methods. We evaluated SES and genetic ancestry in a Northern California lung cancer case-control study (1998-2003) of African Americans and Latinos. Lung cancer case and control participants were frequency matched on age, gender, and race/ethnicity. We assessed case-control differences in individual admixture proportions using the 2-sample t test and analysis of covariance. Logistic regression models examined associations among genetic ancestry, socioeconomic characteristics, and lung cancer. Results. Decreased Amerindian ancestry was associated with higher education among Latino control participants and greater African ancestry was associated with decreased education among African lung cancer case participants. Education was associated with lung cancer among both Latinos and African Americans, independent of smoking, ancestry, age, and gender. Genetic ancestry was not associated with lung cancer among African Americans. Conclusions. Findings suggest that socioeconomic factors may have a greater impact than genetic ancestry on lung cancer among African Americans. The genetic heterogeneity and recent dynamic migration and acculturation of Latinos complicate recruitment; thus, epidemiological analyses and findings should be interpreted cautiously.

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RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Liu WB; Han F; Du XH; Jiang X; Li YH; Liu Y; Chen HQ; Ao L; Cui ZH; Cao J; Liu JY

INSTITUCIÓN / INSTITUTION: Institute of Toxicology, College of Preventive Medicine, Third Military Medical University, Key Laboratory of Medical Protection for Electromagnetic Radiation, Ministry of Education of China, Chongqing 400038, China.

RESUMEN / SUMMARY: Using genome-wide methylation screening, we found Aristaless-like homeobox-4 (ALX4) preferentially methylated in lung cancer. ALX4 is a putative transcription factor that belongs to the family of paired-class homeoproteins involved in epithelial development. However, the role of ALX4 in tumorigenesis remains largely unclear. Here, we analyzed its epigenetic regulation, biological functions, and related molecular mechanisms in lung cancer. CpG island methylation and expression of ALX4
were evaluated by methylation-specific PCR, bisulfite genomic sequencing, RT-PCR, and Western blotting. ALX4 functions were determined by cell viability, colony formation, flow cytometry, and in vivo tumorigenicity assays. ALX4 hypermethylation was detected in 55% (54/98) of primary lung cancers compared with none (0/20) of the normal lung tissue samples tested (P < 0.01). ALX4 was readily expressed in normal lung tissues with an unmethylated status, but downregulated or silenced in 90% (9/10) of lung cancer cell lines with a hypermethylation status. Demethylation experiments further confirmed that loss of ALX4 expression was regulated by CpG island hypermethylation. Re-expression of ALX4 in lung cancer cell lines suppressed cell viability, colony formation, and migration, whereas it induced apoptosis and G1/S arrest and restrained the tumorigenicity in nude mice. These effects were associated with upregulation of proapoptotic proteins caspase-7, -8 and -9, and downregulation of Bcl-2. On the other hand, knockdown of ALX4 expression by siRNA increased cell viability and proliferation, while it inhibited apoptosis and cell cycle arrest. In conclusion, our results suggest that ALX4 is a novel putative tumor suppressor with epigenetic silencing in lung carcinogenesis. © 2013 Wiley Periodicals, Inc.

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TÍTULO / TITLE: - Histological specificity of alterations and expression of KIT and KITLG in non-small cell lung carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Salomonsson A; Jonsson M; Isaksson S; Karlsson A; Jonsson P; Gaber A; Bendahl PO; Johansson L; Brunnstrom H; Jirstrom K; Borg A; Staaf J; Planck M

INSTITUCIÓN / INSTITUTION: - Division of Oncology, Department of Clinical Sciences, Lund University and Skane University Hospital, Lund, Sweden.

RESUMEN / SUMMARY: - Characterization of molecules within important oncogenetic pathways may have future implications for development of therapies and biomarkers in lung cancer. One such target is the tyrosine kinase receptor KIT (c-KIT). We evaluated alterations and expression of KIT and its ligand, KITLG (also known as SCF), in 72 clinical lung tumor specimens of different histologies. Gene copy number, mRNA expression levels, and protein expression were assayed using array-based comparative genomic hybridization, real-time quantitative reverse transcription PCR and immunohistochemistry, respectively. For validation, we investigated copy number alterations and mRNA expression in external microarray data sets of 1,600 and 555 primary lung tumors, respectively. Positivity for KIT staining was most common in large cell neuroendocrine carcinoma (LCNEC) which also showed the highest KIT mRNA expression levels whereas expression was lowest in squamous cell carcinoma (SqCC).
KIT mRNA expression levels were higher in KIT immunopositive samples, but expression was not affected by KIT copy numbers. Copy number gains of KIT were significantly more frequent in SqCC compared with adenocarcinoma in our own series and in the 1,600-sample data set. Immunopositivity for both KIT and KITLG in the same tumor was rare except in LCNEC. Our results highlight an increased KIT mRNA expression and frequent KIT immunopositivity in LCNEC but point out a poor correlation between KIT copy numbers and expression in SqCC, perhaps reflecting the existence of a protective mechanism against KIT alterations in this subgroup. © 2013 Wiley Periodicals, Inc.

[245]

TÍTULO / TITLE: - Hormone use and risk for lung cancer: a pooled analysis from the International Lung Cancer Consortium (ILCCO).
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Pesatori AC; Carugno M; Consonni D; Hung RJ; Papadopoulos A; Landi MT; Brenner H; Muller H; Harris CC; Duell EJ; Andrew AS; McLaughlin JR; Schwartz AG; Wenzlaff AS; Stucker I
INSTITUCIÓN / INSTITUTION: - 1] EPOCA, Epidemiology Research Center, Department of Clinical Sciences and Community Health, Universita degli Studi di Milano, via San Barnaba 8, 20122 Milan, Italy [2] Epidemiology Unit, Fondazione IRCCS Ca’ Granda-Ospedale Maggiore Policlinico, via San Barnaba 8, 20122 Milan, Italy.
RESUMEN / SUMMARY: - Background:The association between oral contraceptive (OC) use, hormone replacement therapy (HRT) and lung cancer risk in women is still debated.Methods:We performed a pooled analysis of six case-control studies (1961 cases and 2609 controls) contributing to the International Lung Cancer Consortium. Potential associations were investigated with multivariable unconditional logistic regression and meta-analytic models. Multinomial logistic regressions were performed to investigate lung cancer risk across histologic types.Results:A reduced lung cancer risk was found for OC (odds ratio (OR)=0.81; 95% confidence interval (CI): 0.68-0.97) and HRT ever users (OR=0.77; 95% CI: 0.66-0.90). Both oestrogen only and oestrogen+progestin HRT were associated with decreased risk (OR=0.76; 95% CI: 0.61-0.94, and OR=0.66; 95% CI: 0.49-0.88, respectively). No dose-response relationship was observed with years of OC/HRT use. The greatest risk reduction was seen for squamous cell carcinoma (OR=0.53; 95% CI: 0.37-0.76) in OC users and in both adenocarcinoma (OR=0.79; 95% CI: 0.66-0.95) and small cell carcinoma (OR=0.37; 95% CI: 0.19-0.71) in HRT users. No interaction with smoking status or BMI was observed.Conclusion:Our findings suggest that exogenous hormones can play a
protective role in lung cancer aetiology. However, given inconsistencies with epidemiological evidence from cohort studies, further and larger investigations are needed for a more comprehensive view of lung cancer development in women.

[246]

**TÍTULO / TITLE:** Appropriate sublobar resection choice for ground glass opacity-dominant clinical stage IA lung adenocarcinoma: wedge resection or segmentectomy.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Tsutani Y; Miyata Y; Nakayama H; Okumura S; Adachi S; Yoshimura M; Okada M

**RESUMEN / SUMMARY:** ABSTRACT BACKGROUND: The purpose of this multicenter study is to characterize ground glass opacity (GGO)-dominant clinical stage IA lung adenocarcinomas and evaluate prognosis of these tumors after sublobar resection such as segmentectomy and wedge resection. METHODS: We evaluated 610 consecutive patients with clinical stage IA lung adenocarcinoma, who underwent complete resection after preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), and revealed 239 (39.2%) patients with GGO-dominant tumors that had >50% GGO component. RESULTS: GGO-dominant tumors rarely exhibited pathological invasiveness, including lymphatic, vascular, or pleural invasion and lymph node metastasis. There was no significant difference in three-year RFS among patients who underwent lobectomy, those who underwent segmentectomy, and those who underwent wedge resection of GGO-dominant tumors (96.4% vs. 96.1% vs. 98.7%; P = 0.44). Furthermore, for GGO-dominant T1b tumors, three-year RFS was similar in patients who underwent lobectomy, those who underwent segmentectomy, and those who underwent wedge resection (93.7% vs. 92.9% vs. 100%; P = 0.66). Two of 84 (2.4%) patients with GGO-dominant T1b tumors had lymph node metastasis. Multivariate Cox analysis showed that tumor size, maximum standardized uptake value on FDG-PET/CT, or surgical procedure did not affect RFS in GGO-dominant tumors. CONCLUSIONS: GGO-dominant clinical stage IA lung adenocarcinomas are a uniform group of tumors that exhibit low grade malignancy and have an extremely favorable prognosis. Patients with GGO-dominant clinical stage IA adenocarcinomas can be successfully treated using wedge resection of a T1a tumor and segmentectomy of a T1b tumor.

[247]
TÍTULO / TITLE: - Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Gnagnarella P; Maisonneuve P; Bellomi M; Rampinelli C; Bertolotti R; Spaggiari L; Palli D; Veronesi G

INSTITUCIÓN / INSTITUTION: - Division of Epidemiology and Biostatistics.

RESUMEN / SUMMARY: - BACKGROUND: To assess whether intake of selected foods and food groups and adherence to a Mediterranean diet are associated with lung cancer risk in heavy smokers. PATIENTS AND METHODS: In the context of a lung cancer screening programme, we invited asymptomatic volunteers, aged 50 years or more, current smokers or recent quitters, who had smoked at least 20 pack-years, to undergo annual low-dose computed tomography. We assessed participants’ diet at baseline using a self-administered food frequency questionnaire and calculated their average daily food intake using an ad hoc computer program and determined their alternate Mediterranean diet (aMED) score. We used Cox proportional hazards regression to assess the association between selected food items, beverages and the aMED score and lung cancer risk. RESULTS: During a mean screening period of 5.7 years, 178 of 4336 participants were diagnosed with lung cancer. At multivariable analysis, red meat consumption was associated with an increased risk of lung cancer [hazard ratio (HR) Q4 versus Q1, 1.73; 95% confidence interval (CI) 1.15-2.61; P-value for trend 0.002], while tea consumption (HR for one or more cup/day versus none, 0.56; 95% CI 0.31-0.99; P-value for trend 0.04) and adherence to a Mediterranean diet (HR for aMED>/=8 versus </=1, 0.10; 95% CI 0.01-0.77) were significantly associated with reduced lung cancer risk. CONCLUSIONS: Among heavy smokers, high red meat consumption and low adherence to a Mediterranean diet are associated with increased risk of lung cancer.

[248]

TÍTULO / TITLE: - Survivin expression is an independent poor prognostic marker in lung adenocarcinoma but not in squamous cell carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Sun PL; Jin Y; Kim H; Seo AN; Jheon S; Lee CT; Chung JH
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi-do, 463-707, Republic of Korea.

RESUMEN / SUMMARY: - Survivin is a member of the inhibitors of apoptosis and frequently overexpressed in various cancer cells. Overexpression of survivin in lung cancer cells attenuates antitumor effect of tyrosine kinase inhibitors. However, data from the previous studies on the clinicopathologic implication of survivin in non-small-cell lung carcinoma (NSCLC) are inconsistent. We investigated the expression of survivin in 373 cases of surgically resected NSCLC. Correlations between the expression of survivin and clinicopathologic, molecular features and prognostic significance were analyzed. In adenocarcinoma, the increased expression of survivin was associated with the presence of vascular invasion, lymph node metastasis, and tumor recurrences, but we didn’t find any correlation with survivin expression and clinicopathological parameters in squamous cell carcinoma. Patients with high survivin expression had significantly shorter disease-free survival (DFS; 42.2 vs. 58.8 months; p = 0.001) and shorter overall survival (OS; 60.8 vs. 71.5 months; p = 0.009) than those with low survivin expression group in adenocarcinoma. In squamous cell carcinoma, the expression of survivin was not associated with prognosis of the patients (DFS; 48.9 vs. 48.7 months; p = 0.837, OS; 61.0 vs. 62.4 months; p = 0.771). Multivariate analysis confirmed that survivin was an independent poor prognostic factor in adenocarcinoma (DFS: hazard ratio (HR), 1.687; 95 % confidence interval (CI), 1.123-2.532; p = 0.012; OS: HR, 1.965; 95 % CI, 1.108-3.486; p = 0.021). There was no statistically significant difference in the expression of survivin among different molecular subgroups (p > 0.05). Our results suggest that survivin is an independent negative prognostic factor in adenocarcinoma, but not in squamous cell carcinoma. The different prognostic roles played by survivin in adenocarcinoma and squamous cell carcinoma highlights the biological differences between these two histologic types.

[249]

TÍTULO / TITLE: - Forcing lateral electron disequilibrium to spare lung tissue: a novel technique for stereotactic body radiation therapy of lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Disher B; Hajdok G; Gaede S; Mulligan M; Battista JJ

INSTITUCIÓN / INSTITUTION: - Department of Physics and Engineering, London Regional Cancer Program, London Health Sciences Centre, 790 Commissioners Road East, London, Ontario, N6A 4L6, Canada. Department of Medical Biophysics, Western
RESUMEN / SUMMARY: - Stereotactic body radiation therapy (SBRT) has quickly become a preferred treatment option for early-stage lung cancer patients who are ineligible for surgery. This technique uses tightly conformed megavoltage (MV) x-ray beams to irradiate a tumour with ablative doses in only a few treatment fractions. Small high energy x-ray fields can cause lateral electron disequilibrium (LED) to occur within low density media, which can reduce tumour dose. These dose effects may be challenging to predict using analytic dose calculation algorithms, especially at higher beam energies. As a result, previous authors have suggested using low energy photons (<10 MV) and larger fields (>5 x 5 cm(2)) for lung cancer patients to avoid the negative dosimetric effects of LED. In this work, we propose a new form of SBRT, described as LED-optimized SBRT (LED-SBRT), which utilizes radiotherapy (RT) parameters designed to cause LED to advantage. It will be shown that LED-SBRT creates enhanced dose gradients at the tumour/lung interface, which can be used to manipulate tumour dose, and/or normal lung dose. To demonstrate the potential benefits of LED-SBRT, the DOSXYZnrc (National Research Council of Canada, Ottawa, ON) Monte Carlo (MC) software was used to calculate dose within a cylindrical phantom and a typical lung patient. 6 MV or 18 MV x-ray fields were focused onto a small tumour volume (diameter approximately 1 cm). For the phantom, square fields of 1 x 1 cm(2), 3 x 3 cm(2), or 5 x 5 cm(2) were applied. However, in the patient, 3 x 1 cm(2), 3 x 2 cm(2), 3 x 2.5 cm(2), or 3 x 3 cm(2) field sizes were used in simulations to assure target coverage in the superior-inferior direction. To mimic a 180 degrees SBRT arc in the (symmetric) phantom, a single beam profile was calculated, rotated, and beams were summed at 1 degrees segments to accumulate an arc dose distribution. For the patient, a 360 degrees arc was modelled with 36 equally weighted (and spaced) fields focused on the tumour centre. A planning target volume (PTV) was generated by considering the extent of tumour motion over the patient’s breathing cycle and set-up uncertainties. All patient dose results were normalized such that at least 95% of the PTV received at least 54 Gy (i.e. D95 = 54 Gy). Further, we introduce ‘LED maps’ as a novel clinical tool to compare the magnitude of LED resulting from the various SBRT arc plans. Results from the phantom simulation suggest that the best lung sparing occurred for RT parameters that cause severe LED. For equal tumour dose coverage, normal lung dose (2 cm outside the target region) was reduced from 92% to 23%, comparing results between the 18 MV (5 x 5 cm(2)) and 18 MV (1 x 1 cm(2)) arc simulations. In addition to reduced lung dose for the 18 MV (1 x 1 cm(2)) arc, maximal tumour dose increased beyond 125%. Thus, LED can create steep dose gradients to spare normal lung, while increasing tumour dose levels (if desired). In the patient simulation, a LED-optimized arc plan was designed using either 18 MV (3 x 1 cm(2)) or 6 MV (3 x 3 cm(2)) beams. Both plans met the D95 dose coverage requirement for the target. However, the LED-optimized plan increased the maximum, mean, and
minimum dose within the PTV by as much as 80 Gy, 11 Gy, and 3 Gy, respectively. Despite increased tumour dose levels, the 18 MV (3 x 1 cm(2)) arc plan improved or maintained the V20, V5, and mean lung dose metrics compared to the 6 MV (3 x 3 cm(2)) simulation. We conclude that LED-SBRT has the potential to increase dose gradients, and dose levels within a small lung tumour. The magnitude of tumour dose increase or lung sparing can be optimized through manipulation of RT parameters (e.g. beam energy and field size).

[250]

TÍTULO / TITLE - Cytokines from the tumor microenvironment modulate sirtinol cytotoxicity in A549 lung carcinoma cells.
RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS - Pal S; Shankar BS; Sainis KB
INSTITUCIÓN / INSTITUTION - Radiation Biology & Health Sciences Division, Bio-Medical Group, Bhabha Atomic Research Centre, Modular Laboratories, Mumbai 400085, India.

RESUMEN / SUMMARY - Cytokines in tumor microenvironment play an important role in the success or failure of molecular targeted therapies. We have chosen tumor necrosis factor alpha (TNF-alpha), TNF related apoptosis inducing ligand (TRAIL), insulin-like growth factor 1 (IGF-1) and transforming growth factor beta (TGF-beta) as representative pro-inflammatory, pro-apoptotic, anti-apoptotic and anti-inflammatory tumor derived cytokines. Analysis of Oncomine database revealed the differential expression of these cytokines in a subset of cancer patients. The effects of these cytokines on cytotoxicity of FDA approved drugs - cisplatin and taxol and inhibitors of epidermal growth factor receptor - AG658, Janus kinase - AG490 and SIRT1 - sirtinol were assessed in A549 lung cancer cells. TRAIL augmented cytotoxicity of sirtinol and IGF-1 had a sparing effect. Since TRAIL and IGF-1 differentially modulated sirtinol cytotoxicity, further studies were carried out to identify the mechanisms. Sirtinol or knockdown of SIRT1 increased the expression of death receptors DR4 and DR5 and sensitized A549 cells to TRAIL. Increased cell death in presence of TRAIL and sirtinol was caspase independent and demonstrated classical features of necroptosis. Inhibition of iNOS increased caspase activity and switched the mode of cell death to caspase mediated apoptosis. Interestingly, sirtinol or SIRT1 knockdown did not increase IGF-1R expression. Instead, it abrogated ligand induced downregulation of IGF-1R and increased cell survival through PI3K-AKT pathway. In conclusion, these findings reveal that the tumor microenvironment contributes to modulation of cytotoxicity of drugs and that combination therapy, with agents that increase TRAIL signaling and suppress IGF-1 pathway may potentiate anticancer effect.
Genetic linkage analysis identifies Pas1 as the common locus modulating lung tumorigenesis and acute inflammatory response in mice.

Selective breeding for the acute inflammatory response (AIR) generated two mouse lines characterized by maximum (AIRmax) and minimum (AIRmin) responses, explained by the additive effect of alleles differentially fixed in quantitative trait loci (QTLs). These mice also differ in their susceptibility to lung tumorigenesis, raising the possibility that the same loci are involved in the control of both phenotypes. To map the QTLs responsible for the different phenotypes, we carried out a genome-wide linkage analysis using single-nucleotide polymorphism arrays in a pedigree consisting of 802 mice, including 693 (AIRmax x AIRmin)F2 intercross mice treated with urethane and phenotyped for AIR and lung tumor multiplicity. We mapped five loci on chromosomes 4, 6, 7, 11 and 13 linked to AIR (logarithm of odds (LOD)=3.56, 3.52, 15.74, 7.74 and 3.34, respectively) and two loci linked to lung tumor multiplicity, on chromosomes 6 and 18 (LOD=12.18 and 4.69, respectively). The known pulmonary adenoma susceptibility 1 (Pas1) locus on chromosome 6 was the only locus linked to both phenotypes, suggesting that alleles of this locus were differentially fixed during breeding and selection of AIR mice. These results represent a step toward understanding the link between inflammation and cancer.
Malignant mesothelioma: Development to therapy.

**RESUMEN / SUMMARY:**
Malignant mesothelioma (MM) is an aggressive cancer of the mesothelium caused by asbestos. Asbestos use has been reduced but not completely stopped. In addition, natural or man-made disasters will continue to dislodge asbestos from old buildings into the atmosphere and as long as respirable asbestos is available, MM will continue to be a threat. Due to the long latency period of MM development, it would still take decades to eradicate this disease if asbestos was completely removed from our lives today. Therefore, there is a need for researchers and clinicians to work together to understand this deadly disease and find a solution for early diagnosis and treatment. This article focuses on developmental mechanisms as well as current therapies available for MM.


Primary small cell carcinoma of the stomach: clinical outcomes and prognoses.

**RESUMEN / SUMMARY:**
Malignant mesothelioma (MM) is an aggressive cancer of the mesothelium caused by asbestos. Asbestos use has been reduced but not completely stopped. In addition, natural or man-made disasters will continue to dislodge asbestos from old buildings into the atmosphere and as long as respirable asbestos is available, MM will continue to be a threat. Due to the long latency period of MM development, it would still take decades to eradicate this disease if asbestos was completely removed from our lives today. Therefore, there is a need for researchers and clinicians to work together to understand this deadly disease and find a solution for early diagnosis and treatment. This article focuses on developmental mechanisms as well as current therapies available for MM.


**AUTORES / AUTHORS:**
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Welding and Lung Cancer in a Pooled Analysis of Case-Control Studies.

**RESUMEN / SUMMARY:**
Welding and Lung Cancer in a Pooled Analysis of Case-Control Studies.


**AUTORES / AUTHORS:**
Kendzia B; Behrens T; Jockel KH; Siemiatycki J; Kromhout H; Vermeulen R; Peters S; Van Gelder R; Olsson A; Bruske I; Wichmann HE; Stucker I; Guida F; Tardon A; Merletti F; Mirabelli D; Richiardi L; Pohlabeln H; Ahrens W; Landi MT; Caporaso N; Consonni D; Zardide D; Szessen-Dabrowska N; Lissowska J;
RESUMEN / SUMMARY: - Several epidemiologic studies have indicated an increased risk of lung cancer among welders. We used the SYNERGY project database to assess welding as a risk factor for developing lung cancer. The database includes data on 15,483 male lung cancer cases and 18,388 male controls from 16 studies in Europe, Canada, China, and New Zealand conducted between 1985 and 2010. Odds ratios and 95% confidence intervals between regular or occasional welding and lung cancer were estimated, with adjustment for smoking, age, study center, and employment in other occupations associated with lung cancer risk. Overall, 568 cases and 427 controls had ever worked as welders and had an odds ratio of developing lung cancer of 1.44 (95% confidence interval: 1.25, 1.67) with the odds ratio increasing for longer duration of welding. In never and light smokers, the odds ratio was 1.96 (95% confidence interval: 1.37, 2.79). The odds ratios were somewhat higher for squamous and small cell lung cancers than for adenocarcinoma. Another 1,994 cases and 1,930 controls had ever worked in occupations with occasional welding. Work in any of these occupations was associated with some elevation of risk, though not as much as observed in regular welders. Our findings lend further support to the hypothesis that welding is associated with an increased risk of lung cancer.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Wu D; Pang Y; Wilkerson MD; Wang D; Hammerman PS; Liu JS


RESUMEN / SUMMARY: - Background:Squamous cell lung cancer (SqCC) is the second most common type of lung cancer in the United States. Previous studies have used gene-expression data to classify SqCC samples into four subtypes, including the primitive, classical, secretory and basal subtypes. These subtypes have different survival outcomes, although it is unknown whether these molecular subtypes predict response to therapy.Methods:Here, we analysed RNAseq data of 178 SqCC tumour samples and characterised the features of the different SqCC subtypes to define signature genes and pathway alterations specific to each subtype. Further, we
compared the gene-expression features of each molecular subtype to specific time points in models of airway development. We also classified SqCC-derived cell lines and their reported therapeutic vulnerabilities. Results: We found that the primitive subtype may come from a later stage of differentiation, whereas the basal subtype may be from an early time. Most SqCC cell lines responded to one of five anticancer drugs (Panobinostat, 17-AAG, Irinotecan, Topotecan and Paclitaxel), whereas the basal-type cell line EBC-1 was sensitive to three other drugs (PF2341066, AZD6244 and PD-0325901). Conclusion: Compared with the other three subtypes of cell lines, the secretory-type cell lines were significantly less sensitive to the five most effective drugs, possibly because of their low proliferation activity. We provide a bioinformatics framework to explore drug repurposing for cancer subtypes based on the available genomic profiles of tumour samples, normal cell types, cancer cell lines and data of drug sensitivity in cell lines.

[257]

TÍTULO / TITLE: - Association of Exon 19 and 21 EGFR Mutation Patterns with Treatment Outcome after First-Line Tyrosine Kinase Inhibitor in Metastatic Non-Small-Cell Lung Cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Lee VH; Tin VP; Choy TS; Lam KO; Choi CW; Chung LP; Tsang JW; Ho PP; Leung DK; Ma ES; Liu J; Shek TW; Kwong DL; Leung TW; Wong MP

INSTITUCIÓN / INSTITUTION: - Departments of *Clinical Oncology and daggerPathology, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, People’s Republic of China; double daggerDepartment of Community Medicine, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, People’s Republic of China; and section signDepartment of Pathology, Hong Kong Sanatorium and Hospital, Hong Kong, People’s Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: This study investigated whether there were differential survival outcomes to first-line tyrosine kinase inhibitors (TKI) in patients with metastatic non-small-cell lung cancer harboring different subtypes of exon 19 and exon 21 mutations on epidermal growth factor receptor (EGFR). METHODS: Of 452 patients with stage IIIIB and IV non-small-cell lung cancer, 192 patients (42.5%) harbored EGFR mutation and 170 (37.5%) received TKI as first-line treatment. EGFR mutation analysis was performed by direct sequencing. Survival and response outcome were compared among different subtypes of exon 19 and exon 21 EGFR mutations in these 170 patients. RESULTS: Patients harboring exon 19 18-nucleotide deletion
(delL747_P753insS) had the shortest median progression-free survival (PFS) (6.5 months), followed by those with 15-nucleotide deletion (delE746_A750) (12.4 months) and mixed insertion/substitution mutations (22.3 months; p = 0.012). However, patients who had exon 19 deletions starting on codon E746 had better median PFS (14.2 months) than those starting on L747 (6.5 months; hazard ratio, 0.445; 95% confidence interval [0.219-0.903]; p = 0.021). Besides, exon 21 L858R derived a longer median PFS than L861R/L861Q (11.4 months versus 2.1 months, respectively; hazard ratio, 0.298; 95% confidence interval [0.090-0.980]; p = 0.034). CONCLUSIONS: Different subtypes of EGFR exon 19 and 21 mutations exhibited differential survival to first-line TKI therapy. Detailed sequence evaluation of exon 19 deletions may provide important prognostic information on survival outcome after TKI.

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**TÍTULO / TITLE:** Sodium Valproate Sensitizes Non-Small Lung Cancer A549 Cells to gammadelta T-Cell-Mediated Killing through Upregulating the Expression of MICA.

**RESUMEN / SUMMARY:** Major histocompatibility complex (MHC) class I chain-related protein A (MICA) is involved in gammadelta T-cell recognition of target tumor cells. The aim of this study was to investigate the feasibility of utilization of sodium valproate (VPA), a histone deacetylase inhibitor, to sensitize non-small cell lung cancer A549 cells to gammadelta T-cell-mediated killing. VPA induced a dose-dependent increase in the mRNA and protein expression of MICA in A549 cells. gammadelta T cells showed cytotoxicity to A549 cells, which was increased by about 50% in the presence of VPA. The concomitant addition of MICA antibody significantly attenuated the VPA-mediated sensitization to gammadelta T-cell killing. VPA enhanced the cleavage of caspase-3 and caspase-9 in A549 cells cocultured with gammadelta T cells, and such enhancement was reversed by the MICA antibody. In conclusion, VPA sensitizes tumor cells to gammadelta T-cell-mediated cytotoxicity through the upregulation of MICA and may thus have benefits in improving gammadelta T-cell-based cancer immunotherapy.

[259]
TÍTULO / TITLE: - p190A RhoGAP is involved in EGFR pathways and promotes proliferation, invasion and migration in lung adenocarcinoma cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Notsuda H; Sakurada A; Endo C; Okada Y; Horii A; Shima H; Kondo T

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai 980-8575, Japan.

RESUMEN / SUMMARY: - Overcoming acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFRTKIs) is an emerging issue in lung cancer treatment. We report evidence that a GTPase-activating protein, p190A RhoGAP (p190), is a potential molecular target for the treatment of lung adenocarcinoma. We documented inhibition of phosphorylation of p190 by EGFR-TKI treatment in lung adenocarcinoma cell lines. Small interfering RNA-mediated knockdown of p190 leads lung adenocarcinoma cells to growth suppression and to inhibition of invasion/migration through inducing cell cycle arrest but not apoptosis. These findings were observed not only in EGFR-TKI-sensitive cells but also in EGFR-TKI-resistant cells; even in cell lines harboring K-ras mutations. The mechanism of this inhibitory effect on growth and invasion/migration through Ras inactivation through disrupting the p190-A RhoGAP/p120RasGAP complex. In addition, a high level of p190 mRNA expression was observed in majority of surgically obtained tissue from lung adenocarcinoma patients. Overexpression of p190 mRNA associated with poor disease-free survival. The results suggest that overexpression of p190 mRNA may be involved in the carcinogenesis of lung adenocarcinoma. These findings indicate that p190 is a possible molecular target for treatment of lung adenocarcinoma.

[260]

TÍTULO / TITLE: - Malignant Pleural Mesothelioma: Role of CT, MRI, and PET/CT in Staging Evaluation and Treatment Considerations.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Truong MT; Viswanathan C; Godoy MB; Carter BW; Marom EM

INSTITUCIÓN / INSTITUTION: - Department of Diagnostic Radiology, Division of Diagnostic Imaging, University of Texas, M.D. Anderson Cancer Center, Houston, TX. Electronic address: mtruong@mdanderson.org.
miR-93-directed downregulation of DAB2 defines a novel oncogenic pathway in lung cancer.

RESUMEN / SUMMARY: The disabled homolog 2 (DAB2) gene was recently identified as a tumor suppressor gene with its expression downregulated in multiple cancer types. The role of DAB2 in lung tumorigenesis, however, is not fully characterized, and the mechanisms of DAB2 dysregulation in lung cancer are not defined. Here we show that low DAB2 levels in lung tumor specimens are significantly correlated with poor patient survival, and that DAB2 overexpression significantly inhibits cell growth in cultured lung cancer cells, indicating its potent tumor suppressor function. We next identify that microRNA miR-93 functions as a potent repressor of DAB2 expression by directly targeting the 3'UTR of the DAB2 mRNA. Using in vitro and in vivo approaches, we demonstrate that miR-93 overexpression has an important role in promoting lung cancer cell growth, and that its oncogenic function is primarily mediated by downregulating DAB2 expression. Our clinical investigations further indicate that high tumor levels of miR-93 are correlated with poor survival of lung cancer patients. The correlations of both low DAB2 and high miR-93 expression levels with poor patient survival strongly support the critical role of the miR-93/DAB2 pathway in determining lung cancer progression.

Detection of aberrant methylation of 10 genes in genomic DNA of lung tumors.

RESUMEN / SUMMARY: The disabled homolog 2 (DAB2) gene was recently identified as a tumor suppressor gene with its expression downregulated in multiple cancer types. The role of DAB2 in lung tumorigenesis, however, is not fully characterized, and the mechanisms of DAB2 dysregulation in lung cancer are not defined. Here we show that low DAB2 levels in lung tumor specimens are significantly correlated with poor patient survival, and that DAB2 overexpression significantly inhibits cell growth in cultured lung cancer cells, indicating its potent tumor suppressor function. We next identify that microRNA miR-93 functions as a potent repressor of DAB2 expression by directly targeting the 3'UTR of the DAB2 mRNA. Using in vitro and in vivo approaches, we demonstrate that miR-93 overexpression has an important role in promoting lung cancer cell growth, and that its oncogenic function is primarily mediated by downregulating DAB2 expression. Our clinical investigations further indicate that high tumor levels of miR-93 are correlated with poor survival of lung cancer patients. The correlations of both low DAB2 and high miR-93 expression levels with poor patient survival strongly support the critical role of the miR-93/DAB2 pathway in determining lung cancer progression.
Treatment Outcomes in Elderly with Advanced-Stage Non-small Cell Lung Cancer.

PURPOSE: Lung cancer remains the top cause of cancer morbidity and mortality in the world. Although the identification of epidermal growth factor receptor (EGFR) gene mutations could predict efficacy of tyrosine kinase inhibitor (TKI), testing for predictive biomarkers are not always possible due to tissue availability. The overall therapeutic decision remains a clinical one for a significant proportion of elderly patients with advanced stage lung cancer but no known EGFR mutation status. The purpose of this study was to compare the outcome of drug treatment modalities in progression-free survival (PFS) and overall survival (OS) for elderly with advanced-stage non-small cell lung cancer (NSCLC) and to identify clinical parameters that could predict treatment outcome.

METHODS: Clinical records of patients aged 70 years or older with advanced-stage NSCLC who have received treatment were reviewed. A group of gender- and histology-matched subjects younger than age 70 years were identified as controls. RESULTS: Fifty-six elderly patients were included. The median age at diagnosis was 73 years; 60.7% received only one line of treatment. Baseline performance status (PS) was the only predictor of improved PFS (p = 0.042) and OS (p = 0.002). There was no difference in survival between the upfront chemotherapy and the TKI groups CONCLUSIONS: In elderly with advanced-stage NSCLC without known EGFR mutation status, use of EGFR-TKI and chemotherapy resulted in comparable survival benefits. Age was not predictive of worse treatment outcome. The baseline PS should be taken into consideration in the therapeutic decision in elderly with NSCLC where the EGFR mutation status is not known.
Epithelial membrane protein 3 (EMP3) is a typical member of the epithelial membrane protein (EMP) family which has been reported to be a tumor suppressor gene in neuroblastomas and gliomas and recently reported to be commonly repressed in esophageal squamous cell carcinoma (ESCC) cell lines. However, the expression and clinical significance of EMP3 protein in lung cancer have not yet been elucidated. In this article, we detected that the expression of EMP3 in non-small cell lung cancer was significantly lower than the expression of normal lung tissues (P<0.01) by western blot. EMP3 expression in lung cancer was significantly related to p-TNM stage (P<0.05) and EMP3 was negatively correlated with proliferation marker Ki67 (r=−0.775; P<0.01). However, no significant correlations were found between EMP3 and other clinical parameters. The post-recurrent survival after radical surgery was poorer in lung cancer patients with lower EMP3 expression (P<0.01). While in vitro, following release from serum starvation of A549 NSCLC cell, the expression of EMP3 was deregulated. Thus, our finding suggests that EMP3 may be a tumor suppressor gene at the late step of lung cancer, and EMP3 may be a potential prognostic marker and therapeutic target of NSCLC.
effectiveness in NSCLC diagnosis. EXPERIMENTAL DESIGN: The plasma levels of IDH1, CA125, Cyfra21-1, and CEA were assayed by ELISA. Blood samples were obtained from 1,422 participants (943 patients with NSCLC and 479 healthy controls). The samples were randomly divided into a training set and a test set. Receiver operating characteristic and binary logistic regression analyses were applied to evaluate diagnostic efficacy and establish diagnostic mathematical models. RESULTS: Plasma IDH1 levels were significantly higher in patients with NSCLCs than in healthy controls (P < 0.001). The diagnostic use of IDH1 in lung adenocarcinoma [area under curve (AUC): 0.858 and 0.810; sensitivity: 77.1% and 76.2%; specificity: 82.9% and 76.6%; in the training set and test set, respectively] was significantly greater than that of CA125, Cyfra21-1, or CEA (P < 0.001). The model combining IDH1 with CEA, CA125, and Cyfra21-1 was more effective for lung adenocarcinoma diagnosis than IDH1 alone (sensitivity and specificity in the training set: 75.8%, 89.6%; test set: 86.3%, 70.7%). In addition, the plasma levels of IDH1 could contribute to the diagnostic model of lung squamous cell carcinoma. CONCLUSIONS: IDH1 can be used as a plasma biomarker for the diagnosis of NSCLCs, particularly lung adenocarcinoma, with relatively high sensitivity and specificity. Clin Cancer Res; 19(18); 5136-45. © 2013 AACR.

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TÍTULO / TITLE: - Long-lasting inhibition of EGFR autophosphorylation in A549 tumor cells by intracellular accumulation of non-covalent inhibitors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Vacondio F; Carmi C; Galvani E; Bassi M; Silva C; Lodola A; Rivara S; Cavazzoni A; Alfieri RR; Petronini PG; Mor M
INSTITUCIÓN / INSTITUTION: - Dipartimento di Farmacia, Universita degli Studi di Parma, Parco Area delle Scienze 27/a, I-43124 Parma, Italy.
RESUMEN / SUMMARY: - In the present study, a small set of reversible or irreversible 4-anilinoquinazoline EGFR inhibitors was tested in A549 cells at early (1h) and late (8h) time points after inhibitor removal from culture medium. A combination of assays was employed to explain the observed long-lasting inhibition of EGFR autophosphorylation. We found that EGFR inhibition at 8h can be due, besides to the covalent interaction of the inhibitor with Cys797, as for PD168393 (2) and its prodrug 4, to the intracellular accumulation of non-covalent inhibitors by means of an active cell uptake, as for 5 and 6. Compounds 5-6 showed similar potency and duration of inhibition of EGFR autophosphorylation as the covalent inhibitor 2, while being devoid of reactive groups forming covalent bonds with protein thiols.
Baseline tumour measurements predict survival in advanced non-small cell lung cancer.

TÍTULO / TITLE: Baseline tumour measurements predict survival in advanced non-small cell lung cancer.

RESUMEN / SUMMARY: The association between tumour measurements and survival has been studied extensively in early-stage and locally advanced non-small cell lung cancer (NSCLC). We analysed these factors in patients with advanced NSCLC. Methods: Data were derived from the E4599 trial of paclitaxel-carboplatin+/-bevacizumab. Associations between the Response Evaluation Criteria in Solid Tumors (RECIST) baseline sum longest diameter (BSLD), response rate, progression-free survival (PFS) and overall survival (OS) were evaluated using univariate and multivariable Cox regression models. Results: A total of 759 of the 850 patients (89%) in the E4599 trial had measurable diseases and were included in this analysis. The median BSDL was 7.5 cm. BSDL predicted OS (hazard ratio (HR) 1.41; P<0.001) and had a trend towards association with PFS (HR 1.14; P=0.08). The median OS was 12.6 months for patients with BSDL <7.5 cm compared with 9.5 months for BSDL >/=7.5 cm. This association persisted in a multivariable model controlling multiple prognostic factors, including the presence and sites of extrathoracic disease (HR 1.24; P=0.01). There was no association between BSDL and response rate. Conclusion: Tumour measurements are associated with survival in the E4599 trial. If validated in other populations, this parameter may provide important prognostic information to patients and clinicians.
OBJECTIVE: The purpose of this study was to evaluate the clinical and radiological features of patients with fungal infection mimicking thoracic malignancy and to establish a diagnostic approach for both clinicians and radiologists to avoid misdiagnosis. METHODS: In this retrospective study, we reviewed clinical and computed tomography (CT) findings from 27 patients who presented with suspicion of thoracic malignancy who were ultimately diagnosed with fungal disease. RESULTS: Patients’ median age was 55.7 (range 31-78) years. The most common clinical findings were cough (48.1 %), expectoration (33.3 %), chest pain (25.9 %), weakness (25.9 %), weight loss (18.5 %), and hemoptysis, dyspnea, and fever (7.4 % each). The median lesion size was 35.5 (range 10-85) mm. CT findings included a solid nodule (51.9 %), solid mass (37 %), or both (11.1 %). Nodule and mass margins were lobulated in 9 (33.3 %) patients, ill-defined in 5 (18.5 %), spiculated in 4 (14.8 %), and smooth in 4 (14.8 %) patients. Additional findings included consolidation in 4 (14.8 %) patients, cavitation in 3 (11.1 %), pleural effusion in 2 (7.4 %), and lymphadenopathy in 11 (40.7 %) patients. In all patients, specific diagnoses were made and confirmed by histopathology; final diagnoses were histoplasmosis (25.9 %), coccidiomycosis (22.2 %), cryptococcosis (22.2 %), aspergillosis (14.8 %), North American blastomycosis (7.4 %), mucormycosis (3.75 %), and paracoccidioidomycosis (3.75 %). CONCLUSIONS: Fungal infection can present with clinical and radiological features that are indistinguishable from thoracic malignancy, such as lung nodules or masses. Because the management and outcomes of fungal infection and malignancy are entirely distinct, the establishment of a specific diagnosis is critical to provide appropriate therapy.

**AUTORES / AUTHORS:** Ryuge S; Sato Y; Jiang SX; Wang G; Kobayashi M; Nagashio R; Katono K; Iyoda A; Satoh Y; Masuda N

**INSTITUCIÓN / INSTITUTION:** Department of Respiratory Medicine, School of Medicine, Kitasato University, Kanagawa, Japan.

**RESUMEN / SUMMARY:**

**BACKGROUND:** The leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5), also known as Gpr49, has been identified as a marker of crypt basal columnar stem cells along the gastrointestinal tract and of bulge stem cells in the hair follicle. The aims of this study were to immunohistochemically examine Lgr5 expression in surgically resected non-small cell lung carcinomas (NSCLC), and evaluate the relationships between Lgr5 expression and the clinicopathological parameters and prognosis of patients. **METHODS:** Lgr5 expression was immunohistochemically studied in 266 consecutive resected NSCLCs, and its associations with clinicopathological parameters including TTF-1 and CDX-2 expressions were evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of Lgr5 expression on survival. **RESULTS:** Lgr5 was detected only in tumors with adenocarcinoma histology, and 16 cases were judged as positive. Among lung adenocarcinomas, Lgr5 expression was significantly associated with a larger tumor size (>5cm) (P=0.033), higher pathological TNM stage of the disease (stage II and III) (P=0.025), TTF-1-negative adenocarcinoma (P=0.042), and poorer prognosis (P=0.026). However, Lgr5 expression was not an independent predictor of poorer survival after controlling for clinicopathological factors. **CONCLUSIONS:** The present study reveals that Lgr5 is expressed in a subset of lung adenocarcinoma, and its expression is related to some clinicopathological parameters and a poorer prognosis, although further studies are required to clarify the biological function of Lgr5 in lung adenocarcinoma.

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**TÍTULO / TITLE:** MiR-199a suppresses the hypoxia-induced proliferation of non-small cell lung cancer cells through targeting HIF1alpha

**RESUMEN / SUMMARY:**

Deregulated microRNAs (miRNAs) are small noncoding RNAs that are involved in the carcinogenesis of various cancers, including lung cancer.
HIF1alpha has been suggested to be a master regulator of hypoxia-induced cell proliferation. The relationship between HIF1alpha expression and the progression of non-small cell lung cancer (NSCLC) is not fully understood, and whether HIF1alpha expression is regulated by miRNAs in this process remains unclear. In this study, we found that the upregulation of HIF1alpha expression and the reduction in miR-199a levels were highly associated with NSCLC progression. NSCLC cells derived from cancer tissues with low miR-199a levels showed high HIF1alpha expression and high proliferation capacity. Moreover, HIF1alpha and glycolysis inhibitors suppress the proliferation of NSCLC cells. MiR-199a overexpression suppressed the hypoxia-induced proliferation of NSCLC cells through targeting elevated HIF1alpha and blocking the downstream upregulation of PDK1 without affecting AKT activation. Together, these results indicate that downregulation of miR-199a is essential for hypoxia-induced proliferation through derepressing the expression of HIF1alpha expression and affecting HIF1alpha mediated glycolytic pathway in NSCLC progression.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lei B; Liu S; Qi W; Zhao Y; Li Y; Lin N; Xu X; Zhi C; Mei J; Yan Z; Wan L; Shen H
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanfang Hospital, Guangzhou, China; Department of Pathology, School of Basic Medical Sciences, Southern Medical University, Guangzhou, China.
RESUMEN / SUMMARY: - AIMS: The aim of this study was to evaluate the prevalence of PBK/TOPK (PDZ-binding kinase/T-LAK cell-originated protein kinase) expression, and explore the prognostic significance of PBK/TOPK expression alone and in combination with Ki67 and p53 expression in non-small-cell lung cancer (NSCLC). METHODS AND RESULTS: We detected PBK/TOPK expression in 30 samples of normal lung tissue, 32 lymph node metastases and 279 primary non-small-cell lung cancers by immunohistochemistry, and analysed the correlation of PBK/TOPK expression with Ki67 and p53 expression in primary tumour tissues. The results showed that PBK/TOPK expression was higher in lymph node metastases (75%) than in primary tumours (44.8%) and normal lung tissues (0%). PBK/TOPK expression was associated with histological type, lymph node metastasis, and TNM stage, and was positively correlated with Ki67 and p53 expression in NSCLC. Univariate and multivariate survival analyses showed that PBK/TOPK expression was significantly associated with an unfavourable prognosis in NSCLC. The prognosis of patients with tumours positive for
both PBK/TOPK expression and Ki67 or p53 expression was also significantly unfavourable. CONCLUSIONS: PBK/TOPK expression is positively correlated with Ki67 and p53 expression, and can be used as an independent prognostic factor in NSCLC.

[273]

- Selective Cytotoxicity and Combined Effects of Camptothecin or Paclitaxel with Sodium-R-Alpha Lipoate on A549 Human Non-Small Cell Lung Cancer Cells.

- Nonsmall cell lung cancer (NSCLC) is the most common type of lung cancer and remains the deadliest form of cancer in the United States and worldwide. New therapies are highly sought after to improve outcome. The effect of sodium-R-alpha lipoate on camptothecin- and paclitaxel-induced cytotoxicity was evaluated on A549 NSCLC and BEAS-2B “normal” lung epithelial cells. Combination indices (CI) and dose reduction indices (DRI) were investigated by studying the cytotoxicity of sodium-R-alpha lipoate (0-16 mM), camptothecin (0-25 nM) and paclitaxel (0-0.06 nM) alone and in combination. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliu bromide (MTT) was used to assess cytotoxicity. The combinational cytotoxic effects of sodium-R-alpha lipoate with camptothecin or paclitaxel were analyzed using a simulation of dose effects (CompuSyn® 3.01). The effects of sodium-R-alpha lipoate on camptothecin- and paclitaxel-induced cytotoxicity varied based on concentrations and treatment times. It was found that sodium-R-alpha lipoate wasn’t cytotoxic toward BEAS-2B cells at any of the concentrations tested. For A549 cells, CIs [(additive (CI = 1); synergistic (CI < 1); antagonistic (CI < 1)] were lower and DRI were higher for the camptothecin/sodium-R-alpha-lipoate combination (CI = approximately 0.17-1.5; DRI = approximately 2.2-22.6) than the paclitaxel/sodium-R-alpha-lipoate combination (CI = approximately 0.8-9.9; DRI = approximately 0.10-5.8) suggesting that the camptothecin regimen was synergistic and that the addition of sodium-R-alpha lipoate was important for reducing the camptothecin dose and potential for adverse effects.

[274]
Olfactory Receptor 51E1 as a Novel Target in Somatostatin Receptor Negative Lung Carcinoids.

Somatostatin receptors (SSTRs) may be used in lung carcinoids (LCs) for diagnosis and therapy, although additional targets are clearly warranted. This study aimed to investigate whether olfactory receptor 51E1 (OR51E1) may be a potential target for LCs. OR51E1 coding sequence was analyzed in LC cell lines, NCI-H727 and NCI-H720. OR51E1 transcript expression was investigated in LC cell lines and frozen specimens by quantitative real-time PCR. OR51E1, SSTR2, SSTR3, and SSTR5 expression was evaluated by immunohistochemistry on paraffin-embedded sections of 73 typical carcinoids (TCs), 14 atypical carcinoids (ACs) and 11 regional/distant metastases, and compared to OctreoScan data. Immunohistochemistry results were rendered semiquantitatively on a scale from 0 to 3+, taking into account the cellular compartmentalization (membrane vs. cytoplasm) and the percentage of tumor cells (<50% vs. >50%). Our results showed that wild-type OR51E1 transcript was expressed in both LC cell lines. OR51E1 mRNA was expressed in 9/12 TCs and 7/9 ACs (p=NS). Immunohistochemically, OR51E1, SSTR2, SSTR3 and SSTR5 were detected in 85%, 71%, 25% and 39% of TCs, and in 86%, 79%, 43% and 36% of ACs, respectively. OR51E1 immunohistochemical scores were higher or equal compared to SSTRs in 79% of TCs and 86% of ACs. Furthermore, in the LC cases where all SSTR subtypes were lacking, membrane OR51E1 expression was detected in 10/17 TCs and ½ ACs. Moreover, higher OR51E1 immunohistochemical scores were detected in 5/6 OctreoScan-negative LC lesions. Therefore, the high expression of OR51E1 in LCs makes it a potential novel diagnostic target in SSTR-negative tumors.

Time to first cigarette and lung cancer risk in Japan.

Our results showed that wild-type OR51E1 transcript was expressed in both LC cell lines. OR51E1 mRNA was expressed in 9/12 TCs and 7/9 ACs (p=NS). Immunohistochemically, OR51E1, SSTR2, SSTR3 and SSTR5 were detected in 85%, 71%, 25% and 39% of TCs, and in 86%, 79%, 43% and 36% of ACs, respectively. OR51E1 immunohistochemical scores were higher or equal compared to SSTRs in 79% of TCs and 86% of ACs. Furthermore, in the LC cases where all SSTR subtypes were lacking, membrane OR51E1 expression was detected in 10/17 TCs and ½ ACs. Moreover, higher OR51E1 immunohistochemical scores were detected in 5/6 OctreoScan-negative LC lesions. Therefore, the high expression of OR51E1 in LCs makes it a potential novel diagnostic target in SSTR-negative tumors.
RESUMEN / SUMMARY: - BACKGROUND: Cigarette smoking is the major cause of lung cancer (LC). Although the time to first cigarette (TTFC) of the day is a distinct indicator of nicotine dependence, little information is available on its possible relation to LC. 
PATIENTS AND METHODS: This case-control study includes a total of 1572 incident LC cases and 1572 non-cancer controls visiting for the first time the Aichi Cancer Center Hospital between 2001 and 2005. We estimated the odds ratio (OR) and 95% confidence interval (CI) for TTFC using a logistic regression model after adjustment for several potential confounders. RESULTS: TTFC was inversely associated with the risk of LC. This association was consistent across histological subtypes of LC. For all LCs considered among ever smokers and after accurate allowance for smoking quantity and duration, besides other relevant covariates, compared with TTFC >60 min, the adjusted ORs were 1.08 (95% CI, 0.73-1.61) for TTFC of 31-60 min, 1.40 (0.98-2.01) for 6-30 min and 1.86 (1.28-2.71) for within 5 min (P<0.001). Statistically marginally significant heterogeneity by histological subtype was observed (P=0.002). CONCLUSIONS: Nicotine dependence, as indicated by the TTFC, is associated with increased risk of LC and is therefore an independent marker of exposure to tobacco smoking.

[276]

TÍTULO / TITLE: - Matrine induction of reactive oxygen species activates p38 leading to caspase-dependent cell apoptosis in non-small cell lung cancer cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Tan C; Qian X; Jia R; Wu M; Liang Z

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Soochow University, Suzhou, Jiangsu 215123, P.R. China.

RESUMEN / SUMMARY: - Non-small cell lung carcinoma (NSCLC) is one of the most refractory cancers in the clinic; it is insensitive to chemotherapy and is usually excised. However, screening natural compounds from herbs is also considered a possible method for its therapy. In the present study, we investigated whether matrine, a natural compound isolated from Sophora flavescens Ait. and exerting an inhibitory effect on lung cancer cells, also indicates inhibition on NSCLC cells and elucidated its molecular mechanism. Firstly, it is confirmed that matrine induces apoptosis of human NSCLC cells with anti-apoptotic factors inhibited and dependent on caspase activity. In addition, we found that matrine increases the phosphorylation of p38 but not its total protein, and inhibition of the p38 pathway with SB202190 partially prevents matrine-induced apoptosis. Furthermore, matrine generates reactive oxygen species (ROS) in a dose- and time-dependent manner, which is reversed by pretreatment with N-acetyl-L-
cysteine (NAC). Additionally, inhibition of cell proliferation and increase of phosphorylation of p38 was also partially reversed by NAC. Collectively, matrine activates p38 pathway leading to a caspase-dependent apoptosis by inducing generation of ROS in NSCLC cells and may be a potential chemical for NSCLC.

[277]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Jiang L; Chang J; Zhang Q; Sun L; Qiu X
INSTITUCIÓN / INSTITUTION: - Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, Liaoning, China, 1.
RESUMEN / SUMMARY: - The mature microRNA hsa-miR-125ª-3p is derived from the 3′ end of pre-miR-125ª. Here, we reported that hsa-miR-125ª-3p suppressed proliferation and induced apoptosis in A549 cells. In addition, wild-type p53 mRNA and protein expression was increased by hsa-miR-125ª-3p over-expression. Moreover, blocking wild-type p53 attenuated the effect of hsa-miR-125ª-3p on apoptosis but could not restore completely. In p53-deficient cell line H1299, hsa-miR-125ª-3p still induced apoptosis. Taken together, these data suggest that hsa-miR-125ª-3p induces apoptosis not only via the p53 pathway in human lung cancer cells. These results provide new insight into the roles of the miR-125ª family in lung cancer.

[278]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Abulaiti A; Shintani Y; Funaki S; Nakagiri T; Inoue M; Sawabata N; Minami M; Okumura M
INSTITUCIÓN / INSTITUTION: - Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan.
RESUMEN / SUMMARY: - INTRODUCTION: Fibroblasts are key components of the tumor microenvironment. We clarified the role of transforming growth factor (TGF)-beta and interleukin (IL)-6 in the interaction between fibroblasts and non-small-cell lung cancer cells.
NSCLC) cells. METHODS: We used NSCLC cells (A549, NCI-H358) and normal human lung fibroblast (NHLF) cells to evaluate phenotypic changes in the presence of human IL-6, TGF-beta1, and conditioned media (CM) from these cells. Possible pathways were evaluated with SB431542, a TGF-beta receptor inhibitor, or an anti-human IL-6 receptor neutralizing antibody (IL-6R-Ab). RESULTS: A549 and NCI-H358 cells incubated with IL-6 (50ng/mL) and TGF-beta1 (2ng/mL) showed significantly increased epithelial-mesenchymal transition (EMT) signaling compared to those treated with TGF-beta1 alone. Furthermore, NHLF cells were synergistically activated by IL-6 and TGF-beta1. IL-6 increased the expression of TGF-beta type I receptors on the surface of A549, NCI-H358 and NHLF cells and enhanced TGF-beta signaling. TGF-beta1 induced phenotypic changes were attenuated by IL-6R-Ab. NHLF cells were activated and A549 cells showed induction of EMT in response to CM from the other cell type. These activities were attenuated by SB431542 or IL-6R-Ab, suggesting that interplay between NSCLC cells and NHLF may lead to increased EMT signaling in NSCLC cells and activation of NHLF cells through TGF-beta and IL-6 signaling. Subcutaneous co-injection of A549 and NHLF cells into mice resulted in a high rate of tumor formation compared with injection of A549 cells without NHLF cells. SB431542 or IL-6R-Ab also attenuated the tumor formation enhanced by co-injection of the two cell types. CONCLUSION: IL-6 enhanced epithelial cell EMT and stimulated tumor progression by enhancing TGF-beta signaling. IL-6 and TGF-beta may play a contributing role in maintenance of the paracrine loop between these two cytokines in the communication between fibroblasts and NSCLC cells for tumor progression.
with median interval to reirradiation of 36 months. Median reirradiation dose was 66Gy (RBE) in 32 fractions. Toxicity was scored with CTCAE v4.0, and survival outcomes were estimated using Kaplan-Meier. RESULTS: Thirty-one patients (94%) completed reirradiation. At a median 11 months' follow-up, 1-year rates of overall survival, progression-free survival, locoregional control, and distant metastasis-free survival were 47%, 28%, 54%, and 39%. Rates of severe (grade 3) toxicity were 9% esophageal, 21% pulmonary; 1 patient had grade 4 esophagitis, and 2 had grade 4 pulmonary toxicity. Nine patients experienced a second in-field failure. CONCLUSIONS: PBT is an option for treating recurrent NSCLC. However, the rates of locoregional recurrence and distant metastasis are high and the potential for toxicity significant. The risks and benefits of PBT must be carefully weighed in each case.

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TÍTULO / TITLE: Phase II study of docetaxel and vinorelbine as adjuvant chemotherapy for resected non-small cell lung cancers.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Chaft JE; Rekhtman N; Sima CS; Rusch V; Kris MG; Zakowski M; Azzoli CG

INSTITUCIÓN / INSTITUTION: Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 300 E, 66th Street, New York, NY, 10065, USA, chaftj@mskcc.org.

RESUMEN / SUMMARY: PURPOSE: For patients with resected stage II-III non-small cell lung cancers (NSCLCs), adjuvant cisplatin-based chemotherapy improves survival over surgery alone. For cisplatin ineligible patients, there is no standard adjuvant option. We evaluated drug delivery and toxicity of docetaxel and vinorelbine in patients who could not receive cisplatin. METHODS: Patients with completely resected stage IB-III NSCLCs were treated with up to 4 cycles of docetaxel and vinorelbine at the recommended phase II dose. The primary endpoint was drug delivery compared to historical delivery of adjuvant cisplatin plus vinorelbine. Secondary endpoints were toxicity and feasibility. RESULTS: Twenty-five patients were enrolled. Overall, 13/25 (52 %, 95 % CI 34-70) completed 4 cycles, and 19/25 (76 %, 95 % CI 60-87) completed >/=3 cycles. Twenty of 25 patients (80 %) experienced a Grade 3 or 4 adverse event. CONCLUSIONS: Delivery of this dose and schedule of docetaxel and vinorelbine was difficult with a dose delivery comparable to cisplatin plus vinorelbine, and cisplatin plus docetaxel, used in this setting.
TÍTULO / TITLE: - Existing models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Meniawy TM; Creaney J; Lake RA; Nowak AK
INSTITUCIÓN / INSTITUTION: - 1] M503, School of Medicine and Pharmacology, University of Western Australia, Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia [2] National Centre for Asbestos Related Disease, Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia [3] Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia.
RESUMEN / SUMMARY: - Background: Recent studies proposed neutrophil-to-lymphocyte ratio (NLR) as a prognostic biomarker in malignant pleural mesothelioma (MPM). We examined baseline prognostic variables including NLR and the EORTC and CALGB models as predictors of overall survival (OS) in MPM. Methods: In this retrospective study, 274 consecutive eligible, newly presenting patients with MPM were included. Of these, 159 received chemotherapy, 10 had tri-modality therapy, 2 underwent surgery only and 103 received supportive care alone. Univariate analyses and multivariate Cox models were calculated for OS. Results: In univariate analysis, poor prognostic factors were: age >/=65 years, nonepithelioid histology, stage III-IV, poor performance status (PS), weight loss, chest pain, low haemoglobin and high platelet count. A baseline NLR>/=5 did not predict worse OS (hazard ratio (HR) 1.25; P=0.122). On multivariate analysis, age, histology, PS, weight loss, chest pain and platelet count remained significant. The EORTC and CALGB prognostic groups were validated as predictive for OS (HR 1.62; P<0.001 and HR 1.65; P<0.001, respectively). Conclusion: Our findings validate standard prognostic variables and the existing EORTC and CALGB models, but not NLR, at initial diagnosis of MPM. In guiding patient management at diagnosis, it is important to consider multiple baseline variables that jointly predict survival.

[281]
TÍTULO / TITLE: - Thrombin induces epithelial-mesenchymal transition via PAR-1, PKC, and ERK1/2 pathways in A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Song JS; Kang CM; Park CK; Yoon HK

[282]
INSTITUCIÓN / INSTITUTION:  - Department of Internal Medicine, Yeouido St Mary’s Hospital, Catholic University Medical College, Seoul, Korea.

RESUMEN / SUMMARY: - ABSTRACT Thrombin activates protease-activated receptor (PAR)-1 and induces a myofibroblast phenotype in normal lung fibroblasts. The origins of myofibroblasts are resident fibroblasts, fibrocytes, and epithelial-mesenchymal transition (EMT). We investigated the effects of thrombin, an important mediator of interstitial lung fibrosis, on EMT in A549 human alveolar epithelial cells. We show that thrombin induced EMT and collagen I secretion through the activation of PAR-1, and PKC and ERK1/2 phosphorylation in A549 cells. These effects were largely prevented by a specific PAR-1 antagonist, short interfering RNA (siRNA) directed against PAR-1, or specific PKCalpha/beta, delta, and epsilon inhibitors. These data indicated that interaction with thrombin and alveolar epithelial cells might directly contribute to the pathogenesis of pulmonary fibrosis through EMT. Targeting PAR-1 on the pulmonary epithelium or specific inhibitors to PKCalpha/beta, delta, and epsilon might stop the fibrotic processes in human idiopathic pulmonary fibrosis by preventing thrombin-induced EMT.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Li J; Fu Y; Zhao B; Xiao Y; Chen R

INSTITUCIÓN / INSTITUTION:  - Department of Infectious Disease, Tangshan Worker’s Hospital, No. 27 Wenhua Road, Tangshan, Hebei, 063000, China, junruili@aliyun.com.

RESUMEN / SUMMARY: - Myeloperoxidase (MPO) is a phase I enzyme playing a crucial role in metabolically activating a wide range of procarcinogens, such as polycyclic aromatic hydrocarbons and aromatic amines. The G463A polymorphism in the promoter region of the MPO gene has been indicated in lung cancer risk. To investigate the precise association of MPO G463A polymorphism with the lung cancer risk, we performed this comprehensive meta-analysis with large available data published to date. The included 24 individual studies involving a total of 8,313 cases and 8,728 controls were identified by searching the PubMed, Embase, and Wanfang databases. The crude odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs) were calculated to estimate the association. Stratified analyses by ethnicity, source of controls, smoking status, and histological types were also conducted. Overall, the MPO G463A polymorphism was negatively related to the development of lung cancer in the following genetic models (A vs. G, OR = 0.90, 95 % CI = 0.82-0.99, P OR = 0.029; GA vs. GG, OR = 0.89, 95 % CI = 0.80-0.98, P OR = 0.022; AA + GA vs. GG, OR = 0.89, 95 % CI = 0.81-0.98, P OR = 0.023). Stratified analyses by
ethnicity indicated that the variant genotype of MPO G463A was associated with a decreased risk of lung cancer in Asians and Caucasians. Similar findings were observed among the smokers and population-based case-control studies. The MPO G463A polymorphism seemed to exert no effect on lung adenocarcinoma and squamous cell carcinoma. The comprehensive meta-analysis shows that the polymorphism of MPO G463A is a protective factor for lung cancer, particularly among the populations of Asians, Caucasians, and smokers.

[284]
**TÍTULO / TITLE:** - Association between myeloperoxidase G-463A polymorphism and lung cancer risk.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Huang C; Ma L; Li D

**INSTITUCIÓN / INSTITUTION:** - Global Health Institute, School of Public Health, Wuhan University, Wuhan, 430071, China.

**RESUMEN / SUMMARY:** - Many epidemiologic studies have investigated the association between myeloperoxidase (MPO) G-463A polymorphism and lung cancer risk, but the results were controversial. We performed a meta-analysis of 25 studies on MPO polymorphism and lung cancer risk published before July 2013. The allele of A was found to be associated with decreased risk of lung cancer compared with G allele (OR, 0.90; 95% CI, 0.82-0.98) in the general population. The significant association remained in the comparison between AA + AG and GG (OR, 0.92; 95% CI, 0.87-0.98). When it was stratified according to Asian population, the association between MPO polymorphism and lung cancer risk was further strengthened. However, no associations were found in the Caucasian population. This meta-analysis has demonstrated that MPO polymorphism might contribute to individual’s susceptibility to lung cancer in Asian population. Caucasian authors could re-investigate the association between MPO polymorphism and lung cancer risk with more specific participants. Future studies focusing on interactions between combined genes and environmental risk factors are warranted.

[285]
**TÍTULO / TITLE:** - Upregulation of miR-136 in human non-small cell lung cancer cells promotes Erk1/2 activation by targeting PPP2R2A.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**Enlace al texto completo (gratuito o de pago):** 1007/s13277-013-1067-6

**Enlace al texto completo (gratuito o de pago):** 1007/s13277-013-1087-2
MicroRNAs (miRNAs) have been integrated into cancer development and progression, because they repress translation of target genes which can be tumor suppressors and oncogenes. A number of miRNAs have been found to be closely related to human non-small cell lung cancer (NSCLC). However, the roles of miR-136 in NSCLC are still largely unknown. Here, we show that miR-136 is significantly upregulated in human NSCLC primary tumors and cell lines compared to their nontumor counterparts. Suppression of miR-136 expression in NSCLC cell line A549 inhibited both anchorage-dependent and anchorage-independent proliferation. Further studies showed that suppression of miR-136 expression attenuated phosphorylation of extracellular-signal-regulated kinase \( \frac{1}{2} \) (Erk1/2). We found that serine/threonine protein phosphatase 2a 55 kDa regulatory subunit B alpha isoform (PPP2R2A, also known as B55alpha) was a direct target of miR-136, and suppression of miR-136 expression led to a robust increase in both mRNA and protein levels of PPP2R2A. We found that miR-136 promoted phosphorylation of Erk1/2 through inhibition of PPP2R2A expression, and forced overexpression of PPP2R2A abrogated promotion of Erk1/2 phosphorylation by miR-136. Moreover, forced overexpression of PPP2R2A abrogated the promoting effect of miR-136 on cell growth and led to a reduced growth rate of NSCLC cells. Our findings indicate that miR-136 promotes Erk1/2 phosphorylation through targeting PPP2R2A in NSCLC cells and suggest that it may serve as a therapeutic target in NSCLC therapy.

[286]


- Enlace al Resumen / Link to its Summary

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computed tomography-defined N0 NSCLC that had an exact tumor-node-metastasis stage after surgery. Logistic regression analysis of group A’s clinical characteristics was used to estimate the independent predictors of N2 lymph node metastasis. A prediction model was then built and internally validated by using cross validation and externally validated in group B. The model was also compared with 2 previously described models. RESULTS: We identified 4 independent predictors of N2 disease: a younger age; larger tumor size; central tumor location; and adenocarcinoma or adenosquamous carcinoma pathology. The model showed good calibration (Hosmer-Lemeshow test: p = 0.96) with an area under the receiver operating characteristic curve (AUC) of 0.756 (95% confidence interval, 0.699 to 0.813). The AUC of our model was better than those of the other models when validated with independent data. CONCLUSIONS: Our prediction model estimated the pretest probability of N2 disease in computed tomography-defined N0 NSCLC and was more accurate than the existing models. Use of our model can be of assistance when making clinical decisions about invasive or expensive mediastinal staging procedures.

[287]

TÍTULO / TITLE: - The Oglycosylation mutant osteopontin alters lung cancer cell growth and migration in vitro and in vivo.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Minai-Tehrani A; Chang SH; Park SB; Cho MH
INSTITUCIÓN / INSTITUTION: - Laboratory of Toxicology, College of Veterinary Medicine, Seoul National University, Seoul 151742, Japan.
RESUMEN / SUMMARY: - Osteopontin (OPN) is an acidic, glycosylated and phosphorylated protein that plays an essential role in determining the aggressiveness and oncogenic potential of several types of cancer, including lung cancer. The OPN function is highly dependent on posttranslational modification (PTM) and regulation of the processes that involve OPN can be mediated through glycosylation. However, the connection between OPN function and its Oglycosylation in lung cancer cells has yet to be investigated. In the present study, this issue was addressed by studying the effects of wildtype (WT) OPN and a triple mutant ™ of OPN, which was mutated at three Oglycosylation sites in lung cancer cells. It was shown that OPN WT rather than OPN TM induced the OPN mediated signaling pathway. The OPN WT expression enhanced capdependent protein translation, NFkappaB activity and glucose uptake, whereas a reduction was observed in cells treated with OPN TM. The results clearly demonstrated that unlike OPN WT, OPN TM did not increase lung cancer cell growth and migration both in vitro and in a xenograft mouse model. Thus, results of the
present study suggested that targeting OPN by introducing OPN TM may be a good strategy for treating lung cancer.

[288]

TÍTULO / TITLE: - The in vitro photodynamic effect of laser activated gallium, indium and iron phthalocyanine chlorides on human lung adenocarcinoma cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Maduray K; Odhav B

INSTITUCIÓN / INSTITUTION: - Durban University of Technology, Department of Biotechnology and Food Technology, Steve Biko Campus, Durban 4001, South Africa. Electronic address: madurayk@yahoo.com.

RESUMEN / SUMMARY: - Metal-based phthalocyanines currently are utilized as a colorant for industrial applications but their unique properties also make them prospective photosensitizers. Photosensitizers are non-toxic drugs, which are commonly used in photodynamic therapy (PDT), for the treatment of various cancers. PDT is based on the principle that, exposure to light shortly after photosensitizer administration predominately leads to the production of reactive oxygen species for the eradication of cancerous cells and tissue. This in vitro study investigated the photodynamic effect of gallium (GaPcCl), indium (InPcCl) and iron (FePcCl) phthalocyanine chlorides on human lung adenocarcinoma cells (A549). Experimentally, 2x10^4 cells/ml were seeded in 24-well tissue culture plates and allowed to attach overnight, after which cells were treated with different concentrations of GaPcCl, InPcCl and FePcCl ranging from 2\mu g/ml to 100\mu g/ml. After 2h, cells were irradiated with constant light doses of 2.5J/cm^2, 4.5J/cm^2 and 8.5J/cm^2 delivered from a diode laser (=661nm). Post-irradiated cells were incubated for 24h before cell viability was measured using the MTT Assay. At 24h after PDT, irradiation with a light dose of 2.5J/cm^2 for each photosensitizing concentration of GaPcCl, InPcCl and FePcCl produced a significant decrease in cell viability, but when the treatment light dose was further increased to 4.5J/cm^2 and 8.5J/cm^2 the cell survival was less than 40%. Results also showed that photoactivated FePcCl decreased cell survival of A549 cells to 0% with photosensitizing concentrations of 40\mu g/ml and treatment light dose of 2.5J/cm^2. A 20\mu g/ml photosensitizing concentration of FePcCl in combination with an increased treatment light dose of either 4.5J/cm^2 or 8.5J/cm^2 also resulted in 0% cell survival. This PDT study concludes that low concentrations on GaPcCl, InPcCl and FePcCl activated with low level light doses can be used for the effective in vitro killing of lung cancer cells.
OBJECTIVE: To determine whether CT-perfusion (CT-p) can be used to evaluate the effects of chemotherapy and anti-angiogenic treatment in patients with non-small-cell lung carcinoma (NSCLC) and whether CT-p and standard therapeutic response assessment (RECIST) data obtained before and after therapy correlate. METHODS: 55 patients with unresectable NSCLC underwent CT-p before the beginning of therapy and 50 of them repeated CT-p 90 days after it. Therapeutic protocol included platinum-based doublets plus bevacizumab for non-squamous carcinoma and platinum-based doublets for squamous carcinoma. RECIST measurements and calculations of blood flow (BF), blood volume (BV), time to peak (TTP) and permeability surface (PS) were performed, and baseline and post-treatment measurements were tested for statistically significant differences. Baseline and follow-up perfusion parameters were also compared based on histopathological subclassification (2004 World Health Organization Classification of Tumours) and therapy response assessed by RECIST. RESULTS: Tumour histology was consistent with large cell carcinoma in 14/50 (28%) cases, adenocarcinoma in 22/50 (44%) cases and squamous cell carcinoma in the remaining 14/50 (28%) cases. BF and PS differences for all tumours between baseline and post-therapy measurements were significant (p=0.001); no significant changes were found for BV (p=0.3) and TTP (p=0.1). The highest increase of BV was demonstrated in adenocarcinoma (5.2±34.1%), whereas the highest increase of TTP was shown in large cell carcinoma (6.9±22.4%), and the highest decrease of PS was shown in squamous cell carcinoma (-21.5±18.5%). A significant difference between the three histological subtypes was demonstrated only for BV (p<0.007). On the basis of RECIST criteria, 8 (16%) patients were classified as partial response (PR), 2 (4%) as progressive disease (PD) and the remaining 40 (80%) as stable disease (SD). Among PR, a decrease of both BF (18±9.6%) and BV (12.6±9.2%) were observed; TTP increased in 3 (37.5%) cases, and PS decreased in 6 (75%) cases. SD patients showed an increase of BF, BV, TTP and PS in 6 (15%), 21 (52.5%), 23 (57.5%) and 2 (5%) cases, respectively. PD patients demonstrated an increase of BF (26±0.2%), BV (2.7±0.1%) and TTP (3.1±0.8%) while only PS decreased (23±0.2%). CONCLUSION: CT-p can adequately evaluate therapy-induced alterations in
NSCLC, and perfusion parameters correlate with therapy response assessment performed with RECIST criteria. ADVANCES IN KNOWLEDGE: Evaluating perfusional parameters, CT-p can demonstrate therapy-induced changes in patients with different types of lung cancer and identify response to treatment with excellent agreement to RECIST measurements.

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**TÍTULO / TITLE**: Tumor-stromal Interactions with Direct Cell Contacts Enhance Motility of Non-small Cell Lung Cancer Cells Through the Hedgehog Signaling Pathway.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL**: Anticancer Res. 2013 Sep;33(9):3715-23.

**AUTORES / AUTHORS**: Choe C; Shin YS; Kim SH; Jeon MJ; Choi SJ; Lee J; Kim J

**INSTITUCIÓN / INSTITUTION**: Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, Republic of Korea. jkimsmc@skku.edu.

**RESUMEN / SUMMARY**: The metastatic potential of non-small cell lung cancer (NSCLC) has been shown to be associated with interactions with the tumor microenvironment, which primarily comprises of cancer-associated fibroblasts (CAFs). Heterotypic cell-cell interactions occur via released signaling molecules and direct physical contact. To investigate the differential contribution of direct cell-cell contact and paracrine signaling factors to NSCLC metastasis, we performed two types of co-cultures: direct co-cultures of the NSCLC cell line H358 with primary cultures of CAFs from patients with resected NSCLC; and indirect co-cultures across a separable membrane. We showed that CAFs more potently induce epithelial-to-mesenchymal transition (EMT) in NSCLC H358 cells through direct contacts than through indirect interactions, as indicated by an elongated and disseminated appearance. Immunocytochemical experiments show that EMT accompanies the expression of mesenchymal cytoskeletal proteins, including vimentin. However, H358 cells proliferate more slowly in direct co-culture than in indirect co-culture. Real-time reverse transcription-polymerase chain reaction (RT-PCR) revealed that H358 cells in direct contact with CAFs up-regulate the expression of the pan-mesenchymal markers alpha-smooth muscle actin (alpha-SMA), fibroblast activation protein (FAP), transforming growth factor-beta (TGFbeta) signaling effector SMAD family number-3 (SMAD3), and hedgehog signaling effector GLI family zinc finger-1 (GLI1), compared with the indirect co-culture system. Furthermore, we found that the direct GLI1 transcription targets snail family zinc finger-1 (SNAI1) and SNAI2 are up-regulated, suggesting that the hedgehog signaling pathway is active in direct co-culture. A scratch wound assay showed that direct contact co-culture increases the motility of H358 cells. In conclusion, these findings provide evidence that paracrine factors and direct physical contact between NSCLC cells and CAFs might control the metastatic potential of NSCLC through the hedgehog signaling pathway.
Molecular subtypes of serous borderline ovarian tumor show distinct expression patterns of benign tumor and malignant tumor-associated signatures.

Borderline ovarian tumors show heterogeneity in clinical behavior. Most have excellent prognosis, although a small percentage show recurrence or progressive disease, usually to low-grade serous carcinoma. The aim of this study was to understand the molecular relationship between these entities and identify potential markers of tumor progression and therapeutic targets. We studied gene expression using Affymetrix HGU133plus2 GeneChip microarrays in 3 low-grade serous carcinomas, 13 serous borderline tumors and 8 serous cystadenomas. An independent data set of 18 serous borderline tumors and 3 low-grade serous carcinomas was used for validation. Unsupervised clustering revealed clear separation of benign and malignant tumors, whereas borderline tumors showed two distinct groups, one clustering with benign and the other with malignant tumors. The segregation into benign- and malignant-like borderline molecular subtypes was reproducible on applying the same analysis to an independent publicly available data set. We identified 50 genes that separate borderline tumors into their subgroups. Functional enrichment analysis of genes that separate borderline tumors to the two subgroups highlights a cell adhesion signature for the malignant-like subset, with Claudins particularly prominent. This is the first report of molecular subtypes of borderline tumors based on gene expression profiling. Our results provide the basis for identification of biomarkers for the malignant potential of borderline ovarian tumor and potential therapeutic targets for low-grade serous carcinoma. Modern Pathology advance online publication, 16 August 2013; doi:10.1038/modpathol.2013.130.

Crizotinib overcomes hepatocyte growth factor-mediated resistance to gefitinib in EGFR-mutant non-small-cell lung cancer cells.

Crizotinib overcomes hepatocyte growth factor-mediated resistance to gefitinib in EGFR-mutant non-small-cell lung cancer cells.
Acquired resistance develops ultimately in most non-small-cell lung cancer patients with epidermal growth factor receptor (EGFR) mutations who initially respond to EGFR tyrosine kinase inhibitors. Overexpression of hepatocyte growth factor (HGF) contributes to a considerable part of acquired resistance. Therefore, novel approaches are required for better management to overcome the resistance. Here, we tested whether crizotinib (PF02341066), a MET kinase inhibitor, can overcome two different HGF-triggered mechanisms of resistance to gefitinib in human EGFR mutant lung cancer cell lines HCC827 and PC-9. Compared with the monotherapy, the combined treatment of crizotinib and gefitinib induced apoptosis and significantly inhibited the growth of cells in the presence of HGF by blocking the MET/PI3K/Akt pathway. Further, we demonstrated that crizotinib plus gefitinib successfully prevented the emergence of gefitinib-resistant HCC827 cells induced by transient exposure to HGF. In vivo, the combination therapy with crizotinib and gefitinib also markedly suppressed the growth of gefitinib-resistant mouse xenografts established by injecting HCC827 cells mixed with HGF-producing fibroblasts (MRC-5 cells) subcutaneously into severe combined immunodeficient mice. In conclusion, these findings provided preclinical evidence that crizotinib can be used in the treatment of HGF-induced resistance to gefitinib in EGFR mutant lung cancer.
fixed paraffin-embedded tissues following macrodissection. The p.L858R substitution was assessed by allele-specific PCR and exon 19 deletions by PCR and DNA fragment analysis. Using a robust process from patient sampling to screening methods, we analyzed samples from 1,403 patients. The EGFR status could be successfully determined for 1,322 patients. EGFR mutations were detected in 179 (13.5%) patients, with female and adenocarcinoma histology predominance. Mutated patients were significantly older than nonmutated patients. Similar mutation rates were obtained with primary tumors and metastases, and with surgical resection, bronchial biopsies, CT-guided needle biopsies and transbronchial needle aspiration. The sensitivity of our assays allowed us to detect EGFR mutations in samples poor (<10%) in tumor cells. Finally, the mutation rate was much higher in tumors expressing the TTF-1 antigen (145/820; 17.7%) than in TTF-1 negative tumors (3/218; 1.4%). The results obtained through routine analysis of more than 1,300 samples indicated that all types of specimen can be analyzed without any significant bias. TTF-1 immunostaining may be used to predict negative EGFR mutation status.

[294]
TÍTULO / TITLE: - Evaluating the clinical significance of serum HE4 levels in lung cancer and pulmonary tuberculosis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Liu W; Yang J; Chi PD; Zheng X; Dai SQ; Chen H; Xu BL; Liu WL
INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in Southern China, and Department of Clinical Laboratory Medicine, Sun Yat-Sen University Cancer Centre, Guangzhou, China.
RESUMEN / SUMMARY: - OBJECTIVE: To evaluate whether serum human epididymis protein 4 (HE4) levels could be used as a marker to differentiate lung cancer from pulmonary tuberculosis (PTB) and as a prognostic indicator in patients with non-small-cell lung cancer (NSCLC). DESIGN: HE4 levels were measured in serum samples from 106 healthy controls, 190 lung cancer patients, 114 patients with PTB and 24 patients with pneumonia using enzyme-linked immunosorbent assay. RESULTS: Serum HE4 levels in lung cancer patients were significantly higher than those in patients with PTB and healthy controls (P < 0.001). Using the optimal cut-off value of 94.01 pmol/l, HE4 levels distinguished lung cancer from PTB with a sensitivity of 61.6% and a specificity of 93.0%. After adjusting for age and smoking status, a binary unconditional logistic regression model provided a sensitivity of 67.4% and a specificity of 86.0% for differentiating between these two diseases. In the NSCLC group, serum HE4 levels were significantly higher in patients at advanced stages (Stage I-II vs. Stage III-IV, P =
Higher levels of serum HE4 (≥83.90 pmol/l) were significantly correlated with a worse 3-year survival rate for patients with NSCLC (P < 0.05). CONCLUSION: Serum HE4 may be used as a potential marker to differentiate lung cancer from PTB and healthy controls. In addition, higher levels of HE4 predict poor prognosis in NSCLC patients.

[295]

TÍTULO / TITLE: - Alpha-smooth muscle actin (ACTA2) is required for metastatic potential of human lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Lee HW; Park YM; Lee SJ; Cho HJ; Kim DH; Lee JI; Kang MS; Seol HJ; Shim YM; Nam DH; Kim HH; Joo KM
INSTITUCIÓN / INSTITUTION: - Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University School of Medicine.
RESUMEN / SUMMARY: - PURPOSE: Metastatic relapse of primary lung cancer leads to therapeutic resistance and unfavorable clinical prognosis; therefore, identification of key molecules associated with metastatic conversion has significant clinical implications. We previously identified a link between early brain metastasis of lung adenocarcinoma (ADC) and amplification of the alpha-smooth muscle actin (ACTA2) gene. The aim of present study was to investigate the prognostic and functional significance of ACTA2 expression in cancer cells for the metastatic potential of lung ADCs. EXPERIMENTAL DESIGN: ACTA2 expression was analyzed in tumor cells from 263 patients with primary lung ADCs by immunohistochemistry, and was correlated with clinicopathological parameters. The expression of ACTA2 in human lung ADC cells was modulated with shRNAs and siRNAs specifically targeting ACTA2. RESULTS: The patients with lung ADCs with high ACTA2 expression in tumor cells showed significantly enhanced distant metastasis and unfavorable prognosis. ACTA2 downregulation remarkably impaired in vitro migration, invasion, clonogenicity, and transendothelial penetration of lung ADC cells without affecting proliferation. Consistent with the in vitro results, depletion of ACTA2 in human lung ADC PC14PE6 cells significantly reduced their metastatic potential without altering their tumorigenic potential. Expression of c-MET and FAK in lung ADC cells was also reduced by ACTA2-targeting siRNAs and shRNAs, and was accompanied by a loss of mesenchymal characteristics. CONCLUSIONS: These findings indicate that ACTA2 regulates c-MET and FAK expression in lung ADC cells, which positively and selectively influence metastatic potential. Therefore, ACTA2 could be a promising prognostic biomarker and/or therapeutic target for metastatic lung ADC.
Inhibition of tumor growth and metastasis in non-small cell lung cancer by LY2801653, an inhibitor of several oncokinases, including MET.

**Purpose:** Lung cancer is the leading cause of cancer-related death worldwide. Sustained activation, overexpression, or mutation of the MET pathway is associated with a poor prognosis in a variety of tumors, including non-small cell lung cancer (NSCLC), implicating the MET pathway as a potential therapeutic target for lung cancer. Previously, we reported on the development of LY2801653: a novel, orally bioavailable oncokinase inhibitor with MET as one of its targets. Here, we discuss the evaluation of LY2801653 in both preclinical in vitro and in vivo NSCLC models.

**Experimental Design/RESULTS:** Treatment with LY2801653 demonstrated tumor growth inhibition in tumor cell lines and patient-derived tumor xenograft models as a single agent (37.4% - 90.0% inhibition) or when used in combination with cisplatin, gemcitabine, or erlotinib (66.5% - 86.3% inhibition). Mechanistic studies demonstrated that treatment with LY2801653 inhibited the constitutive activation of MET-pathway signaling and resulted in inhibition of NCI-H441 cell proliferation, anchorage-independent growth, migration, and invasion. These in vitro findings were confirmed in the H441 orthotopic model where LY2801653 treatment significantly inhibited both primary tumor growth (87.9% inhibition) and metastasis (64.5% inhibition of lymph node and 67.7% inhibition of chest wall). Tumor-bearing animals treated with LY2801653 had a significantly greater survival time (87% increase compared to the vehicle-treated mice). In the MET-independent NCI-H1299 orthotopic model, treatment with LY2801653 demonstrated a significant inhibition of primary tumor growth but not metastasis. **CONCLUSIONS:** Collectively, these results support clinical evaluation of LY2801653 in NSCLC and suggest that differences in the MET activation of tumors may be predictive of response.

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**Experimental Design/RESULTS:** Treatment with LY2801653 demonstrated tumor growth inhibition in tumor cell lines and patient-derived tumor xenograft models as a single agent (37.4% - 90.0% inhibition) or when used in combination with cisplatin, gemcitabine, or erlotinib (66.5% - 86.3% inhibition). Mechanistic studies demonstrated that treatment with LY2801653 inhibited the constitutive activation of MET-pathway signaling and resulted in inhibition of NCI-H441 cell proliferation, anchorage-independent growth, migration, and invasion. These in vitro findings were confirmed in the H441 orthotopic model where LY2801653 treatment significantly inhibited both primary tumor growth (87.9% inhibition) and metastasis (64.5% inhibition of lymph node and 67.7% inhibition of chest wall). Tumor-bearing animals treated with LY2801653 had a significantly greater survival time (87% increase compared to the vehicle-treated mice). In the MET-independent NCI-H1299 orthotopic model, treatment with LY2801653 demonstrated a significant inhibition of primary tumor growth but not metastasis. **CONCLUSIONS:** Collectively, these results support clinical evaluation of LY2801653 in NSCLC and suggest that differences in the MET activation of tumors may be predictive of response.
PURPOSE: Amplification of MYC is one of the most common genetic alterations in lung cancer, contributing to a myriad of phenotypes associated with growth, invasion and drug resistance. Murine genetics has established both the centrality of somatic alterations of Kras in lung cancer, as well as the dependency of mutant Kras tumors on MYC function. Unfortunately, drug-like small-molecule inhibitors of KRAS and MYC have yet to be realized. The recent discovery, in hematologic malignancies, that BET bromodomain inhibition impairs MYC expression and MYC transcriptional function established the rationale of targeting KRAS-driven NSCLC with BET inhibition. EXPERIMENTAL DESIGN: We performed functional assays to evaluate the effects of JQ1 in genetically defined NSCLC cells lines harboring KRAS and/or LKB1 mutations. Furthermore, we evaluated JQ1 in transgenic mouse lung cancer models expressing mutant kras or concurrent mutant kras and lkb1. Effects of bromodomain inhibition on transcriptional pathways were explored and validated by expression analysis. RESULTS: While JQ1 is broadly active in NSCLC cells, activity of JQ1 in mutant KRAS NSCLC is abrogated by concurrent alteration or genetic knock-down of LKB1. In sensitive NSCLC models, JQ1 treatment results in the coordinate downregulation of the MYC-dependent transcriptional program. We found that JQ1 treatment produces significant tumor regression in mutant kras mice. As predicted, tumors from mutant kras and lkb1 mice did not respond to JQ1. CONCLUSIONS: Bromodomain inhibition comprises a promising therapeutic strategy for KRAS mutant NSCLC with wild-type LKB1, via inhibition of MYC function. Clinical studies of BET bromodomain inhibitors in aggressive NSCLC will be actively pursued.
RESUMEN / SUMMARY: - Epidermal growth factor receptor (EGFR) gene mutations activate the KRAS-RAF-MEK-ERK pathway in lung cancer cells. EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib induce apoptosis of cancer cells, but prolonged treatment is often associated with acquired resistance. Here, we identified a novel MEK1/2 inhibitor, CZ0775, and compared its cytotoxic effects to those of AZD6244 (selumetinib) in non-small cell lung cancer (NSCLC) cell lines harboring EGFR mutations. The lapatinib-sensitive HCC827 and PC9 and lapatinib-resistant H1650 and H1975 cell lines showed poor responses to CZ0775 and AZD6244 monotherapy with an IC50 > 10 μM. By contrast, combination treatment with lapatinib and CZ0775 inhibited cell proliferation and produced a 2-fold higher number of annexin V-labeled cells than lapatinib alone in H1975 cells. Furthermore, combination treatment decreased phosphorylated extracellular signal related kinase (p-ERK) and survivin levels and upregulated the expression of the pro-apoptotic protein BIM. siRNA-mediated BIM depletion reduced caspase-3 activity (~40%) in lapatinib and CZ0775 treated H1975 cells. An in vitro ERK activity assay showed that p-ERK levels were approximately a 3-fold lower in H1975 cells treated with CZ0775 and lapatinib combination than in cells treated with lapatinib alone. CZ0775 was more cytotoxic than AZD6244 when used in combination with lapatinib. Our results suggest that combination treatment with CZ0774 and EGFR inhibitors is a promising therapeutic approach for the treatment of EGFR-TKI-resistant lung cancers and its effect is mediated by the inhibition of ERK and the induction of BIM.

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TÍTULO / TITLE: - Tropomyosin-related Kinase B Inhibitor Has Potential for Tumor Regression and Relapse Prevention in Pulmonary Large Cell Neuroendocrine Carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Odate S; Onishi H; Nakamura K; Kojima M; Uchiyama A; Kato M; Katano M

INSTITUCIÓN / INSTITUTION: - Department of Cancer Therapy and Research, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. onishi@surg1.med.kyushu-u.ac.jp.

RESUMEN / SUMMARY: - Large cell neuroendocrine carcinoma (LCNEC) has an especially poor prognosis, and an effective therapeutic strategy has yet to be established. We have previously shown that the expressions of tropomyosin-related kinase B (TRKB) and brain-derived neurotrophic factor (BDNF) are high in LCNEC and that TRKB/BDNF signaling is involved in the proliferation, tumorigenesis, and invasive nature of LCNEC. Therefore, TRKB/BDNF signaling may offer a potential therapeutic target for LCNEC treatment. In the present study, we evaluated whether the TRKB tyrosine kinase
inhibitor, k252a, has effects on tumor regression and relapse prevention on LCNEC, using a murine xenograft model. The LCNEC cell line and NCI-H810 cells were subcutaneously implanted into the flanks or intrathoracically injected into the bilateral pleural cavities of BALB/c nude mice. k252a significantly inhibited tumor volume, expression of matrix metalloproteinases and the formation of pleural dissemination by LCNEC. These results suggest that k252a has potential for tumor regression and relapse prevention in LCNEC. Since many patients with LCNEC suffer through the use of ineffective therapeutic strategies, a clinical trial using the TRKB inhibitor for LCNEC is urgently required.

[300]

**TÍTULO / TITLE:** Therapeutic strategy for lower limb lymphedema and lymphatic fistula after resection of a malignant tumor in the hip joint region: A case report.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Hara H; Mihara M; Hayashi A; Kanemaru M; Todokoro T; Yamamoto T; Iida T; Hino R; Koshima I

**INSTITUCIÓN / INSTITUTION:** Department of Plastic and Reconstructive Surgery, The University of Tokyo, Japan.

**RESUMEN / SUMMARY:** Lymphatic fistula complicating lymphedema is thought to occur due to communication between lymph vessels and the skin, which has yet to be shown objectively. The objective of this case report is to show the pathology and treatment using simultaneous lymphatic fistula resection and lymphatico-venous anastomosis (LVA). A 40-year-old woman underwent extended resection and total hip arthroplasty for primitive neuroectodermal tumor in the right proximal femur 23 years ago. Right lower limb lymphedema developed immediately after surgery and lymphatic fistula appeared in the posterior thigh. On ICG lymphography, lymph reflux toward the distal side dispersing in a fan-shape reticular pattern from the lymphatic fistula region was noted after intracutaneous injection of ICG into the foot. We performed simultaneous lymphatic fistula resection and of LVA. Pathological examination showed that the epidermis and stratum corneum of the healthy skin were lost in the lymphatic fistula region. Dilated lymph vessels were open in this region. The examinations provide the first objective evidence that the cause of lymphatic fistula may be lymph reflux from lymphatic stems to precollectors through lymphatic perforators. © 2013 Wiley Periodicals, Inc. Microsurgery, 2013.

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**TÍTULO / TITLE**: MiR-200ª enhances the migrations of A549 and SK-MES-1 cells by regulating the expression of TSPAN1.

**RESUMEN / SUMMARY**: MicroRNA-200ª (miR-200ª) has been reported to regulate tumour progression in several tumours; however, little is known about its role in non-small cell lung cancer cells (NSCLCs). Here, we found that miR-200ª was up-regulated in A549 and SK-MES-1 cells compared with normal lung cells HELF. By a series of gain-of-function and loss-of-function studies, over-expression of miR-200ª was indicated to enhance cells migration, and its knock-down inhibited migration of cells in NSCLC cell lines. Furthermore, miR-200ª was identified to induce TSPAN1 expression which was related to migration. TSPAN1 was proved to induce migration, and so up-regulation of TSPAN1 by miR-200ª may explain why over-expressing miR-200ª promotes NSCLC cells migration.


**AUTORES / AUTHORS**: Chen Y; Peng W; Lu Y; Chen J; Zhu YY; Xi T

**INSTITUCIÓN / INSTITUTION**: School of Life Science and Technology, China Pharmaceutical University, Nanjing, 210009, China.

**RESUMEN / SUMMARY**: Deregulation of c-Jun NH2-terminal kinase (JNK) signaling is now increasingly reported in a variety of human malignancies. Non-small cell lung cancer (NSCLC) is among such human malignancies with aberrant JNK activation; yet the exact role(s) of JNK deregulation in NSCLC biology, in particular in vivo, remains unclear. Here, we demonstrated a specific role of JNK in the control of the tumor-initiating capacity of A549 human non-small cell lung cancer cells derived from human lung adenocarcinoma, a major subtype of NSCLC. Despite its potent inhibitory activity on A549 cell growth in vitro, SP600125, a reversible JNK inhibitor, failed to inhibit the growth of pre-established A549 xenografts in vivo when systemically administered. Nevertheless, the same SP600125 treatment caused a marked reduction in the tumor-initiating population within the A549 tumors, suggesting that JNK may be specifically required in vivo for the maintenance of the...
tumor-initiating population of tumor cells rather than for proliferation and survival of the entire cell population. Furthermore, A549 cells either pre-treated with SP600125 or transiently transfected with siRNAs against the JNK genes in vitro showed substantially reduced ability to initiate tumor formation upon implantation into nude mice, implying that the cell intrinsic JNK activity of A549 cells is essential for the maintenance of their tumor-initiating capacity. To our knowledge, this is the first demonstration that JNK is involved in the control of the tumor-initiating capacity of NSCLC cells. Our findings also give rise to an intriguing possibility that therapies targeting JNK could contribute to prevention of relapse and/or metastasis of NSCLC through elimination of tumor-initiating cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hsia TC; Tsai CW; Liang SJ; Chang WS; Lin LY; Chen WC; Tu CY; Tsai CH; Bau DT
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RESUMEN / SUMMARY: - Aim: The study aimed to evaluate the association and interaction of ataxia telangiectasia mutated (ATM) genetic polymorphisms with lung cancer risk in Taiwan, where lung cancer is the primary cause of cancer-related death.
MATERIALS AND METHODS: In this hospital-based matched case-control study, associations of up to seven ATM single nucleotide polymorphisms (rs600931, rs652311, rs227060, rs228589, rs227092, rs624366 and rs189037) with lung cancer risk were investigated among Taiwanese. In this study, 358 lung cancer patients and 716 age- and gender-matched healthy controls were genotyped and the genetic-lifestyle interaction were analyzed. RESULTS: The results showed that the percentages of GG, AG and AA for ATM rs652311 genotypes were significantly different at 34.6%, 48.9% and 16.5% in the lung cancer patient group and 39.9%, 51.0% and 9.1% in non-cancer control group, respectively. We further analyzed the genetic-lifestyle effects on lung cancer risk and found that the contribution of ATM rs652311 A allele-bearing genotypes to lung cancer susceptibility was enhanced in the cigarette smokers and not enhanced in the non-smokers (p=0.0045 and 0.2758, respectively). CONCLUSION: Our results provide evidence that the A allele of ATM rs652311 may be associated with lung cancer risk, and may enhance the effects of smoking habit on lung cancer development.
**TÍTULO / TITLE:** CD90 Is a Diagnostic Marker to Differentiate Between Malignant Pleural Mesothelioma and Lung Carcinoma With Immunohistochemistry.

**RESUMEN / SUMMARY:** Objectives: To pathologically distinguish mesothelioma from lung carcinoma, particularly adenocarcinoma. Methods: We conducted immunohistochemical analyses on clinical specimens, including 26 cases of mesothelioma, 28 cases of lung adenocarcinoma, and 33 cases of lung squamous cell carcinoma. Results: We found that CD90 expression was useful in making a differential diagnosis between epithelioid mesothelioma and lung adenocarcinoma, whereas sarcomatoid mesothelioma and lung carcinoma specimens, irrespective of the histologic types, were negative in general. The sensitivity and specificity of CD90 expression in epithelioid mesothelioma and lung adenocarcinoma were comparable to those of well-established markers used for the differential diagnosis. Conclusions: These data collectively indicate that CD90 is a novel diagnostic marker that contributes to a diagnosis of epithelioid mesothelioma.


**AUTORES / AUTHORS:** Kawamura K; Hiroshima K; Suzuki T; Chai K; Yamaguchi N; Shingyoji M; Yusa T; Tada Y; Takiguchi Y; Tatsumi K; Shimada H; Tagawa M

**INSTITUCIÓN / INSTITUTION:** Division of Pathology and Cell Therapy, Chiba Cancer Center Research Institute, 666-2 Nitona, Chuo-ku, Chiba 260-8717, Japan; e-mail: mtagawa@chiba-cc.jp.

**RESUMEN / SUMMARY:**

**RESUMEN / SUMMARY:**

**TÍTULO / TITLE:** 4-Methoxychalcone enhances cisplatin-induced oxidative stress and cytotoxicity by inhibiting the Nrf2/ARE-mediated defense mechanism in A549 lung cancer cells.

**RESUMEN / SUMMARY:** Objectives: To pathologically distinguish mesothelioma from lung carcinoma, particularly adenocarcinoma. Methods: We conducted immunohistochemical analyses on clinical specimens, including 26 cases of mesothelioma, 28 cases of lung adenocarcinoma, and 33 cases of lung squamous cell carcinoma. Results: We found that CD90 expression was useful in making a differential diagnosis between epithelioid mesothelioma and lung adenocarcinoma, whereas sarcomatoid mesothelioma and lung carcinoma specimens, irrespective of the histologic types, were negative in general. The sensitivity and specificity of CD90 expression in epithelioid mesothelioma and lung adenocarcinoma were comparable to those of well-established markers used for the differential diagnosis. Conclusions: These data collectively indicate that CD90 is a novel diagnostic marker that contributes to a diagnosis of epithelioid mesothelioma.

**REVISTA / JOURNAL:** Mol Cells. 2013 Sep 16.

**AUTORES / AUTHORS:** Lim J; Lee SH; Cho S; Lee IS; Kang BY; Choi HJ

**INSTITUCIÓN / INSTITUTION:** College of Pharmacy, CHA University, Seongnam, 463-836, Korea.

**RESUMEN / SUMMARY:** Objectives: To pathologically distinguish mesothelioma from lung carcinoma, particularly adenocarcinoma. Methods: We conducted immunohistochemical analyses on clinical specimens, including 26 cases of mesothelioma, 28 cases of lung adenocarcinoma, and 33 cases of lung squamous cell carcinoma. Results: We found that CD90 expression was useful in making a differential diagnosis between epithelioid mesothelioma and lung adenocarcinoma, whereas sarcomatoid mesothelioma and lung carcinoma specimens, irrespective of the histologic types, were negative in general. The sensitivity and specificity of CD90 expression in epithelioid mesothelioma and lung adenocarcinoma were comparable to those of well-established markers used for the differential diagnosis. Conclusions: These data collectively indicate that CD90 is a novel diagnostic marker that contributes to a diagnosis of epithelioid mesothelioma.
suggesting that the suppression of overexpressed Nrf2 could be an attractive therapeutic strategy to overcome cancer drug resistance. In the present study, we aimed to find small molecule compounds that enhance the sensitivity of tumor cells to cisplatin induced cytotoxicity by suppressing Nrf2-mediated defense mechanism. A549 lung cancer cells were shown to be more resistant to the anti-cancer drug cisplatin than HEK293 cells, with higher Nrf2 signaling activity; constitutively high amounts of Nrf2-downstream target proteins were observed in A549 cells. Among the three chalcone derivatives 4-methoxy-chalcone (4-MC), hesperidin methylchalcone, and neohesperidin dihydrochalcone, 4-MC was found to suppress transcriptional activity of Nrf2 in A549 cells but to activate it in HEK293 cells. 4-MC was also shown to down-regulate expression of Nrf2 and the downstream phase II detoxifying enzyme NQO1 in A549 cells. The PI3K/Akt pathway was found to be involved in the 4-MC-induced inhibition of Nrf2/ARE activity in A549 cells. This inhibition of Nrf2 signaling results in the accelerated generation of reactive oxygen species and exacerbation of cytotoxicity in cisplatin-treated A549 cells. Taken together, these results suggest that the small molecule compound 4-MC could be used to enhance the sensitivity of tumor cells to the therapeutic effect of cisplatin through the regulation of Nrf2/ARE signaling.

[306] TÍTULO / TITLE: - Docetaxel in the Treatment of Non-small Cell Lung Cancer (NSCLC) - An Observational Study Focusing on Symptom Improvement.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pircher A; Wasle IK; Mian M; Gamerith G; Ulsperger E; Studnicka M; Mohn-Staudner A; Hilbe W; Fiegl M
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RESUMEN / SUMMARY: - BACKGROUND: Results of an observational study on docetaxel-based therapy in non-small cell lung cancer (NSCLC) with focus on symptom control and therapy response, are reported. PATIENTS AND METHODS: A total of 233 patients with NSCLC treated with docetaxel-containing therapy were analyzed. RESULTS: The pre-existing symptoms of cough, dyspnea and pain markedly improved after three cycles of docetaxel-based therapy. Regression of symptoms was strongly associated with therapy response, but unexpectedly, patients with stable disease had also a substantial benefit. Alltogether, the response after three cycles was complete in 0.9% and partial in 26.6% of patients, respectively. CONCLUSION: Symptom control was achieved in the majority of cases, which received three cycles of docetaxel-based therapy. Thus, a clinical benefit was regularly reached shortly after initiation of chemotherapy.
TÍTULO / TITLE: Neural Networks for Nodal Staging of Non-Small Cell Lung Cancer with FDG PET and CT: Importance of Combining Uptake Values and Sizes of Nodes and Primary Tumor.

RESUMEN / SUMMARY: Purpose: To evaluate the effect of adding lymph node size to three previously explored artificial neural network (ANN) input parameters (primary tumor maximum standardized uptake value or tumor uptake, tumor size, and nodal uptake at N1, N2, and N3 stations) in the structure of the ANN. The goal was to allow the resulting ANN structure to relate lymph node uptake for size to primary tumor uptake for size in the determination of the status of nodes as human readers do. Materials and Methods: This prospective study was approved by the institutional review board, and informed consent was obtained from all participants. The authors developed a back-propagation ANN with one hidden layer and eight processing units. The data set used to train the network included node and tumor size and uptake from 133 patients with non-small cell lung cancer with surgically proved N status. Statistical analysis was performed with the paired t test. Results: The ANN correctly predicted the N stage in 99.2% of cases, compared with 72.4% for the expert reader (P < .001). In categorization of N0 and N1 versus N2 and N3 disease, the ANN performed with 99.2% accuracy versus 92.2% for the expert reader (P < .001). Conclusion: The ANN is 99.2% accurate in predicting surgical-pathologic nodal status with use of four fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT)-derived parameters. Malignant and benign inflammatory lymph nodes have overlapping appearances at FDG PET/CT but can be differentiated by ANNs when the crucial input of node size is used. © RSNA, 2013


TÍTULO / TITLE: Lewis Lung Carcinoma Progression Is Facilitated by TIG-3 Fibroblast Cells.

RESUMEN / SUMMARY: Lewis Lung Carcinoma Progression Is Facilitated by TIG-3 Fibroblast Cells.
BACKGROUND: The interactions of tumor cells with stromal fibroblasts influence tumor biology, but the exact mechanisms involved are still unclear. In the present study, we evaluated the effects of a human lung fibroblast cell line, TIG-3, on Lewis lung carcinoma (LLC) cells both in vitro and in vivo. MATERIALS AND METHODS: LLC and TIG-3 cells were co-cultured/co-implanted in vitro and in vivo. Cell invasion was assayed. Local tumor growth, as well as lung metastasis, were evaluated after subcutaneous cell co-implantation into NOD/SCID/gamma-null (NOG) mice. LLC, and TIG-3 cells were pre-treated with either SB431542, a small molecule TGF-beta receptor antagonist, or siRNA for transforming growth factor (TGF)-beta before co-culture or co-implantation, and the effects of pre-treatments were compared both in cell culture and in mice. RESULTS: Subcutaneous LLC tumor growth (L group) in NOG mice was significantly increased by co-implantation of TIG-3 cells (L+T group) at four weeks. The number of macroscopic lung metastases was also significantly increased in the L+T group in comparison to the L group. In vitro cell invasion was significantly increased in the L+T group in comparison to the L group. In vitro expression of phosphorylated-SMAD3 was significantly increased in the L+T group in comparison to the L group. Furthermore, pre-treatment with either SB431542 or siRNA for TGF-beta reduced the invasiveness both in culture and in mice. CONCLUSION: This study suggested that in vitro as well as in vivo progression of LLC was facilitated by co-culture/co-implantation with TIG-3 cells, and that this process was at least in part dependent on TGF-beta-mediated interactions.

[309]

TÍTULO / TITLE: - Antiproliferative, Cell-Cycle Dysregulation Effects of Novel Asiatic Acid Derivatives on Human Non-small Cell Lung Cancer Cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wang L; Xu J; Zhao C; Zhao L; Feng B
INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Dalian Medical University.
RESUMEN / SUMMARY: - Asiatic acid (AA) is a pentacyclic triterpene in Centella asiatica known to inhibit proliferation and induce apoptosis in several tumor cell lines. In the current study, we synthesized five AA derivatives and examined their inhibitory activities on growth in non-small cell lung cancer cell lines, A549 and PC9/G. Four derivatives were found to have stronger cell growth inhibitory activity than AA. Among
them, compound A-3 showed the most significant antiproliferative effects on tumor. Growth of A549 and PC9/G cells was inhibited by A-3 in a dose- and time-dependent manner. To determine the cellular gene expression changes in A549 and PC9/G cells treated with A-3, Affymetrix GeneChip® Human Genome U133 Plus 2.0 Array were used to screen transcriptome differences. Expression levels of 1121 genes in A549 and 1873 genes in PC9/G were significantly altered upon treatment with 10 microM A-3 after 48 h, with 357 overlapping genes. The signaling pathways molecules involved in the antiproliferative and cell cycle dysregulation effects of A-3 identified using microarray were further validated via Western blot analyses. The results collectively indicate that A-3 induces inhibition of cell proliferation via downregulation of the Ras/Raf/MEK/ERK pathway and cell cycle arrest at G1/S and G2/M.

[310]

TÍTULO / TITLE: - Haemoptysis as a prognostic factor in lung adenocarcinoma after curative resection.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hu P; Wang G; Cao H; Ma H; Sui P; Du J
INSTITUCIÓN / INSTITUTION: - Institute of Oncology, Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan 250021, People’s Republic of China.
RESUMEN / SUMMARY: - Background: Haemoptysis is a common symptom of lung cancer. Its prognostic role and mechanisms are still poorly understood. Methods: We retrospectively reviewed 666 consecutive patients with primary lung adenocarcinoma who underwent complete resection. The prognostic value of haemoptysis with respect to overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS) was analysed. To further explore the possible mechanisms of haemoptysis, we evaluated vascular endothelial growth factor (VEGF) expression, tumour necrosis, vascular invasion and extratumoural microvessel density (MVD) in 112 randomly selected patients. Results: Haemoptysis predicted poor OS, DSS and DFS in operable lung adenocarcinoma (all P<0.001). In addition, haemoptysis was associated with high white blood cell (WBC) count (P=0.032), high fibrinogen (Fib; P<0.001), high tumour greatest dimension (P<0.001), severe vascular invasion (P=0.002) and central tumour location (P<0.001). We obtained no statistically significant differences of VEGF expression, tumour necrosis and extratumoural MVD in haemoptysis and non-haemoptysis groups. Conclusion: Our study demonstrates that haemoptysis predicts poor OS, DSS and DFS in lung adenocarcinoma after curative resection. Vascular invasion rather than angiogenesis or tumour necrosis could be the most important mechanism of haemoptysis in lung adenocarcinoma.
Lymph Node Ratio Predicts Recurrence and Survival After R0 Resection for Non-Small Cell Lung Cancer.

**RESUMEN / SUMMARY:**

**BACKGROUND:** Current TNM non-small cell lung cancer (NSCLC) staging uses only the anatomic location of lymph nodes to define N status. Several other cancer staging systems have found lymph node ratio (LNR)-the number of positive lymph nodes/total lymph nodes resected-to be a better predictor of survival after resection. The purpose of this study is to evaluate LNR as a predictor of recurrence and survival after R0 resection for NSCLC. **METHODS:** A total of 1,143 consecutive patients underwent R0 resection for NSCLC between 1999 and 2008 at a high-volume single institution with 26% (n = 302) having N1 and N2 disease. The primary endpoints of the study were long-term survival and recurrence as a function of LNR. Cox proportional hazard models and Kaplan-Meier survival analyses were utilized to assess associations between LNR, N status, and pathologic stage with survival and recurrence after lung cancer resection. **RESULTS:** Median follow-up was 44 months and was complete in 97% of patients. Nodal status of patients in this study was as follows: N0 disease, 73.5%; N1 disease, 18.7%; and N2 disease, 7.8%. There were 132 recurrences in patients with nodal disease (43.7%). The pathologic stage of patients in the study was as follows: stage IIA, 47%; stage IIB, 17%; stage IIIA, 35%; and stage IIIB, 1%. Mean total number of lymph nodes sampled was 11.1 +/- 6.0 and mean number of positive lymph nodes 2.4 +/- 2.0. Upon statistical modeling, LNR was found to be independently associated with decreased survival after resection for NSCLC (hazard ratio 2.63, confidence interval: 1.41 to 4.91, p = 0.002). **CONCLUSIONS:** In patients undergoing resection for NSCLC, increasing lymph node ratio is independently associated with decreased survival and decreased time to recurrence after R0 resection.
Lung cancer risk among bakers, pastry cooks and confectionary makers: the SYNERGY study.

INTRODUCTION: Some studies have suggested increased lung cancer risks among bakers, however the results overall were inconsistent. The authors studied lung cancer risks among bakers and baking-related occupations in the SYNERGY pooled case-control database from 16 countries. METHODS: Occupation in a baking-related job was identified from the subjects’ job histories. ORs adjusted for log(age), study centre, smoking behaviour and ever employment in a job with known exposure to occupational lung carcinogens were calculated by unconditional logistic regression. Findings were stratified by sex, histological subtype of lung cancer and smoking status. RESULTS: 19,366 cases (15,606 men) and 23,670 control subjects (18,528 men) were included. 473 cases (415 men, 58 women) and 501 controls (437 men, 64 women) had ever worked in baking or a related job. We did not observe an increased risk for men in baking (OR 1.01; 95% CI 0.86 to 1.18). No linear trends were observed for duration of employment. Some results suggested increased lung cancer risks for women, for example, for working as a baker for >30 years and in never-smokers, but after exclusion of one study these increased risks disappeared. DISCUSSION: The findings from this study do not suggest increased lung cancer risks in baking-related professions.

The Role of Vimentin Intermediate Filaments in the Progression of Lung Cancer.

INTRODUCTION: Some studies have suggested increased lung cancer risks among bakers, however the results overall were inconsistent. The authors studied lung cancer risks among bakers and baking-related occupations in the SYNERGY pooled case-control database from 16 countries. METHODS: Occupation in a baking-related job was identified from the subjects’ job histories. ORs adjusted for log(age), study centre, smoking behaviour and ever employment in a job with known exposure to occupational lung carcinogens were calculated by unconditional logistic regression. Findings were stratified by sex, histological subtype of lung cancer and smoking status. RESULTS: 19,366 cases (15,606 men) and 23,670 control subjects (18,528 men) were included. 473 cases (415 men, 58 women) and 501 controls (437 men, 64 women) had ever worked in baking or a related job. We did not observe an increased risk for men in baking (OR 1.01; 95% CI 0.86 to 1.18). No linear trends were observed for duration of employment. Some results suggested increased lung cancer risks for women, for example, for working as a baker for >30 years and in never-smokers, but after exclusion of one study these increased risks disappeared. DISCUSSION: The findings from this study do not suggest increased lung cancer risks in baking-related professions.
There is an accumulation of evidence in the literature demonstrating the integral role of vimentin intermediate filaments in the progression of lung cancers. Vimentin intermediate filament (IF) proteins have been implicated in many aspects of cancer initiation and progression, including tumorigenesis, epithelial-to-mesenchymal transition (EMT), and the metastatic spread of cancer. Specifically, vimentin IFs have been recognized as an essential component regulating EMT, major signal transduction pathways involved in EMT and tumor progression, cell migration and invasion, the positioning and anchorage of organelles such as mitochondria, and cell-cell and cell-substrate adhesion. In tumorgenesis, vimentin forms a complex with 14-3-3 and Beclin 1 to inhibit autophagy via an AKT-dependent mechanism. Vimentin is a canonical marker of EMT and recent evidence has shown it to be an important regulator of cellular motility. Transcriptional regulation of vimentin through HIF-1 may be a potential driver of EMT. Finally, vimentin regulates 14-3-3 complexes and controls various intracellular signaling and cell cycle control pathways by depleting the availability of free 14-3-3. There are many exciting advances in our understanding of the complex role of vimentin IFs in cancer, pointing to the key role vimentin IFs may play in tumor progression.

RESUMEN / SUMMARY: Sphingosine kinase 2 (SphK2) as a conserved lipid kinase has not been thoroughly elucidated in non-small cell lung cancer (NSCLC). The aim of the present study was to evaluate the expression of SphK2 in NSCLC tissues and to determine its correlation with clinicopathologic characteristics and its impact on patient prognosis. We assessed the expression of SphK2 and proliferating cell nuclear antigen (PCNA) (as a proliferative index) by immunohistochemistry in 180 NSCLC patient’s formalin-fixed paraffin-embedded tissue blocks. Relationship between the expression of SphK2 and PCNA and various clinicopathological features in these patients was evaluated. We detected that expression of SphK2 was gradually
upregulated from normal, metaplasia/dysplasia tissues to NSCLC tissues. At the same time, PCNA expression followed a similar pattern. Statistical analysis showed that expression of SphK2 in NSCLC tissues was strongly associated with PCNA expression, histology grade, live vaccine strain invasion, lymph node status, clinical stage, tumors size, and histology type. Patients with SphK2 overexpression in their tissues had lower overall survival (OS) and disease-free survival (DFS) rates than those with low SphK2 expression. Using uni- and multivariate analysis, we found that SphK2 overexpression was an independent prognostic factor for both OS and DFS. The expression of SphK2 parallels the progression of NSCLC, and SphK2 overexpression may represent a novel and potentially independent biomarker for the prognosis of patients with NSCLC.

[315]

TÍTULO / TITLE: - Effects of water soluble PM2.5 extracts exposure on human lung epithelial cells (A549): A proteomic study.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Huang Q; Zhang J; Peng S; Tian M; Chen J; Shen H

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Urban Environment and Health, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen, 361021, People’s Republic of China.

RESUMEN / SUMMARY: - Exposure to airborne particulate matter (PM)2.5, a PM with aerodynamic diameter of less than 2.5 microm, is known to be associated with a variety of adverse health effects. However, the molecular mechanisms involved in fine PM toxicity are still not well characterized. The present study aims to provide new insights into the cytotoxicity of PM2.5 on human lung epithelial cells (A549) at the proteomic level. Two-dimensional difference gel electrophoresis revealed a total of 27 protein spots, whose abundance were significantly altered in A549 cells exposed to water-soluble PM2.5 extracts (WSPE). Among these, 12 spots were upregulated while 15 were downregulated. Twenty-two proteins were further identified by matrix-assisted laser desorption/ionization time-of-flight tandem mass/mass spectrometry and database search. The results revealed that oxidative stress, metabolic disturbance, dysregulation of signal transduction, aberrant protein synthesis and degradation, as well as cytoskeleton disorganization are major factors contributing to WSPE-mediated toxicity in human lung cells. It is further proposed that induction of apoptosis through p53, c-Myc and p21 pathways may be one of the key toxicological events occurred in A549 cells under WSPE stress. The data obtained here will aid our understanding of the toxic mechanisms related to PM2.5, and develop useful biomarkers indicative of inhalable PM2.5 exposure. Copyright © 2013 John Wiley & Sons, Ltd.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Carbone A; Pennati M; Parrino B; Lopergolo A; Barraja P; Montalbano A; Spano V; Sbarra S; Doldi V; De Cesare M; Cirrincione G; Diana P; Zaffaroni N

INSTITUCIÓN / INSTITUTION: - Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche (STEBICEF), Universita degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy.

RESUMEN / SUMMARY: - In this study, we describe the synthesis of new nortopsentin analogues, 1H-pyrrolo[2,3-b]pyridine derivatives and their biological effects in experimental models of diffuse malignant peritoneal mesothelioma (DMPM), a rare and rapidly fatal disease, poorly responsive to conventional therapies. The three most active compounds, 1f (3-[2-(5-fluoro-1-methyl-1H-indol-3-yl)-1,3-thiazol-4-yl]-1H-pyrrolo[2,3-b]pyridine), 3f (3-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]-1-methyl-1H-pyrrolo[2,3-b]pyridine), and 1l (3-[2-(5-fluoro-1-methyl-1H-indol-3-yl)-1,3-thiazol-4-yl]-1-methyl-1H-pyrrolo[2,3-b]pyridine), which were shown to act as cyclin-dependent kinase 1 inhibitors, consistently reduced DMPM cell proliferation and induced a caspase-dependent apoptotic response, with a concomitant reduction of the expression of the active Thr(34)-phosphorylated form of the antiapoptotic protein survivin. Moreover, the combined treatment of DMPM cells with 3f derivative and paclitaxel produced a synergistic cytotoxic effect, which was paralleled by an enhanced apoptotic response. In the mouse model, i.p. administration of 1f, 3f, and 1l derivatives was effective, resulting in a significant tumor volume inhibition of DMPM xenografts (range, 58-75%) at well-tolerated doses, and two complete responses were observed in each treatment group.

TÍTULO / TITLE: - Metformin inhibits lung cancer cells proliferation through repressing microRNA-222.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Wang Y; Dai W; Chu X; Yang B; Zhao M; Sun Y
Metformin, which is commonly used as an oral anti-hyperglycemic agent of the biguanide family, may reduce cancer risk and improve prognosis. However, the mechanism by which metformin affects various cancers, including lung cancer, remains unknown. MiR-222 induces cell growth and cell cycle progression via direct targeting of p27, p57 and PTEN in cancer cells. In the present study, we used A549 and NCI-H358 human lung cancer cell lines to study the effects and mechanisms of metformin. Metformin treatment reduced expression of miR-222 in these cells (p < 0.05). As a result, protein abundance of p27, p57 and PTEN were increased in cells exposed to metformin. Therefore, these data provide novel evidence for a mechanism that may contribute to the anti-neoplastic effects of metformin suggested by recent population studies and justifying further work to explore potential roles for it in lung cancer treatment.

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Regulation of SIRT2 levels for human non-small cell lung cancer therapy.

Seven Sirtuin family members (SIRT1-7), comprising a family of NAD+-dependent protein deacetylases and ADP-ribosyltransferases, are key proteins that regulate multiple physiological processes. SIRT2 was recently reported to play an important role in carcinogenesis. However, its role in non-small cell lung cancer (NSCLC) has not yet been investigated. In this study, we analyzed the expression pattern of SIRT2 in NSCLC tissues from clinical patients and in cell lines, and found that SIRT2 was significantly down-regulated at both the mRNA and protein levels in tumor than non-tumor tissues or cells, which were corroborated by the NSCLC tissue microarray results. Overexpression of SIRT2 in A549 and H1299 cells caused cell proliferation inhibition, cell apoptosis induction and cell cycle arrest. Further analysis showed that SIRT2 overexpression increased the ROS (reactive oxygen species) production and p27 levels. Moreover, up-regulation of SIRT2 in NSCLC cells increased the sensitivity to Cisplatin treatment. Taken together, our results implied that down-
regulation of SIRT2 was associated with NSCLC, and regulation of SIRT2 might be an important target for NSCLC therapy.
RESUMEN / SUMMARY: Magnolol, a hydroxylated biphenyl agent isolated from herbal planet Magnolia officinalis, is a component of traditional Asian herbal teas. It has been reported to have anti-microbial, anti-inflammatory, and anti-cancer activity. Non-small cell lung cancer (NSCLC) cell lines (A549, H441 and H520) and normal human bronchial epithelial cells (HBECs) were used to evaluate the cytotoxic effect of magnolol. We show that magnolol inhibited cellular proliferation, increased DNA fragmentation, and decreased mitochondrial membrane potential in all NSCLC cells, but had no cytotoxic effect on HBECs. Magnolol triggered the release of pro-apoptotic proteins: Bid, Bax and cytochrome c from mitochondria, but did not activate the caspase-3, -8, and -9, suggesting that magnolol induces apoptosis of NSCLC cell lines via a caspase-independent pathway. The caspase-independent pathway is mediated through the activation of nuclear translocation of apoptosis-inducing factor, endonuclease G and cleaved poly(ADP-ribose) polymerase, which played important roles in mediating cell death. Furthermore, magnolol inhibited PI3K/AKT and ERK1/2 activity, but up-regulated p38 and JNK activity in A549 cell lines. The results of this study provided a basis for understanding and developing magnolol as a novel treatment of NSCLC.

TÍTULO / TITLE: Large-cell neuroendocrine lung tumor presenting as acute pancreatitis.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Dinis Silva J; Pinto Marques P; Brito MJ; Cortes J; Senhorinho R; Heredia V; Nunes A

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Hospital do Espirito Santo de Evora EPE, Evora, Portugal.

TÍTULO / TITLE: Tumor-to-tumor metastasis from lung cancer: a clinicopathological postmortem study.
RESUMEN / SUMMARY: This study examined 47 cases of lung cancer concomitant with other tumors and found eight cases (17 %) with nine foci of tumor-to-tumor metastasis, defined as metastasis of lung cancer into another tumor. Donor lung cancers were four adenocarcinomas, two squamous cell carcinomas, and two small cell carcinomas. Tumor-to-tumor metastasis was found in five of six renal cell carcinomas (83 %), one of eight thyroid papillary carcinomas (13 %), one of three adrenocortical adenomas (33 %), one of three pancreatic endocrine microadenomas (33 %), and another lung cancer (one of six cases of multiple lung cancers, 17 %). The higher recipient incidence in renal cell carcinoma was statistically significant compared with prostatic carcinoma (0/16, P < 0.001), colorectal carcinoma (0/7, P = 0.005), and gastric carcinoma (0/5, P = 0.015). Generalized metastases were found in 88 % of the tumor-to-tumor metastasis cases. The total clinical course of patients with tumor-to-tumor metastasis was shorter than that of the patients without tumor-to-tumor metastasis (mean, 5.4 versus 18.8 months; P = 0.046). Tumor-to-tumor metastasis sometimes mimicked undifferentiated recipient tumor cells. Immunostains for thyroid transcription factor 1 (TTF-1), Napsin A, cytokeratin 7 (CK7), and CK5/6 were useful to confirm tumor-to-tumor metastasis. However, TTF-1-, Napsin A-, and/or CK7-negative lung adenocarcinoma components metastasized to renal cell carcinoma in three cases, and recipient renal cell carcinomas were focally Napsin A+ (two cases) or CK7+ (two cases). Tumor-to-tumor metastasis can occur as a result of metastasis from lung cancer with more aggressive behavior. Tumor-to-tumor metastasis should be carefully distinguished from undifferentiated recipient tumor cells.

INSTITUCIÓN / INSTITUTION: - Department of Histology and Cell Biology, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan.

RESUMEN / SUMMARY: - Epigenetic parameters such as DNA methylation and histone modifications play pivotal roles in carcinogenesis. Global histone modification patterns have been implicated as possible predictors of cancer recurrence and prognoses in a great variety of tumor entities. Our study was designed to evaluate the association among trimethylated histone H3 at lysine 27 (H3K27me3), clinicopathological variables and outcome in early-stage non-small cell lung cancer (NSCLC). The expression of H3K27me3 and its methyl-transferase, enhancer of zeste homolog 2 (EZH2) together with proliferating cell nuclear antigen (PCNA) were evaluated by immunohistochemistry in normal lung tissue (n=5) and resected NSCLC patients (n=42). In addition, the specificity of antibody for H3K27me3 was tested by western blot analysis. The optimal cut-off point of H3K27me3 expression for prognosis was determined by the X-tile program. The prognostic significance was determined by means of Kaplan-Meier survival estimates and log-rank tests. As a result, enhanced trimethylation of H3K27me3 was correlated with longer overall survival (OS) and better prognosis (P<0.05). Moreover, both univariate and multivariate analyses indicated that H3K27me3 level was a significant and independent predictor of better survival (hazard ratio, 0.187; 95% confidence interval, 0.066-0.531, P=0.002). Furthermore, H3K27me3 expression was positively correlated with DNA methylation level at CCGG sites while reversely related to EZH2 expression (P<0.05). In conclusion, H3K27me3 level defines unrecognized subgroups of NSCLC patients with distinct epigenetic phenotype and clinical outcome, and can probably be used as a novel predictor for better prognosis in NSCLC patients.

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TÍTULO / TITLE: - Interobserver Agreement of Qualitative Analysis and Tumor Delineation of 18F-Fluoromisonidazole and 3’-Deoxy-3’-18F-Fluorothymidine PET Images in Lung Cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Thureau S; Chaumet-Riffaud P; Modzelewski R; Fernandez P; Tessonnier L; Vervueren L; Cachin F; Berriolo-Riedinger A; Olivier P; Kolesnikov-Gauthier H; Blagosklonov O; Bridji B; Devillers A; Collombier L; Courbon F; Gremillet E; Houzard C; Caignon JM; Roux J; Aide N; Brenot-Rossi I; Doyeux K; Dubray B; Vera P

INSTITUCIÓN / INSTITUTION: - Nuclear Medicine and Radiotherapy, Henri Becquerel Cancer Center and Rouen University Hospital, and QuantIF-LITIS (EA [Equipe d’Accueil] 4108), Faculty of Medicine, University of Rouen, Rouen, France.
RESUMEN / SUMMARY: - As the preparation phase of a multicenter clinical trial using (18)F-fluoro-2-deoxy-d-glucose ((18)F-FDG), (18)F-fluoromisonidazole ((18)F-FMISO), and 3'-deoxy-3'-(18)F-fluorothymidine ((18)F-FLT) in non-small cell lung cancer (NSCLC) patients, we investigated whether 18 nuclear medicine centers would score tracer uptake intensity similarly and define hypoxic and proliferative volumes for 1 patient and we compared different segmentation methods. METHODS: Ten (18)F-FDG, ten (18)F-FMISO, and ten (18)F-FLT PET/CT examinations were performed before and during curative-intent radiotherapy in 5 patients with NSCLC. The gold standards for uptake intensity and volume delineation were defined by experts. The between-center agreement (18 nuclear medicine departments connected with a dedicated network, SFMN-net [French Society of Nuclear Medicine]) in the scoring of uptake intensity (5-level scale, then divided into 2 levels: 0, normal; 1, abnormal) was quantified by kappa coefficients (kappa). The volumes defined by different physicians were compared by overlap and kappa. The uptake areas were delineated with 22 different methods of segmentation, based on fixed or adaptive thresholds of standardized uptake value (SUV). RESULTS: For uptake intensity, the kappa values between centers were, respectively, 0.59 for (18)F-FDG, 0.43 for (18)F-FMISO, and 0.44 for (18)F-FLT using the 5-level scale; the values were 0.81 for (18)F-FDG and 0.77 for both (18)F-FMISO and (18)F-FLT using the 2-level scale. The mean overlap and mean kappa between observers were 0.13 and 0.19, respectively, for (18)F-FMISO and 0.2 and 0.3, respectively, for (18)F-FLT. The segmentation methods yielded significantly different volumes for (18)F-FMISO and (18)F-FLT (P < 0.001). In comparison with physicians, the best method found was 1.5 x maximum SUV (SUVmax) of the aorta for (18)F-FMISO and 1.3 x SUVmax of the muscle for (18)F-FLT. The methods using the SUV of 1.4 and the method using 1.5 x the SUVmax of the aorta could be used for (18)F-FMISO and (18)F-FLT. Moreover, for (18)F-FLT, 2 other methods (adaptive threshold based on 1.5 or 1.6 x muscle SUVmax) could be used. CONCLUSION: The reproducibility of the visual analyses of (18)F-FMISO and (18)F-FLT PET/CT images was demonstrated using a 2-level scale across 18 centers, but the interobserver agreement was low for the (18)F-FMISO and (18)F-FLT volume measurements. Our data support the use of a fixed threshold (1.4) or an adaptive threshold using the aorta background to delineate the volume of increased (18)F-FMISO or (18)F-FLT uptake. With respect to the low tumor-background ratio of these tracers, we suggest the use of a fixed threshold (1.4).

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TÍTULO / TITLE: - Clinical Significance of Serum Angiopoietin-1 in Malignant Peritoneal Mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 3109/07357907.2013.830734
We have previously reported that angiopoietin-1 was correlated with pulmonary fibrosis. Here, we investigated the serum levels of angiopoietin-1 in patients with malignant peritoneal mesothelioma, which originate from mesenchymal cells similar to lung fibroblasts. We showed that patients with peritoneal mesothelioma had significantly higher serum levels of angiopoietin-1 in comparison with a population with a history of asbestos exposure without peritoneal mesothelioma, and the Kaplan-Meier method revealed a significant correlation between serum angiopoietin-1 levels and survival. This is the first report about the relationship between angiopoietin-1 and peritoneal mesothelioma.

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A regulatory variant in CYP2E1 affects the risk of lung squamous cell carcinoma.

Cytochrome P450 2E1 (CYP2E1), an ethanol-inducible enzyme, has been shown to metabolically activate various carcinogens, which is critical for the development of cancers. It has been demonstrated that CYP2E1 polymorphisms alter the transcriptional activity. However, studies on the association between CYP2E1 -1239G>C polymorphism and non-small cell lung cancer have reported conflicting results. Thus, the gain of the present study was to investigate whether CYP2E1 -1239G>C polymorphism is associated with the development of non-small cell lung cancer in Chinese population. A case-control study was conducted in which CYP2E1 -1239G>C polymorphism was analyzed in 526 Chinese patients with non-small cell lung cancer and 526 age-matched healthy controls by polymerase chain reaction-restriction fragment length polymorphism. Odds ratios were estimated by multivariate logistic regression. A meta-analysis was conducted to evaluate the association of CYP2E1 -1239G>C polymorphism with the risk of lung cancer in Chinese population by calculating pooled odds ratio (OR). For CYP2E1 -1239G>C polymorphism, -1239C allele carriers (OR = 0.67; 95% confidence interval (CI) = 0.51-0.87; P = 0.002) were associated with a decreased risk of non-small cell lung cancer when compared with -1239GG homozygotes. In the group analyses by pathological types, for lung squamous
cell carcinoma and other types, the ORs of the C allele carriers were 0.60 (95 % CI = 0.41-0.88; P = 0.009) and 0.54 (95 % CI = 0.30-0.99; P = 0.045). In the group analysis of smoking status, the OR for the -1239C allele-containing genotype was higher than that for -1239GG genotype (OR = 0.57; 95 % CI = 0.40-0.81; P = 0.002) among smokers, but not among nonsmokers. Moreover, when the risk associated with CYP2E1 polymorphism was further evaluated within strata of <25 and >/=25 pack-years smoked, this effect between susceptible genotypes and smoking was mostly evident among light smokers (<25 pack-years) with OR of 0.42 (95 % CI 0.23-0.79), but not among heavy smokers with OR of 0.87 (95 % CI 0.53-1.43). In the group analyses by TNM stage, there was no significant difference between CYP2E1 -1239G>C polymorphism and the risk of non-small cell lung cancer. Meta-analysis data also showed that the carriers of CYP2E1 -1239C allele had a protect effect on the risk of lung cancer in Chinese with overall OR of 0.77 (95 % CI 0.66-0.90). CYP2E1 -1239G>C polymorphism was associated with a decreased risk of development of non-small cell lung cancer in Chinese patients. The association displays a manner of gene-environment interaction between this polymorphism and smoking status.
also observed using dominant or recessive genetic models. This meta-analysis demonstrated that the three common variations (rs4324798, rs3117582, and rs9295740) on 6p21 are risk factors associated with increased lung cancer susceptibility, but these associations vary in different ethnic populations.
**TÍTULO / TITLE:** - The emerging role of SOX2 in cell proliferation and survival and its crosstalk with oncogenic signaling in lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Chou YT; Lee CC; Hsiao SH; Lin SE; Lin SC; Chung CH; Chung CH; Kao YR; Wang YH; Chen CT; Wei YH; Wu CW

**INSTITUCIÓN / INSTITUTION:** - Institute of Biotechnology, National Tsing Hua University, Hsinchu, Taiwan.

**RESUMEN / SUMMARY:** - Tumor cells have long been observed to share several biological characteristics with normal stem/progenitor cells; however, the oncogenic mechanisms underlying the lung stem/progenitor cell signaling remain elusive. Here we report that SOX2, a self-renewal factor in lung stem/progenitor cells, is highly expressed in a subclass of lung cancer cells, the proliferation, survival and chemoresistance of which are dependent on SOX2 signaling. Overexpression of SOX2 promotes oncogenic phenotypes in lung cancer cells; knockdown of SOX2 attenuated cell proliferation. We observed that SOX2 increased the expression of EGFR, and EGFR activation further upregulated SOX2 levels, forming a positive feedback loop. SOX2 expression promoted chemoresistance, and silencing of SOX2 perturbed mitochondrial function, causing marked apoptosis and autophagy. SOX2 induced BCL2L1, the ectopic expression of which rescued the effects of SOX2 silencing on apoptosis, autophagy, and mitochondrial function. SOX2 promoted tumor formation, along with increased cell proliferation in a xenograft mouse model. SOX2 expression is associated with poor prognosis in lung cancer patients; moreover, SOX2, EGFR and BCL2L1 expression levels were significantly correlated in lung tumors. Our findings support the emerging role of SOX2 in cell proliferation and survival by eliciting oncogenic EGFR and BCL2L1 signaling with potential applications as a prognosis marker and a therapeutic target in lung cancer. Stem Cells 2013.

[330]

**TÍTULO / TITLE:** - Afatinib, Erlotinib and Gefitinib in the First-Line Therapy of EGFR Mutation-Positive Lung Adenocarcinoma: A Review.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Kohler J; Schuler M

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Germany.
- Non-small cell lung cancer (NSCLC) consists of several histomorphologically defined phenotypes that display an enormous genetic variability. In recent years, epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma has emerged as a unique subset of NSCLC in terms of etiopathogenesis and tumor biology. Since the introduction of the reversible EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib, patients with metastatic EGFR mutation-positive lung cancer can be offered a therapeutic alternative that has proven its superiority over standard platinum-based chemotherapy. However, primary or acquired resistance limits the therapeutic success of these targeted agents. Irreversible inhibitors targeting all ErbB family receptor tyrosine kinases, such as afatinib and dacomitinib, have been developed to confer sustained disease control in ErbB-dependent cancers. The large LUX-Lung 3 phase III trial recently reported afatinib to be clearly superior over the most effective platinum doublet in patients with EGFR mutation-positive lung cancer. To fully exploit the clinical activity of afatinib, proactive management of its gastrointestinal and dermatologic toxicities is advised. © 2013 S. Karger GmbH, Freiburg.

Enlace al Resumen / Link to its Summary

TÍTULO / TITLE: - Nemo-like kinase (NLK) inhibits the progression of NSCLC via negatively modulating Wnt signaling pathway.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1002/jcb.24635

AUTORES / AUTHORS: - Lv L; Wan C; Chen B; Li M; Liu Y; Ni T; Yang Y; Liu Y; Cong X; Xue Q; Mao G

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Affiliated Hospital of Nantong University, Nantong, 226001, Jiangsu, China.

RESUMEN / SUMMARY: - Nemo-like kinase (NLK), an evolutionarily conserved serine/threonine kinase, is a critical regulator of various cancers. NLK expression was evaluated by Western blot in 8 paired fresh non-small-cell lung cancer (NSCLC) tissues and immunohistochemistry (IHC) on 83 paraffin-embedded slices. NLK was lowly expressed in NSCLC and significantly associated with NSCLC histological differentiation, clinical stage, lymph node status and Ki-67. Multivariate analysis indicated that low NLK expression was an independent prognostic factor for NSCLC patients’ low survival rate. In vitro, after the release of NSCLC cell line A549 from serum starvation, the expression of NLK was down-regulated, whereas the cell-cycle-related proteins were up-regulated. In addition, we used RNA interference to knock down NLK expression, then observed its effects on NSCLC’s growth in vitro. Western blot analyses indicated that deletion of NLK was positively correlated with cell-cycle-related proteins. The present investigation demonstrated that suppression of NLK expression resulted in
significant promotion of proliferation in NSCLC cells. And flow cytometry further indicated that loss of NLK promoted cell proliferation by facilitating S-phase and mitotic entry. Besides, the transcription activity of beta-catenin/TCF in A549 cells was remarkably enhanced when NLK was knocked down, which suggested that NLK participated in NSCLC cell proliferation via medulating Wnt signaling pathway. Based on these findings, we can provide a potential strategy for NSCLC therapy. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[332]
TÍTULO / TITLE: - Hematein, a casein kinase II inhibitor, inhibits lung cancer tumor growth in a murine xenograft model.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 3892/ijo.2013.2087
AUTORES / AUTHORS: - Hung MS; Xu Z; Chen Y; Smith E; Mao JH; Hsieh D; Lin YC; Yang CT; Jablons DM; You L
INSTITUCIÓN / INSTITUTION: - Thoracic Oncology Laboratory, Department of Surgery, Comprehensive Cancer Center, University of California, San Francisco, CA 94115, USA.
RESUMEN / SUMMARY: - Casein kinase II (CK2) inhibitors suppress cancer cell growth. In this study, we examined the inhibitory effects of a novel CK2 inhibitor, hematein, on tumor growth in a murine xenograft model. We found that in lung cancer cells, hematein inhibited cancer cell growth, Akt/PKB Ser129 phosphorylation, the Wnt/TCF pathway and increased apoptosis. In a murine xenograft model of lung cancer, hematein inhibited tumor growth without significant toxicity to the mice tested. Molecular docking showed that hematein binds to CK2alpha in durable binding sites. Collectively, our results suggest that hematein is an allosteric inhibitor of protein kinase CK2 and has antitumor activity to lung cancer.

[333]
TÍTULO / TITLE: - Nonexamination of Lymph Nodes and Survival After Resection of Non-Small Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1016/j.athoracsur.2013.05.021
AUTORES / AUTHORS: - Osarogiagbon RU; Yu X
BACKGROUND: Nonexamination of lymph nodes is an extreme example of the variability of pathologic nodal staging of non-small cell lung cancer. We compared the prevalence, characteristics, and survival of patients without lymph nodes (pNX) to patients with documented pathologic N0 and pathologic N1 non-small cell lung cancer. METHODS: A retrospective analysis was done of non-small cell lung cancer resections in the US Surveillance, Epidemiology, and End Results database from 1998 to 2009. RESULTS: Thirteen percent of all resections (18% of node negative resections) were pNX, including 6% of all node-negative lobar or greater resections and 51% of sublobar resections. Thirty-five percent of pNX resections were lobar or greater compared with 90% of pathologic N0 (p < 0.0001). Advanced age and surgery in rural locations were also significantly associated with pNX resection. The median duration of survival was 3 years in the pNX cohort, 6.4 years in the N0 cohort (p < 0.0001), and 2.8 years in the N1 group, with respective 5-year survival rates of 47%, 67%, and 45% (p < 0.0001). These survival differences remained after adjustment for potentially confounding factors. CONCLUSIONS: Patients with pNX resections are a high-risk subset, with survival approximating pathologic N1, not N0. They should have further attempts at retrieving lymph nodes for examination or be offered postoperative adjuvant chemotherapy. We predict that treatment modalities that fail to address lymph nodes are likely to yield inferior survival in comparison to surgery with proper lymph node examination. The proportion of pNX lung resections may be a sentinel quality indicator for lung cancer programs.

[334]

TÍTULO / TITLE: The contribution of risk prediction models to early detection of lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Field JK; Chen Y; Marcus MW; McRonald FE; Raji OY; Duffy SW

INSTITUCIÓN / INSTITUTION: Roy Castle Lung Cancer Research Programme, Department of Molecular and Clinical Cancer Medicine, The University of Liverpool Cancer Research Centre, Liverpool, UK.

RESUMEN / SUMMARY: Low-dose computed tomography screening is a strategy for early diagnosis of lung cancer. The success of such screening will be dependent upon identifying populations at sufficient risk in order to maximise the benefit-to-harm ratio of the intervention. To facilitate this, the lung cancer risk prediction community has established several risk models with good predictive performance. This review focuses

[335]

TÍTULO / TITLE: - INDUCTION BUT NOT INHIBITION OF COX-2 CONFERS HUMAN LUNG CANCER CELL APOPTOSIS BY CELECOXIB.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ramer R; Walther U; Borchert P; Lauffer S; Linnebacher M; Hinz B
INSTITUCIÓN / INSTITUTION: - University of Rostock, Germany;
RESUMEN / SUMMARY: - The antitumorigenic mechanism of the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib is still a matter of debate. Among different structurally related COX-2 inhibitors, only celecoxib was found to cause apoptosis and cell death of human lung cancer cells (IC50 values of 19.96 μM [A549], 12.48 μM [H460] and 41.39 μM [H358]) that was paralleled by a time- and concentration-dependent upregulation of COX-2 and peroxisome proliferator activated receptor gamma (PPARgamma) at mRNA and protein levels. Apoptotic death of celecoxib-treated cancer cells was suppressed by the PPARgamma antagonist GW-9662 and by siRNA targeting PPARgamma, and surprisingly also by the selective COX-2 inhibitor NS-398 and siRNA targeting COX-2. NS-398 (1 μM) was shown to suppress celecoxib-induced COX-2 activity. Among the COX-2-dependent prostaglandins (PGs) induced upon celecoxib treatment, PGD2 and 15-deoxy-Delta12,14-PGJ2 were found to induce a cytosol-to-nucleus translocation of PPARgamma as well as a PPARgamma-dependent apoptosis. Celecoxib-elicited PPARgamma translocation was inhibited by NS-398. Finally, a COX-2- and PPARgamma-dependent cytotoxic action of celecoxib was also proven for primary human lung tumor cells. Together, our data demonstrate a proapoptotic mechanism of celecoxib involving initial upregulation of COX-2 and PPARgamma and a subsequent nuclear translocation of PPARgamma by COX-2-dependent PGs.

[336]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Frost G
INSTITUCIÓN / INSTITUTION: - Health & Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN, UK.

RESUMEN / SUMMARY: - Background: The Great Britain (GB) Asbestos Survey is a prospective cohort of asbestos workers in GB. The objective of this study was to investigate determinants of mesothelioma latency, paying particular attention to indicators of intensity of asbestos exposure such as occupation, sex, and presence of asbestosis. Methods: The analysis included members of the cohort who died with mesothelioma between 1978 and 2005. The primary outcome was the latency period defined as the time from first occupational exposure to asbestos to death with mesothelioma. Generalised gamma accelerated failure-time models were used to estimate time ratios (TRs). Results: After excluding missing data, there were 614 workers who died with mesothelioma between 1978 and 2005. Total follow-up time was 9280 person-years, with a median latency of 22.8 years (95% confidence interval (CI) 16.0-27.2 years). In the fully adjusted model, latency was around 29% longer for females compared with males (TR=1.29, 95% CI=1.18-1.42), and 5% shorter for those who died with asbestosis compared with those who did not (TR=0.95, 95% CI=0.91-0.99). There was no evidence of an association between latency and occupation. Conclusion: This study did not find sufficient evidence that greater intensity asbestos exposures would lead to shorter mesothelioma latencies.

[337]

TÍTULO / TITLE: - Pulmonary tumor thrombotic microangiopathy with circulatory failure treated with imatinib.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Ogawa A; Yamadori I; Matsubara O; Matsubara H

INSTITUCIÓN / INSTITUTION: - Department of Clinical Science, National Hospital Organization Okayama Medical Center, Japan.

RESUMEN / SUMMARY: - Pulmonary tumor thrombotic microangiopathy is a lethal, yet difficult to diagnose, complication of gastrointestinal carcinoma. Even if properly diagnosed, there is no treatment, especially after a circulatory collapse. We herein report a case of pulmonary tumor thrombotic microangiopathy with circulatory failure due to pulmonary hypertension. The patient was temporarily successfully treated with imatinib, an inhibitor of the platelet-derived growth factor receptor. Pulmonary hypertension was dramatically ameliorated and the patient was able to be weaned from percutaneous cardiopulmonary support within 20 days of treatment. Imatinib may be effective for ameliorating pulmonary hypertension that is caused by pulmonary tumor thrombotic microangiopathy.
Comparison of 2 monoclonal antibodies for immunohistochemical detection of BRAF V600E mutation in malignant melanoma, pulmonary carcinoma, gastrointestinal carcinoma, thyroid carcinoma, and gliomas.

BRAF mutation is seen in a variety of human neoplasms including cutaneous malignant melanoma, papillary thyroid carcinoma, colorectal carcinoma, non-small cell lung carcinoma, pleomorphic xanthoastrocytoma, and others. Currently, there are 2 commercially available monoclonal antibodies for the detection of BRAF V600E mutation; however, a full and practical comparison of their performance in various tumor types on an automated staining platform has not been done. We investigated their sensitivity and specificity in detecting the BRAF V600E mutation in a series of 152 tumors including 31 malignant melanomas, 25 lung carcinomas, 32 gastrointestinal carcinomas, 23 thyroid carcinomas, 35 gliomas, and 6 other malignancies. In this series, the concordance rate between immunohistochemistry (IHC) and mutational analyses was 97% (148/152) for VE1 and 88% (131/149) for anti-B-Raf. The sensitivity and specificity were 98% (60/61) and 97% (88/91) for monoclonal VE1 and 95% (58/61) and 83% (73/88) for anti-B-Raf, respectively. There were 4 cases with discordant IHC and mutational results for monoclonal VE1 in contrast to 18 cases for anti-B-Raf. Our studies showed that IHC with monoclonal VE1 has a better performance compared with anti-B-Raf in an automated staining platform and confirmed that clone VE1 provides excellent sensitivity and specificity for detecting the BRAF V600E mutation in a variety of tumor types in a clinical setting.

The relationship between KRAS gene mutations and HLA class I antigen downregulation in the metastasis of non-small cell lung cancer.

In this study, we investigate the relationship between KRAS gene mutations and HLA class I antigen downregulation in the metastasis of non-small cell lung cancer. We found that KRAS mutations are associated with HLA class I antigen downregulation in the metastasis of non-small cell lung cancer.

He XP; Song FJ; Liu XY; Wang Z; Li XX; Liu FY; Chen G; Jiang WP
OBJECTIVE: To investigate the association between v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS) gene mutations and levels of human leucocyte antigen (HLA) class I antigen in primary lung tumours and metastatic lymph nodes of patients with non-small cell lung cancer (NSCLC).

METHODS: Patients with NSCLC undergoing tumour resection were enrolled. KRAS codon 12 mutations were analysed in normal lung and lymph node tissue, primary lung tumours and metastatic lymph nodes using polymerase chain reaction-restriction fragment length polymorphism analysis. HLA class I antigen immunostaining was examined using flow cytometry.

RESULTS: A total of 65 patients participated in the study. All normal lung tissues had positive HLA class I antigen immunostaining. The majority of primary lung tumours (56/65) and all of the metastatic lymph nodes (31/31) had downregulated HLA class I antigen immunostaining. There was a positive correlation between downregulated HLA class I antigen in primary tumours and metastatic lymph nodes. There was a negative correlation between KRAS codon 12 mutations and the level of HLA class I antigen in primary and metastatic tumours.

CONCLUSIONS: KRAS codon 12 mutations appear to be important in the downregulation of HLA class I antigen in NSCLC. Abnormal activation of the oncogenic KRAS pathway might provide a new treatment target for NSCLC.

[340]

**TÍTULO / TITLE:** - Coadministration of Erlotinib and Curcumin Augmentatively Reduces Cell Viability in Lung Cancer Cells.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 1002/ptr.5056

**AUTORES / AUTHORS:** - Yamauchi Y; Izumi Y; Yamamoto J; Nomori H

**INSTITUCIÓN / INSTITUTION:** - Division of General Thoracic Surgery, Department of Surgery, School of Medicine, Keio University, Japan.

**RESUMEN / SUMMARY:** - Resistance to erlotinib in lung cancer cases includes T790M mutant epidermal growth factor receptor and c-Met gene amplification, but other unknown mechanisms account for about 30% of the resistance. Activation of the nuclear factor kappa B (NFκB)-related pathways in association with the reduction in ikappaB level may be one of such potential mechanisms. It is known that curcumin inhibits the inducible activation of NFκB at least in part by sustaining ikappaB expression level. Therefore, we evaluated the effects of coadministration of erlotinib and curcumin on lung cancer cells. We found that erlotinib and curcumin augmentatively reduced cell viability. Studies in PC9 cells showed that induction of apoptosis was involved. Expression of ikappaB was elevated in PC9 cells by curcumin.
administration, and pretreatment with siRNAs for ikappaB significantly attenuated the reduction in cell viability after coadministration of erlotinib and curcumin. Furthermore, coadministration of erlotinib and/or curcumin augmentatively attenuated the growth of PC9 tumors in mice. These results suggested the existence of an augmentative tumor growth inhibitory effect between erlotinib and curcumin, and this effect was at least in part mediated by the increase in the expression of ikappaB induced by curcumin. Copyright © 2013 John Wiley & Sons, Ltd.

[341] TÍTULO / TITLE - Phase II study of oral S-1 plus cisplatin with bevacizumab for advanced non-squamous non-small cell lung cancer. RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary REVISTA / JOURNAL: Lung Cancer. 2013 Oct;82(1):103-8. doi: 10.1016/j.lungcan.2013.07.008. Epub 2013 Aug 5. ●● Enlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.07.008 AUTORES / AUTHORS: - Kaira K; Tomizawa Y; Yoshino R; Miura Y; Yoshii A; Iwasaki Y; Koga Y; Ono A; Hisada T; Minato K; Sato K; Kazama T; Ishihara S; Kohyama K; Fueki N; Saito R; Sunaga N INSTITUCIÓN / INSTITUTION: - Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Showa-machi, Maebashi, Gunma 371-8511, Japan. Electronic address: kkaira1970@yahoo.co.jp. RESUMEN / SUMMARY: BACKGROUND: We conducted a phase II study to evaluate the efficacy and safety of S-1 plus cisplatin with bevacizumab followed by maintenance bevacizumab in patients with advanced non-squamous non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: Chemotherapy-naive patients received S-1 plus cisplatin with bevacizumab. S-1 (80mg/m(2)) was administered orally twice daily for 14 days, cisplatin (60mg/m(2)) on day 1, and bevacizumab (15mg/kg) on day 1 and every 3 weeks for 4-6 cycles. Patients with an objective response or stable disease received maintenance bevacizumab every 3 weeks until disease progression. RESULTS: Thirty patients were enrolled in this study. The median number of chemotherapy was four (range, 1-6 cycles), and the median number of bevacizumab alone was three (range, 1-31 cycles). The grade ¼ toxicities were neutropenia (23%), thrombocytopenia (10%), febrile neutropenia (3%), hypertension (17%), pneumonia (7%), and bowel perforation (3%). The objective response rate was 71% (95% CI, 55-88%) for a disease control rate of 100%. The median progression-free and overall survival times were 7.0 months and 20.0 months, respectively. CONCLUSIONS: S-1 plus cisplatin with bevacizumab is an active and well-tolerated regimen in patients with chemotherapy-naive non-squamous NSCLC.
Glypican-5 es un nuevo supresor de metástasis en cáncer de pulmón no pequeño.

**RESUMEN / SUMMARY:** Glypican-5 (GPC5) podría ser un gen potencial supresor de tumor en cáncer de pulmón no pequeño (NSCLC). El presente estudio se propone clarificar el patrón de expresión de GPC5 y explorar sus posibles funciones en NSCLC. La expresión del gen GPC5 fue más baja en tejido canceroso de pulmón comparado con tejido no canceroso adyacente. La expresión del gen GPC5 en el grupo de metástasis linfática fue significativamente más baja que en el grupo no-metástasis. El estudio de microarrays (TMA) encontró que la tasa de sobrevida total del grupo GPC5 positivo fue significativamente más alta que en el grupo GPC5 negativo en el subgrupo de AC. El sobreexpresar GPC5 en líneas de cáncer de pulmón no pequeño significativamente suprimió su migración, invasión, y actividades de proliferación en el cultivo in vitro. Nuestros datos sugieren que GPC5 es un nuevo supresor de metástasis en NSCLC y podría ser un potencial biomarcador que predice la metástasis de NSCLC.

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Chest Tube Tip Culture as a Predictor of Postoperative Infection in Lung Cancer Operations.


Yamauchi Y; Isaka M; Maniwa T; Takahashi S; Kurai H; Ohde Y

Institución / Institution: Division of General Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan. Electronic address: yoshikanay@2004.jukuin.keio.ac.jp.

**RESUMEN / SUMMARY:** Fondo del estudio: La infección postoperatoria es una de las complicaciones más frecuentemente observadas después de la resección de pulmón y debe ser abordada en la gestión perioperatoria. Este estudio evaluó la significación clínica de la cultura de punta de tubo de toraco relevante a la infección postoperatoria. **MÉTODOS:** Desde septiembre de 2002 hasta diciembre de 2011, 1,438 pacientes que sometieron a operaciones de cáncer de pulmón en Shizuoka...
Cancer Center Hospital were evaluated. Postoperative infections, including surgical site infection, postoperative pneumonia, and postoperative empyema without fistula, were defined as those occurring within 30 days of thoracotomy. RESULTS: Postoperative infections developed in 84 of the 1,438 patients (5.8%), including 42 (2.9%) with surgical site infection, 36 (2.5%) with pneumonia, and 13 (0.9%) with empyema. The sensitivity, specificity, and positive predictive value of chest tube tip culture were 23%, 98%, and 41.3%, respectively. Multivariate analysis demonstrated that the independent risk factors associated with the development of postoperative infections were coexisting diabetes mellitus and positive chest tube tip culture. Positive chest tube tip culture was the only independent risk factor associated with surgical site infection. The independent risk factors associated with postoperative pneumonia were age 70 years or older, coexisting diabetes mellitus, and positive chest tube tip culture. Finally, positive chest tube tip culture was the only independent risk factor associated with postoperative empyema. CONCLUSIONS: Positive chest tube tip culture strongly predicts postoperative infections in lung cancer surgery and necessitates careful observation in the perioperative period.
[345]

**TÍTULO / TITLE:** - Targeting PKCepsilon by miR-143 regulates cell apoptosis in lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Zhang N; Su Y; Xu L

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

**RESUMEN / SUMMARY:** - Non-small cell lung cancer (NSCLC) is one of the most common causes for lung cancer and cancer-related death. The imbalance between cell proliferation and apoptosis was suggested to play an important role in cancer pathogenesis and PKCepsilon is one of the widely recognized targets. Here, we demonstrate that miR-143 is aberrantly downregulated in NSCLC tissue and negatively correlates with expression of PKCepsilon. We show that miR-143 specifically targets the 3'-UTR of PKCepsilon and regulates its expression. Treatment with miR-143 inhibitor mimics cell proliferation and apoptosis imbalance in NSCLC, while inhibition of PKCepsilon can reverse it. Our findings suggest that targeting PKCepsilon overexpression in NSCLC should be beneficial for lung cancer therapy.

[346]

**TÍTULO / TITLE:** - Potentiation of anticancer effect of valproic acid, an antiepileptic agent with histone deacetylase inhibitory activity, by the cyclin-dependent kinase inhibitor P276-00 in human non-small-cell lung cancer cell lines.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Shirsath N; Rathos M; Chaudhari U; Sivaramakrishnan H; Joshi K

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Piramal Life Sciences, Piramal Enterprises Limited, 1 Nirlon Complex, Goregaon (East), Mumbai, Maharashtra 400 063, India.

**RESUMEN / SUMMARY:** - BACKGROUND: P276-00 is a novel cyclin-dependent kinase (CDK) inhibitor is in Phase II clinical trials. Valproic acid (VPA), an antiepileptic agent has been associated with anticancer activity, through the inhibition of histone deacetylase I. Here we investigate the effect of the combination of VPA and P276-00,
in non-small-cell lung cancer (NSCLC) cell lines. MATERIALS AND METHODS: Cell growth inhibition was studied using the Propidium iodide (PI) assay. Cell cycle analysis and recovery were detected by flow cytometry. The expression levels of various proteins were detected by western blot. Inhibition of colony formation in H460 was checked in vitro. In vivo efficacy was studied in H460 xenograft model. RESULTS: The combination of P276-00 and VPA showed synergistic effect on p53+ and p53- NSCLC cell lines in antiproliferative assay at both constant and non-constant ratio with marked decrease in colony forming potential. Flow cytometric analysis confirmed a significant time dependent increase in apoptosis with 64% apoptotic population at 96h compared to VPA (1%) and P276-00 (28%) alone ($p<0.0001$). Incubation of the cells after treatment, in fresh medium without drugs, led to the recovery of cells treated with P276-00 alone but not the cells treated with the combination of both the drugs. The combination treatment up-regulated tumor suppressor proteins like p53, p21 and p27 along with down-regulation of proliferation and survival proteins viz. cyclin D1 and Bcl-2. This was also associated with the upregulation of the pro-apoptotic protein Bax and significant accumulation of hyperacetylated histones in the combination treatment. Interestingly, VPA in combination with P276-00 was much more effective as an antitumor agent than alone, in the H460 xenograft tumor model in SCID mice. CONCLUSIONS: This study indicates that the combination of HDAC inhibitor VPA with CDK inhibitor P276-00 is promising novel molecularly targeted therapeutic approach for NSCLC treatment.

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TÍTULO / TITLE: Aerosolised 5-azacytidine suppresses tumour growth and reprogrammes the epigenome in an orthotopic lung cancer model.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Reed MD; Tellez CS; Grimes MJ; Picchi MA; Tessema M; Cheng YS; March TH; Kuehl PJ; Belinsky SA

INSTITUCIÓN / INSTITUTION: Lung Cancer Program, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108, USA.

RESUMEN / SUMMARY: Background: Epigenetic silencing by promoter methylation and chromatin remodelling affects hundreds of genes and is a causal event for lung cancer. Treatment of patients with low doses of the demethylating agent 5-azacytidine in combination with the histone deacetylase inhibitor entinostat has yielded clinical responses. The subcutaneous dosing route for consecutive days and reduced bioavailability of 5-azacytidine because of inactivation by cytidine deaminase may limit the expansion of epigenetic therapy into Phase III trials. To mitigate these barriers, an
aerosol of 5-azacytidine was generated and characterised. Methods: The effect of aerosol vs systemic delivery of 5-azacytidine on tumour burden and molecular response of engrafted lung tumours in the nude rat was compared. Results: Pharmacokinetics revealed major improvement in the half-life of 5-azacytidine in lung tissue with aerosol delivery. Aerosolised 5-azacytidine significantly reduced lung tumour burden and induced global demethylation of the epigenome at one-third of the comparable effective systemic dose. High commonality for demethylation of genes was seen in tumours sampled throughout lung lobes and across treated animals receiving the aerosolised drug. Conclusion: Collectively, these findings show that aerosolised 5-azacytidine targets the lung, effectively reprogrammes the epigenome of tumours, and is a promising approach to combine with other drugs for treating lung cancer.
TÍTULO / TITLE: Late radiologic changes after stereotactic ablative radiotherapy for early stage lung cancer: A comparison of fixed-beam versus arc delivery techniques.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1016/j.radonc.2013.08.034

AUTORES / AUTHORS: Senthi S; Dahele M; van de Ven PM; Slotman BJ; Senan S

INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands. Electronic address: s.senthi@vumc.nl

RESUMEN / SUMMARY: BACKGROUND AND PURPOSE: To characterize the radiologic changes occurring following arc stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer relative to those following fixed-beam SABR.

METHODS: Twenty-nine patients treated with arc SABR without local recurrence and more than two years follow-up were retrospectively evaluated using a published scoring system. The late morphologic patterns, timing and severity of radiologic change were assessed and compared to 54 patients treated with fixed-beam SABR that we previously assessed using the same system.

RESULTS: The baseline characteristics and follow-up of both cohorts were well matched and SABR technique was not associated with morphologic differences before 6 months (p=0.23). Thereafter the predicted probabilities of a modified-conventional pattern following arc and fixed-beam SABR were 96.3% vs. 68.9%, respectively (OR 11.7, 95% CI 3.38-40.8, p<0.001). In addition, at 1 year follow-up the predicted probabilities of arc and fixed-beam SABR patients having expected or pronounced radiologic changes were 64.9% and 22.1%, respectively (OR=6.56, 95% CI: 3.13-13.7, p<0.001).

CONCLUSIONS: Post-SABR radiologic changes differ with delivery technique, which has important implications during follow-up. Confirmation in larger studies is required and etiologic factors remain to be determined.

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TÍTULO / TITLE: Erlotinib in the treatment of advanced squamous cell NSCLC.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 4149/neo_2013_086

AUTORES / AUTHORS: Fiala O; Pesek M; Finek J; Krejci J; Havel L; Hrnčiarik M; Salajka F; Bortliček Z; Benesova L; Minarík M

RESUMEN / SUMMARY: Erlotinib is an epidermal growth factor receptor tyrosine-kinase inhibitor. Clinical trials have shown its efficacy in advanced non-small cell lung cancer (NSCLC). We conducted a large retrospective study based on clinical experience aiming to prove erlotinib’s efficacy and safety in patients with advanced-stage squamous cell
NSCLC. Totally 375 patients with advanced-stage (IIIB, IV) squamous cell NSCLC were treated with erlotinib. Erlotinib was continued until disease progression or intolerable toxicity. 1 (0.3%) complete response (CR), 28 (7.5%) partial responses (PR) and 198 (52.8%) stable diseases (SD) were achieved. Overall response rate (ORR) and disease control rate (DCR) were 7.8% and 60.5%, respectively. Median progression-free survival (PFS) was 3.0 months and median overall survival (OS) was 7.6 months. PFS of patients with CR/PR, SD and PD were 7.6, 3.9 and 1.0 months, respectively (P

Keywords: squamous cell, NSCLC, erlotinib, targeted treatment, EGFR-TKI.

[351]

TÍTULO / TITLE: - Suppression of Wnt signaling by the miR-29 family is mediated by demethylation of WIF-1 in non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Tan M; Wu J; Cai Y
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Shanghai Tenth People’s Hospital, Tongji University, Shanghai 200072, China.
RESUMEN / SUMMARY: - Wnt inhibitory factor-1 (WIF-1) silencing induced by promoter hypermethylation is a common mechanism of aberrant activation of the Wnt signaling pathway in non-small-cell lung cancer (NSCLC). However, the activity of regulators associated with the methylation of the WIF-1 gene remains unclear. Here, we investigated the role of three DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) in the expression of WIF-1. The three DNMTs were up-regulated in NSCLC tumor tissues and suppression of DNMT3A and DNMT3B restored the expression of WIF-1 in NSCLC cells. The miR-29 family (miR-29a, -29b, and -29c), which negatively regulates DNMT3A and DNMT3B, was examined in association with the Wnt/beta-catenin signaling pathway. A positive correlation between the expression of WIF-1 and that of MiR-29s was observed in NSCLC tissues. Methylation-specific PCR and Western blotting indicated that miR-29s positively regulate WIF-1 expression by inhibiting the methylation of its promoter. Furthermore, miR-29 overexpression downregulated beta-catenin expression, inhibited cell proliferation and induced apoptosis. The expression of miR-29a and miR-29b was partially regulated by DNMT3A and DNMT3B in a positive feedback loop. Taken together, our findings show that miR-29s suppress the Wnt signaling pathway through demethylation of WIF-1 in NSCLC.

[352]
RESUMEN / SUMMARY: - Pulmonary sleeve resection in locally advanced lung cancer using cryopreserved allograft for pulmonary artery replacement.


AUTORES / AUTHORS: - Berthet JP; Boada M; Paradela M; Molins L; Matecki S; Marty-Ané CH; Gomez-Caro A

INSTITUCIÓN / INSTITUTION: - General Thoracic Surgery Department, Hospital Clinic, University of Barcelona, Barcelona, España; Division of Thoracic Surgery, Arnaud de Villeneuve University Hospital, Montpellier, France; U1046, INSERM, Montpellier University 1, Montpellier University 2, Montpellier, France. Electronic address: jeanphilippe.berthet@gmail.com.

RESUMEN / SUMMARY: - BACKGROUND: During lobectomy, resection of pulmonary artery, followed by reconstruction or replacement with or without concomitant sleeve bronchial resection, is feasible in selected cases. We report morbidity, mortality, and technical issues in pulmonary artery replacement using a cryopreserved arterial allograft after sleeve resection for centrally located non-small cell lung carcinoma (NSCLC). METHODS: We reviewed clinical and pathologic data of patients who underwent arterial sleeve lobectomy with pulmonary artery replacement in our institution from 2007 to 2012. RESULTS: Of 178 centrally located NSCLCs, sleeve resections were performed in 92 (51%), pneumonectomies in 33 (18%), and lobectomies in 53 (31%). Of the 32 (34.7%) pulmonary reconstructions (excluding tangential suture), 20 (21.7%) were end-to-end anastomosis, 2 (2.1%) were pericardial patch reconstructions, and 10 (11%) were PA replacements. Clinical T staging was cT2a in 4 patients, cT2b in 3, cT3 in 2, and cT4 in 1. Four patients received concurrent induction chemoradiotherapy. Three patients underwent a double-sleeve right lobectomy. Cryopreserved allografts used were descending thoracic aorta (n = 3) and pulmonary arteries (n = 7). Complete resection (R0) was achieved in all patients. Final N staging was pN0 (n = 4), pN1 (n = 5), and pN2 (n = 1). There was no operative mortality. Four patients had major morbidity, including 1 early conduit thrombosis treated by pneumonectomy completion. Graft patency, assessed by contrast-enhanced computed tomography scan, was 90%. Mean follow-up was 25 +/- 14 (range, 8-47) months (30% for >36 months). Overall 5-year survival was 66.7%, and the estimated median disease-free survival was 42 months. CONCLUSIONS: In central NSCLCs, conservative surgery using a cryopreserved arterial allograft to replace the pulmonary artery after extended segmental resection could avoid pneumonectomy in selected patients.
**TÍTULO / TITLE:** Old wine in new pipes? Treatment of advanced non-small cell lung cancer with trofosfamide.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Reissig A; Walther M

**INSTITUCIÓN / INSTITUTION:** Department of Internal Medicine I, Pneumology and Allergology, Jena University Hospital, Friedrich-Schiller-University Jena, Germany. angelika.reissig@med.uni-jena.de

**RESUMEN / SUMMARY:** BACKGROUND: The aim of this retrospective study was to examine the effect of oral trofosfamide in patients with advanced non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: Patients with histologically or cytologically proven NSCLC, who had received at least 2 other therapies, were enrolled. The primary clinical end point was progression-free survival (PFS); secondary end points included overall survival (OS), response rate and toxicity. RESULTS: 23 patients were enrolled, 1 of whom was excluded due to non-compliance. The patients had received a median of 3 prior therapies (range 2-4). Regarding all 22 patients, median PFS was 14 weeks (95% confidence interval (CI) 9.96-18.04). The median OS was 32 weeks (95% CI 17.12-46.88). The median duration of trofosfamide therapy was 10.5 weeks (interquartile range 6.5-17.3). 20 patients (90.9%) had stable disease; 2 were not assessable. Trofosfamide therapy was stopped in 4 patients (18.2%) due to side effects. CONCLUSION: Trofosfamide is an orally applicable, well-tolerated and cost-effective drug that works in patients with advanced NSCLC, who have undergone at least 2 lines of therapy. Trofosfamide seems to be a therapeutic option in NSCLC as a further therapy line. These preliminary data need to be confirmed in a larger trial.

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**TÍTULO / TITLE:** Treatment of the postoperative recurrence of lung cancer in octogenarians.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Surg Today. 2013 Sep 12.

**AUTORES / AUTHORS:** Yasuda M; Nagashima A; Haro A; Saitoh G

**INSTITUCIÓN / INSTITUTION:** Department of Chest Surgery, Kitakyushu Municipal Medical Center, 2-1-1 Basyaku, Kokurakita-ku, Kitakyushu, 802-0077, Japan, ikyoku189@kmmc.jp.

**RESUMEN / SUMMARY:** PURPOSE: Guidelines for the treatment of postoperative recurrent lung cancer in octogenarians do not exist. In this study, we investigated the prognosis of patients with recurrence after the resection of lung cancer and discuss the
management of recurrent tumors in octogenarians. METHODS: This study clinicopathologically evaluated 135 octogenarians who underwent resections for lung cancer at a single institution between 1992 and 2010. We retrospectively reviewed the clinical records of 37 patients with confirmed recurrence. The overall survival of the patients and the treatments used for postoperative recurrence were evaluated.

RESULTS: Among 37 patients, six underwent intensive treatment, 14 underwent palliative treatment and 17 received supportive care only. The overall survival rates of the patients in the antitumor treatment groups tended to be associated with a better prognoses than those of the patients in the supportive care only group, but they did not exhibit significantly better prognoses at 1 year (p = 0.202). However, among the patients with a good performance status, the intensive treatment group tended to exhibit prolonged survival. Of the 37 patients with recurrent tumors, five (14 %) died of other diseases. CONCLUSIONS: Antitumor treatment of postoperative recurrent lung cancer in octogenarians may not always improve the survival rate. However, carefully selecting patients for intensive therapy, such as those with a good performance status, may lead to longer survival rates after postoperative recurrence in octogenarians.
were ALK positive by FISH, Ventana IHC, CST IHC, and RT-PCR, respectively. The sensitivity and specificity of Ventana IHC were 100% and 98%, respectively. Two Ventana IHC-positive cases, which were also CST IHC score of 3+, showed FISH negative, but their ALK rearrangement was confirmed by RT-PCR and direct sequencing. The sensitivity and specificity of CST IHC with staining intensity score of 1+ or more were 100% and 95%, respectively. Five (25%, of 20) patients with CST IHC score of 1+ were both FISH and RT-PCR negative. The sensitivity and specificity of RT-PCR for detection of ALK fusion were 98% and 95%, respectively. The total accordance rate between ALK RT-PCR and Ventana IHC was 97%. CONCLUSIONS: The novel fully automated IHC assay is a reliable screening tool in routine pathologic laboratories for identification of patients with ALK rearrangement for targeted therapy in lung ADC.

[356]
TÍTULO / TITLE: - Real-time soft tissue motion estimation for lung tumors during radiotherapy delivery.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1118/1.4818655
AUTORES / AUTHORS: - Rottmann J; Keall P; Berbeco R
INSTITUCIÓN / INSTITUTION: - Brigham and Women’s Hospital, Dana Farber-Cancer Institute and Harvard Medical School, Boston, Massachusetts 02115.
RESUMEN / SUMMARY: - Purpose: To provide real-time lung tumor motion estimation during radiotherapy treatment delivery without the need for implanted fiducial markers or additional imaging dose to the patient. Methods: 2D radiographs from the therapy beam’s-eye-view (BEV) perspective are captured at a frame rate of 12.8 Hz with a frame grabber allowing direct RAM access to the image buffer. An in-house developed real-time soft tissue localization algorithm is utilized to calculate soft tissue displacement from these images in real-time. The system is tested with a Varian TX linear accelerator and an AS-1000 amorphous silicon electronic portal imaging device operating at a resolution of 512 x 384 pixels. The accuracy of the motion estimation is verified with a dynamic motion phantom. Clinical accuracy was tested on lung SBRT images acquired at 2 fps. Results: Real-time lung tumor motion estimation from BEV images without fiducial markers is successfully demonstrated. For the phantom study, a mean tracking error <1.0 mm [root mean square (rms) error of 0.3 mm] was observed. The tracking rms accuracy on BEV images from a lung SBRT patient (approximately 20 mm tumor motion range) is 1.0 mm. Conclusions: The authors demonstrate for the first time real-time markerless lung tumor motion estimation from BEV images alone. The described system can operate at a frame rate of 12.8 Hz and does not require prior knowledge to establish traceable landmarks for tracking on
the fly. The authors show that the geometric accuracy is similar to (or better than) previously published markerless algorithms not operating in real-time.
Aberrant hypermethylation and reduced expression of disabled-2 promote the development of lung cancers.

Disabled-2 (Dab2) is considered a tumor suppressor and is downregulated in cancers. We examined the promoter methylation status and expression levels of Dab2, and investigated their roles in the development of lung cancers. Methylation-specific PCR was employed to analyze the methylation status of Dab2 in 100 lung cancer tissues. The cytoplasmic and nuclear expression of the Dab2 protein was determined using western blot analysis. Demethylation treatment using 5-Aza-2-deoxycytidine (5-Aza-dC) was performed in three lung cancer cell lines. Dab2 expression was upregulated by Dab2 transfection or interrupted by Dab2 siRNA in lung cancer cells. Proliferative and invasive ability tests were performed with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTS) and a Matrigel invasion assay, respectively. The methylation rate of Dab2 was significantly higher in lung cancer tissues compared to normal lung tissues. Dab2 methylation correlated with the reduced nuclear and cytoplasmic expression of Dab2, as well as the TNM stage and lymphatic metastasis of lung cancers. Treatment with 5-Aza-dC was able to eliminate the hypermethylation of Dab2, enhance Dab2 expression, and inhibit beta-catenin expression, and the proliferative and invasive ability of lung cancer cells. Upregulation of Dab2 expression reduced beta-catenin expression and proliferation and invasiveness of lung cancer cells. However, interruption of Dab2 expression induced the opposite results. Dab2 methylation is common in lung cancers, and is one of the most important factors responsible for the reduced expression of Dab2. Aberrant hypermethylation and reduced expression of Dab2 promote the development of lung cancers.
Histopatología de adenocarcinoma de pulmón basada en la nueva clasificación IASLC/ATS/ERS: Estratificación prognóstica con biomarcadores de función y metabolismo.

RESUMEN / SUMMARY:
OBJETIVO: Correlacionar los resultados del subtipado histopatológico y graduación del adenocarcinoma de pulmón con los valores máximos de absorción estándar (SUVmax) en tomografía de emisión de positrones (PET)/tomografía computarizada y los valores promedio de coeficiente de difusión aparente (ADC) en resonancia magnética ponderada en difusión (DWI).

MATERIALS AND METHODS: Se incluyeron 43 pacientes. Los valores de SUVmax y ADC de los tumores fueron medidas y correlacionadas con los subtipos y graduaciones histológicas del adenocarcinoma de pulmón basados en el esquema de clasificación IASLC/ATS/ERS. La supervivencia sin enfermedad (DFS) fue estimada por el método de Kaplan-Meier y el test de rangos logarítmicos se utilizó para evaluar diferencias entre los tres subtipos histológicos o subgrupos clasificados con los resultados del estudio de biomarcadores de imagen.

RESULTADOS: Cinco (12.5%) tumores pertenecían a bajo grado, 30 (70%) a grado intermedio, y 8 (18.5%) a alto grado, los pacientes con histología de bajo grado tuvieron menor riesgo de recurrencia que los con histología de grado intermedio o alto (P = 0.048). Se observó una diferencia significativa en los valores de SUVmax y ADC entre los tres grados histológicos (Ps < 0.001). En cuanto a DFS, una menor actividad metabólica (PET) o una mayor difusión funcional (DWI) indicaron una mayor DFS. Cuando los pacientes (n = 30; 70% de pacientes) con gradación histológica intermedia se agruparon considerando ambos resultados de SUVmax y ADC, combinar ambos criterios de imagen biomarcador ayudó a estratificar a los pacientes de manera más precisa (P = 0.006). CONCLUSION: Los valores de SUVmax y ADC correlacionan bien con los grados histológicos del adenocarcinoma de pulmón, y combinar ambos resultados del estudio de biomarcadores de imagen resulta en una estratificación más útil de los pacientes en diferentes subconjuntos pronósticos que los resultados de cada estudio.

BACKGROUND: Reliable mortality data are sparse for developing countries. Furthermore, risk factor prevalence information is hardly available and thus not taken into consideration when estimating mortality. METHODS: The authors used a validated, statistical model combined with representative smoking prevalence from WHO STEPS surveys to estimate lung cancer mortality for six Sub-Saharan African countries (Benin, Malawi, Mozambique, Niger, Sierra Leone, Swaziland). Results were compared to a reference database (GLOBOCAN). Using different smoking prevalence scenarios, future lung cancer deaths were estimated. RESULTS: The prevalence of current moderate smoking among males ranged from 8.7% to 34.6%. Prevalence was much lower among females. For all countries considered, our mortality estimates were higher than GLOBOCAN estimates that do not consider prevalence: Overall, we estimated 2405 lung cancer deaths for 2008 compared to 531 deaths estimated by GLOBOCAN. Up to 2030, lung cancer deaths are expected to increase in general and by over 100% in Benin and Niger. Even under the assumption of decrease in smoking prevalence, lung cancer mortality will rise. CONCLUSION: On the bases of detailed smoking prevalence information, our findings implicate a higher lung cancer burden in low income countries. The epidemiologic transition in African low-income countries alludes to the need for targeted health prevention efforts.

Therapeutic strategy for advanced EGFR mutant non-small-cell lung carcinoma.

BACKGROUND: Reliable mortality data are sparse for developing countries. Furthermore, risk factor prevalence information is hardly available and thus not taken into consideration when estimating mortality. METHODS: The authors used a validated, statistical model combined with representative smoking prevalence from WHO STEPS surveys to estimate lung cancer mortality for six Sub-Saharan African countries (Benin, Malawi, Mozambique, Niger, Sierra Leone, Swaziland). Results were compared to a reference database (GLOBOCAN). Using different smoking prevalence scenarios, future lung cancer deaths were estimated. RESULTS: The prevalence of current moderate smoking among males ranged from 8.7% to 34.6%. Prevalence was much lower among females. For all countries considered, our mortality estimates were higher than GLOBOCAN estimates that do not consider prevalence: Overall, we estimated 2405 lung cancer deaths for 2008 compared to 531 deaths estimated by GLOBOCAN. Up to 2030, lung cancer deaths are expected to increase in general and by over 100% in Benin and Niger. Even under the assumption of decrease in smoking prevalence, lung cancer mortality will rise. CONCLUSION: On the bases of detailed smoking prevalence information, our findings implicate a higher lung cancer burden in low income countries. The epidemiologic transition in African low-income countries alludes to the need for targeted health prevention efforts.
INSTITUCIÓN / INSTITUTION: - Service de Pneumologie, Hopital Tenon, Assistance Publique-Hopitaux de Paris, France; Equipe de Recherche 2 et GRC-UPMC 04 Theranoscan, Universite Pierre et Marie Curie, Paris VI, France. Electronic address: jacques.cadranel@tnn.aphp.fr.

RESUMEN / SUMMARY: - Activating mutation in exons 19 or 21 of epidermal growth factor receptor (EGFR) in non-small-cell lung cancers (NSCLC) are associated with increased sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib. Cancer patients harboring activating EGFR mutations benefit from first-line TKI therapy. Yet 10% of patients present a primary TKI resistance, while 50% of the others develop a secondary resistance within 9-12 months after starting TKI. The RECIST’s definition of progression appears flawed when applied to EGFR-mutated NSCLC patients. Most often, tumor volume shrinking widely exceeds 30% during TKI response and kinetics of growth is low during relapse. At present, secondary resistance mechanisms associated with progression are better known: clonal selection of EGFR resistance mutation (T790M mutation in exon 20), amplification of transmembrane receptors for other growth factors (c-met, HER family, IGF1R, or AXL), downstream molecular alterations in EGFR signaling pathway (PI3K or PTEN), and epithelial-mesenchymal transition or transdifferentiation to small-cell cancer. The best strategy for secondary resistance is not well-defined: maintaining TKI therapy, switching to chemotherapy, combining both treatments, or using new therapies targeting other signaling pathways.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Lowery AE; Krebs P; Coups EJ; Feinstein MB; Burkhalter JE; Park BJ; Ostroff JS

INSTITUCIÓN / INSTITUTION: - School of Medicine, University of Pittsburgh, 5115 Centre Ave, Suite 140, Pittsburgh, PA, USA, lowerya@upmc.edu.

RESUMEN / SUMMARY: - PURPOSE: Pain, fatigue, dyspnea, and distress are commonly reported cancer-related symptoms, but few studies have examined the effects of multiple concurrent symptoms in longer-term cancer survivors. We examined the impact of varying degrees of symptom burden on health-related quality of life (HRQOL) and performance status in surgically treated non-small cell lung cancer (NSCLC) survivors. METHODS: A sample of 183 NSCLC survivors 1-6 years post-surgical treatment completed questionnaires assessing five specific symptoms (pain, fatigue, dyspnea, depression, and anxiety), HRQOL, and performance status. The number of
concurrent clinically significant symptoms was calculated as an indicator of symptom burden. RESULTS: Most survivors (79.8%) had some degree of symptom burden, with 30.6% reporting one clinically significant symptom, 27.9% reporting two symptoms, and 21.3% reporting three or more symptoms. Physical HRQOL significantly decreased as the degree of symptom burden increased, but mental HRQOL was only significantly decreased in those with three or more symptoms. Receiver-operating characteristic (ROC) curves showed that having multiple concurrent symptoms (two or more) was most likely associated with limitations in functioning (area under a ROC curve = 0.75, sensitivity = 0.81, specificity = 0.54). CONCLUSIONS: Two or more clinically significant symptoms are identified as the “tipping point” for showing adverse effects on HRQOL and functioning. This highlights the need for incorporating multiple-symptom assessment into routine clinical practice. Comprehensive symptom management remains an important target of intervention for improved post-treatment HRQOL and functioning among lung cancer survivors.

[363]

- Driver mutations among never smoking female lung cancer tissues in China identify unique EGFR and KRAS mutation pattern associated with household coal burning.

- Lung cancer in never smokers, which has been partially attributed to household solid fuel use (i.e., coal), is etiologically and clinically different from lung cancer attributed to tobacco smoking. To explore the spectrum of driver mutations among lung cancer tissues from never smokers, specifically in a population where high lung cancer rates have been attributed to indoor air pollution from domestic coal use, multiplexed assays were used to detect >40 point mutations, insertions, and deletions (EGFR, KRAS, BRAF, HER2, NRAS, PIK3CA, MEK1, AKT1, and PTEN) among the lung tumors of confirmed never smoking females from Xuanwei, China [32 adenocarcinomas (ADCs), 7 squamous cell carcinomas (SCCs), 1 adenosquamous carcinoma (ADSC)]. EGFR mutations were detected in 35% of tumors. 46% of these involved EGFR exon 18 G719X, while 14% were exon 21 L858R mutations.
KRAS mutations, all of which were G12C_3G>T, were observed in 15% of tumors. EGFR and KRAS mutations were mutually exclusive, and no mutations were observed in the other tested genes. Most point mutations were transversions and were also found in tumors from patients who used coal in their homes. Our high mutation frequencies in EGFR exon 18 and KRAS and low mutation frequency in EGFR exon 21 are strikingly divergent from those in other smoking and never smoking populations from Asia. Given that our subjects live in a region where coal is typically burned indoors, our findings provide new insights into the pathogenesis of lung cancer among never smoking females exposed to indoor air pollution from coal.

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| TÍTULO / TITLE: | - Small Cell Carcinoma of the Esophagus: A SEER Database Analysis. |
| RESUMEN / SUMMARY: | - Enlace al Resumen / Link to its Summary |
| AUTORES / AUTHORS: | - Kukar M; Groman A; Malhotra U; Warren GW; Bogner P; Nwogu CE; Demmy TL; Yendamuri S |
| INSTITUCIÓN / INSTITUTION: | - Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA. |
| RESUMEN / SUMMARY: | - BACKGROUND: Small cell cancer (SCC) of the esophagus is an uncommon malignancy with perceived poor prognosis, but there are few data to guide therapeutic decisions. We examined the Surveillance, Epidemiology, and End Results (SEER) database to identify prognostic factors for survival. METHODS: All patients with esophageal cancer in the SEER database between 1973 and 2009 were included. Univariate and multivariate analyses were performed in patients with and without SCC, examining the relationship of small cell histology, surgery, and other potential prognostic factors with overall survival (censored at 72 months). RESULTS: Of 64,799 esophageal cancer patients identified in the SEER database, 387 (0.6%) had small cell histology. As compared with non-small cell histology, patients with small cell histology were similar in age and race but had a higher proportion of women (p < 0.001), had a higher stage at diagnosis (p < 0.001), and were less likely to undergo surgical resection (p < 0.01). Multivariate predictors associated with poor survival in the overall cohort included age, female gender, black race, and stage. In patients treated with surgery, multivariate predictors associated with poor survival included age, male gender, race, and stage but not small cell histology. In patients with small cell histology, both age and stage were associated with poor survival, but surgery and preoperative radiotherapy were associated with improved survival. CONCLUSIONS: SCC of the esophagus presents at an advanced stage and confers a poor prognosis. The survival benefit of surgery and radiotherapy suggests that all esophageal SCC patients should
be considered for preoperative radiotherapy and surgery in a stage-appropriate fashion.

[365] **TÍTULO / TITLE:** - Targeting SHP2 for EGFR inhibitor resistant non-small cell lung carcinoma.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1016/j.bbrc.2013.09.028)

**AUTORES / AUTHORS:** - Xu J; Zeng LF; Shen W; Turchi JJ; Zhang ZY
**INSTITUCIÓN / INSTITUTION:** - Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, United States.
**RESUMEN / SUMMARY:** - Targeted therapy with inhibitors of epidermal growth factor receptor (EGFR) has produced a noticeable benefit to non-small cell lung cancer (NSCLC) patients whose tumors carry activating mutations (e.g. L858R) in EGFR. Unfortunately, these patients develop drug resistance after treatment, due to acquired secondary gatekeeper mutations in EGFR (e.g. T790M). Given the critical role of SHP2 in growth factor receptor signaling, we sought to determine whether targeting SHP2 could have therapeutic value for EGFR inhibitor resistant NSCLC. We show that SHP2 is required for EGF-stimulated ERK1/2 phosphorylation and proliferation in EGFR inhibitor resistant NSCLC cell line H1975, which harbors the EGFR T790M/L858R double-mutant. We demonstrate that treatment of H1975 cells with II-B08, a specific SHP2 inhibitor, phenocopies the observed growth inhibition and reduced ERK1/2 activation seen in cells treated with SHP2 siRNA. Importantly, we also find that II-B08 exhibits marked anti-tumor activity in H1975 xenograft mice. Finally, we observe that combined inhibition of SHP2 and PI3K impairs both the ERK1/2 and PI3K/AKT signaling axes and produces significantly greater effects on repressing H1975 cell growth than inhibition of either protein individually. Collectively, these results suggest that targeting SHP2 may represent an effective strategy for treatment of EGFR inhibitor resistant NSCLCs.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](https://doi.org/1007/s13277-013-1104-5)
**REVISTA / JOURNAL:** - Tumour Biol. 2013 Aug 23.

**AUTORES / AUTHORS:** - Fan CF; Miao Y; Lin XY; Zhang D; Wang EH
ATF4 is a member of the cAMP-responsive element-binding protein family of basic zipper-containing proteins, a family of transcription factors phosphorylated at serines residues by protein kinase A. The family has been proved to be able to stimulate the transcription of the genes containing CRE elements. Elevated ATF4 expression was detected in some tumors including breast carcinoma compared to their corresponding nontumor tissues. p-ATF4 (ser 245), a phosphorylated form of ATF4 protein at serine 245 site, was believed to be an active type of this protein. However, its expression and clinical significance in malignant tumors including non-small cell lung cancer were not reported up to date. In the current study, we investigate the expression of p-ATF4 (ser 245) in non-small cell lung cancer using tissue microarray and immunohistochemistry. p-ATF4 (ser 245) immunostaining was detected in nucleus and cytoplasm in cancer cells and normal lung epithelial cells. Compared to bronchial epithelium and submucosal glands (total positive rate, 14.6 % (12/82)), there was increased expression of p-ATF4 (ser 245) in non-small cell lung cancer cells (total positive rate, 42.7 % (35/82)) (p < 0.05). In addition, increased expression of p-ATF4 (ser 245) was associated with lymph node metastasis and advanced TNM stages (III and IV) in non-small cell lung cancer (p < 0.05). Immunofluorescent staining confirmed nuclear and cytoplasmic expression of p-ATF4 (ser 245) in lung and cancer tissues, and also in non-small cell lung cancer cell lines including NCI-H157 and LTE cells. These results indicate that increased expression of p-ATF4 (ser 245) may contribute to cancer development of non-small cell lung cancer and may be a potential cancer marker.

[367]

TITULO / TITLE: - Age-period-cohort effect on lung cancer mortality in southern España.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ocana-Riola R; Mayoral-Cortes JM; Blanco-Reina E
INSTITUCIÓN / INSTITUTION: - aAndalusian School of Public Health bGranada Biomedical Research Institute, Granada cDepartment of Pharmacology, School of Medicine, University of Malaga, Malaga dDepartment of Epidemiology and Occupational Health, Andalusian Health Government, Seville, España.
RESUMEN / SUMMARY: - The aim of this study was to evaluate the age-period-cohort effects on lung cancer mortality in Andalusia (southern España) as a whole as well as in each of its eight provinces during the period between 1981 and 2008. A population-
based ecological study was conducted. In all, 74 255 deaths from lung cancer were analysed for individuals aged between 40 and 84 years who died in Andalusia during the period of study. A nonlinear regression model was estimated for both sexes and each geographical area. The effects of age, year of death and birth cohort were parameterized using B-spline smoothing functions. There is an upward trend in mortality by age until around the age of 75 years, from which point the trend turns downwards for men and remains stable for women. The analysis of the cohort effect revealed a steady fall in the lung cancer mortality risk for male generations born after 1950. The mortality risk for women is increasing for the generations born after 1932. The death rates for men declined from 1995 until the end of the study period. For women, the death rates increased from the end of the 1990s. There is a similar age-period-cohort effect on lung cancer mortality in all the provinces of Andalusia and for Andalusia as a whole. If the current trends continue, it can be expected that these effects will continue to reduce male mortality and increase female mortality.

[368]

TÍTULO / TITLE: - Spontaneous Mesotheliomas in F344/N Rats Are Characterized by Dysregulation of Cellular Growth and Immune Function Pathways.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Blackshear PE; Pandiri AR; Ton TV; Clayton NP; Shockley KR; Peddada SD; Gerrish KE; Sills RC; Hoenerhoff MJ

INSTITUCIÓN / INSTITUTION: - 1Integrated Laboratory Systems, Inc., Research Triangle Park, North Carolina, USA.

RESUMEN / SUMMARY: - Aged male Fischer 344/N rats are prone to developing spontaneous peritoneal mesotheliomas that arise predominantly from the tunica vaginalis of the testes. A definitive cause for the predominance of this neoplasm in F344/N rats is unknown. Investigation of the molecular alterations that occur in spontaneous rat mesotheliomas may provide insight into their pathogenesis as well enable a better understanding regarding the mechanisms underlying chemically induced mesothelioma in rodents. Mesothelial cell function represents a complex interplay of pathways related to host defense mechanisms and maintenance of cellular homeostasis. Global gene expression profiles of spontaneous mesotheliomas from vehicle control male F344/N rats from 2-year National Toxicology Program carcinogenicity bioassays were analyzed to determine the molecular features of these tumors and elucidate tumor-specific gene expression profiles. The resulting gene expression pattern showed that spontaneous mesotheliomas are associated with upregulation of various growth factors, oncogenes, cytokines, pattern recognition response receptors, and pathogen-associated molecular patterns receptors, and the
production of reactive oxygen and nitrogen species, as well as downregulation of apoptosis pathways. Alterations in these pathways in turn trigger molecular responses that stimulate cell proliferation and promote tumor survival and progression.

[369]

**TÍTULO / TITLE:** Interfraction variation in lung tumor position with abdominal compression during stereotactic body radiotherapy.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Mampuya WA; Nakamura M; Matsuo Y; Ueki N; Iizuka Y; Fujimoto T; Yano S; Monzen H; Mizowaki T; Hiraoka M

**INSTITUCIÓN / INSTITUTION:** Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan.

**RESUMEN / SUMMARY:** Purpose: To assess the effect of abdominal compression on the interfraction variation in tumor position in lung stereotactic body radiotherapy (SBRT) using cone-beam computed tomography (CBCT) in a larger series of patients with large tumor motion amplitude. Methods: Thirty patients with lung tumor motion exceeding 8 mm who underwent SBRT were included in this study. After translational and rotational initial setup error was corrected based on bone anatomy, CBCT images were acquired for each fraction. The residual interfraction variation was defined as the difference between the centroid position of the visualized target in three dimensions derived from CBCT scans and those derived from averaged intensity projection images. The authors compared the magnitude of the interfraction variation in tumor position between patients treated with \([n = 16 (76 fractions)]\) and without \([n = 14 (76 fractions)]\) abdominal compression. Results: The mean +/- standard deviation (SD) of the motion amplitude in the longitudinal direction before abdominal compression was 19.9 +/- 7.3 (range, 10-40) mm and was significantly \((p < 0.01)\) reduced to 12.4 +/- 5.8 (range, 5-30) mm with compression. The greatest variance of the interfraction variation with abdominal compression was observed in the longitudinal direction, with a mean +/- SD of 0.79 +/- 3.05 mm, compared to -0.60 +/- 2.10 mm without abdominal compression. The absolute values of the 95th percentile of the interfraction variation for one side in each direction were 3.976.21 mm (posterioranterior), 4.163.76 mm (caudalcranial), and 2.902.32 mm (rightleft) without abdominal compression, and 2.145.03 mm (posterioranterior), 3.939.23 mm (caudalcranial), and 2.375.45 mm (rightleft) with abdominal compression. An absolute interfraction variation greater than 5 mm was observed in six (9.2%) fractions without and 13 (17.1%) fractions with abdominal compression. Conclusions: Abdominal compression was effective for reducing the amplitude of tumor motion. However, in most of the authors’ patients, the use of abdominal compression seemed to increase the interfraction variation in...
tumor position, despite reducing lung tumor motion. The daily tumor position deviated more systematically from the tumor position in the planning CT scan in the lateral and longitudinal directions in patients treated with abdominal compression compared to those treated without compression. Therefore, target matching is required to correct or minimize the interfraction variation.

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Prognosis of unexpected and expected pathologic n1 non-small cell lung cancer.

**RESUMEN**

BACKGROUND: This study was undertaken to compare clinicopathologic features and survival between patients with unexpected N1 (clinical N0-pathologic N1) and expected N1 disease (clinical N1-pathologic N1) after operation for non-small cell lung cancer. METHODS: From 2003 to 2009, 305 patients who were found to have pathologic N1 disease after complete resection were retrospectively analyzed. Among these, 177 patients had negative findings for both computed tomography (CT) and positron emission tomography (PET)/CT (group cN0). Sixty-eight patients had negative CT and positive PET/CT or positive CT and negative PET/CT findings (group cN0-1). Sixty patients had positive findings for both CT and PET/CT (group cN1). RESULTS: Patients in the cN1 group had larger tumors (p < 0.001), greater pathologic T stage (p = 0.018), and greater percentage of squamous cell carcinoma (p < 0.001) than did those in the other groups. Patients in the cN1 group had a greater number of positive N1 lymph nodes (p = 0.004) and more frequent extracapsular nodal invasion (p < 0.001). The 5-year overall survival was 66%, 63%, and 58% in groups cN0, cN0-1, and cN1, respectively (cN0 vs cN0-1, p = 0.958; cN0 vs cN1, p = 0.038). The 5-year disease-free survival was 54%, 52%, and 39% in groups cN0, cN0-1, and cN1, respectively (cN0 vs cN0-1, p = 0.862; cN0 vs cN1, p = 0.01). CONCLUSIONS: Patients with unexpected N1 disease showed better survival than did those with expected N1 disease, which seemed to be related to the pathologically minimal extent of the primary tumor and nodal involvement.

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Phase I dose escalation study of the PKCiota inhibitor aurothiomalate for advanced non-small-cell lung cancer, ovarian cancer, and pancreatic cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Mansfield AS; Fields AP; Jatoi A; Qi Y; Adjei AA; Erlichman C; Molina JR

INSTITUCIÓN / INSTITUTION: aDepartment of Medical Oncology, Mayo Clinic, Rochester, Minnesota bDepartment of Cancer Biology, Mayo Clinic, Jacksonville, Florida cDepartment of Internal Medicine, Greater Baltimore Medical Center, Baltimore, Maryland dDepartment of Medicine, Roswell Park Cancer Institute, Buffalo, New York, USA.

RESUMEN / SUMMARY: Protein kinase C iota (PKCiota) is overexpressed in non-small-cell lung cancer, ovarian, and pancreatic cancers, where it plays a critical role in oncogenesis. The gold compound aurothiomalate (ATM) has been shown to inhibit PKCiota signaling and exerts potent antitumor activity in preclinical models. We sought to determine the maximum tolerated dose (MTD) of ATM. We conducted a phase I dose escalation trial of ATM in patients with non-small-cell lung cancer, ovarian or pancreatic cancer. Patients received ATM intramuscularly weekly for three cycles (cycle duration 4 weeks) at 25, 50, or 75 mg in a 3+3 design. The dose was not escalated for individual patients. Blood samples were analyzed for elemental gold levels. Patients were evaluated every 4 weeks for toxicity and every 8 weeks for response. Fifteen patients were enrolled in this study. Six patients were treated at 25 mg, seven at 50 mg, and two at 75 mg. There was one dose-limiting toxicity at 25 mg (hypokalemia), one at 50 mg (urinary tract infection), and none at 75 mg. There were three grade 3 hematologic toxicities. The recommended MTD of ATM is 50 mg. Patients received treatment for a median of two cycles (range 1-3). There appeared to be a dose-related accumulation of steady-state plasma concentrations of gold consistent with linear pharmacokinetics. In summary, this phase I study was successful in identifying ATM 50 mg intramuscularly weekly as the MTD. Future clinical investigations targeting PKCiota are currently in progress.

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[372]
BACKGROUND: Many studies have reported that transverse computed tomography (CT) imaging findings correlate with prognosis of patients with small peripheral lung neoplasm with lepidic growth. However, no studies have examined this correlation with the aid of three-dimensional (3D) CT data. PURPOSE: To determine the most efficacious imaging factor for differentiation of lepidic growth type lung neoplasms with good prognosis from those with poor prognosis. MATERIAL AND METHODS: We evaluated CT findings, nodule patterns, SUVmax on FDG-PET/CT, as well as nodule volume and ratios of solid parts to nodule volume that were semi-automatically measured on CT images of 64 pulmonary nodules of ≤2 cm in 60 consecutive patients (24 men and 36 women; mean age, 65 years). For logistic modeling, we used all of the significant factors observed between the neoplasms with good and with poor prognosis as independent variables to estimate the statistically significant factors for discriminating invasive adenocarcinomas with lepidic growth (lesions with poor prognosis, n = 42) from the other neoplasms, including preinvasive lesions (lesions with good prognosis, n = 22), resulting in a recommendation for the optimal criterion for predicting lesions with poor prognosis. RESULTS: The logistic regression model identified the ratio of the solid part to the whole volume of a pulmonary nodule as the only significant factor (P = 0.04) for differentiating lepidic growth type lung neoplasms with good prognosis from those with poor prognosis. A ratio of 0.238 or more showed the highest discriminatory accuracy of 84% with 91% sensitivity and 76% specificity. CONCLUSION: Computer-aided analyses of pulmonary nodules proved most useful for establishing the optimal criterion for differentiation of lepidic growth type lung neoplasms with good prognosis from those with poor prognosis.
RESUMEN / SUMMARY: - BACKGROUND: Lung cancer has the highest mortality rate among malignant tumors. Proteomics is a powerful tool to identify protein biomarkers. The identification of protein biomarkers associated with lung adenocarcinoma would have significance for making prognoses and designing targeted therapies. METHODS: In our study, we applied a two-dimensional difference gel electrophoresis approach coupled to a matrix-assisted laser desorption/ionization time-of-flight mass spectrometric analysis for the identification of proteins differentially expressed between lung adenocarcinoma and the paired normal bronchial epithelial tissues derived from seven patients (four of them developed distant metastasis after operation). In addition, we chose two candidate proteins and examine their expression levels in lung adenocarcinoma and adjacent normal tissues using immunohistochemistry methods, and their expression levels in serum of patients and healthy donors by ELISA. RESULT: In this study, 173 proteins were found to be differentially expressed (ratio>1.5 or< -1.5, P<=0.05), and 22 of them were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Thirteen proteins were at lower levels in the lung adenocarcinoma group, while nine proteins were at higher abundance. Immunohistochemistry analysis confirmed the expression levels of the two candidate proteins. The differential expression of the candidate secreted protein in serum from lung adenocarcinoma samples and healthy controls was showed by ELISA. CONCLUSION: Our results demonstrated a differential protein expression pattern for lung adenocarcinoma compared with the paired normal bronchial epithelial tissues. Further functional validation of candidate proteins is ongoing and might provide new insights in lung adenocarcinoma.

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TÍTULO / TITLE: - Surgical Results of Synchronous Multiple Primary Lung Cancers: Similar to the Stage-Matched Solitary Primary Lung Cancers?

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Yu YC; Hsu PK; Yeh YC; Huang CS; Hsieh CC; Chou TY; Hsu HS; Wu YC; Huang BS; Hsu WH

INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; Department of Surgery, National Yang-Ming University Hospital, I-Lan, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND: Treatment for synchronous multiple primary lung cancers (SMPLC) remains controversial. Some surgeons treat SMPLC like advanced lung cancer, whereas other surgeons treat SMPLC as separate primary lung cancers. In
this study, survival of SMPLC patients and matched-stage solitary primary lung cancer (SPLC) patients after surgical treatment were compared. METHODS: Prospective medical records between 2001 and 2011 were retrospectively reviewed. RESULTS: A total of 1,995 patients underwent pulmonary resection for lung cancer in a tertiary referral center. Only 97 patients met the modified criteria of Martini and Melamed for SMPLC. The median follow-up time was 38.3 months. The 3-year and 5-year overall survival rates were 83.1% and 69.6%, respectively. In the univariate analysis, males, smokers, and tumor size greater than 3 cm demonstrated significantly worse survival. After multivariate analysis, only tumor size (p = 0.018; hazard ratio 3.199) was identified as an independent predictor of survival. In addition, there was no significant difference in overall survival between the matched-stage SMPLC and SPLC without mediastinal lymph node involvement. Subgroup analysis in the multiple synchronous adenocarcinoma (n = 78) group demonstrated no significant difference between similar and different comprehensive histologic subtyping with respect to overall survival (61.3% versus 68.8%, p = 0.474). CONCLUSIONS: The surgical results for SMPLC were compatible and acceptable with those for SPLC even with similar histologic subtyping, instead of T4 or M1 stages in the current TNM classification system. Preoperatively, tumor size was the only independent prognostic factor for SMPLC with surgical intervention.

[375]

**TÍTULO / TITLE:** The combination of TRPM8 and TRPA1 expression causes an invasive phenotype in lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Tumour Biol. 2013 Sep 15.

**AUTORES / AUTHORS:** Du GJ; Li JH; Liu WJ; Liu YH; Zhao B; Li HR; Hou XD; Li H; Qi XX; Duan YJ

**INSTITUCIÓN / INSTITUTION:** Institute of Pharmacy, Pharmacy College of Henan University, Jinming street, Kaifeng, 475004, Henan Province, China, 724200@henu.edu.cn.

**RESUMEN / SUMMARY:** Our recent studies have shown that hypothermic microenvironment promotes tumor progression and that the molecular sensors for cold are the transient receptor potential (TRP) channels TRPM8 and TRPA1. To evaluate the contribution of TRPM8 and TRPA1 to cancer malignancy, we screened cell subpopulations from Lewis lung cancer (LLC) using limiting dilutions and Western blotting. We identified that LLC-1 cells express 3-fold more TRPM8 than TRPA1, LLC-2 cells express TRPM8 at levels similar to TRPA1, and LLC-3 cells express TRPM8 at one-third the level of TRPA1. LLC-2 cells showed greater adhesion, migration, invasiveness and resistance to hypothermia than LLC-1 and LLC-3 cells, although LLC-2 cells had a
longer doubling time. TRPM8 or TRPA1 knockdown using siRNA promoted cell proliferation and decreased adhesion and invasiveness in LLC-2 cells. When assessed for UCP2 staining, LLC-1 cells showed increased staining compared to LLC-2 cells, both of which had more UCP2-positive cells than the LLC-3 subpopulation. In an autophagy assay, hypothermia induced substantially less autophagy in LLC-1 cells than in LLC-2 cells, which displayed decreased autophagy compared to LLC-3 cells. Moreover, mice injected with LLC-2 cells had significantly more spontaneous and experimental lung metastases and a shorter overall survival time than mice injected with LLC-1 or LLC-3 cells. Importantly, LLC-2 cells were also more resistant to activated spleen CTL and the chemotherapeutic drug doxorubicin than LLC-1 and LLC-3 cells in vitro. Collectively, our data suggest that TRPM8 induces UCP2 to trigger metabolic transformation, whereas TRPA1 induces autophagy during adverse conditions, and the combination of both genes contributes directly to an invasive phenotype in lung cancer.

[376]

**TÍTULO / TITLE:** Pharmacokinetic and pharmacodynamic study of Gefitinib in a mouse model of non-small-cell lung carcinoma with brain metastasis.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Chen Y; Wang M; Zhong W; Zhao J

**INSTITUCIÓN / INSTITUTION:** The Respiratory Department of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Peking 100730, China.

**RESUMEN / SUMMARY:** INTRODUCTION: Some studies showed that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib could improve the outcome of non-small-cell lung cancer (NSCLC) patients with brain metastasis (BM), while the concentration of gefitinib in cerebrospinal fluid (CSF) was low. Therefore, we designed the present study to investigate whether gefitinib could actively penetrate blood brain barrier (BBB) in a mouse model of lung cancer brain metastasis (BM). MATERIALS AND METHODS: In vitro MDCK-MDR1 assay was used to determine permeability and efflux ratio (RE) of gefitinib. In vivo pharmacokinetic and pharmacodynamic evaluation was performed in both normal nude mice and a BM model established by intra-carotid artery (ICA) injection of PC-9 cells. RESULTS: The result showed that RE of gefitinib at the concentrations of 1muM and 10muM was 4.12 and 4.05, respectively, but significantly decreased to 1 and 1.35 after adding a P-glycoprotein (P-gp) inhibitor, cyclosporine A. In both normal mice and BM model, dose dependent increase of gefitinib was detected in the blood, brain and CSF at the doses of 50, 100 and 200mg/kg. In BM model, AUCtotalbrain/AUCtotalblood in 50mg/kg and 200mg/kg...
groups were 0.4 and 0.7, respectively, while AUCCSF/AUCfreeblood were 0.21 and 0.18, respectively. Positive correlation between concentration of gefitinib in CSF and pEGFR modulation in the brain tumor was identified. CONCLUSION: Gefitinib is a P-gp substrate and has limited active BBB penetration. Increased doses of gefitinib potentially accelerated passive permeability.

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[377]

**TÍTULO / TITLE**: Long Interspersed Nucleotide Element 1 Hypomethylation Is Associated With Poor Prognosis of Lung Adenocarcinoma.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1016/j.athoracsur.2013.06.035

**AUTORES / AUTHORS**: Ikeda K; Shiraishi K; Eguchi A; Shibata H; Yoshimoto K; Mori T; Baba Y; Baba H; Suzuki M

**INSTITUCIÓN / INSTITUTION**: Department of Thoracic Surgery, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan. Electronic address: koei@cg7.so-net.ne.jp.

**RESUMEN / SUMMARY**: BACKGROUND: Genome-wide DNA hypomethylation is known to play important roles in genomic instability and carcinogenesis. Methylation in long interspersed nucleotide element 1 (LINE-1) is a good indicator of the global DNA methylation level within a cell. The aim of this study was to evaluate prognostic significance of LINE-1 hypomethylation in lung adenocarcinoma. METHODS: A consecutive series of 211 lung adenocarcinoma patients who underwent curative resections without any preoperative chemotherapy or radiotherapy at Kumamoto University Hospital between April 2010 and December 2012 were included. The LINE-1 methylation levels were quantified in tumor and noncancerous tissue by Pyrosequencing assay. RESULTS: Higher histologic grade and positive findings for vascular invasion were significantly associated with lower methylation levels. The disease-free survival in the hypomethylation group was significantly shorter than that of the non-hypomethylation group. The prognostic difference was more obvious in advanced cases (stage II, III) than in stage I cases. CONCLUSIONS: The LINE-1 methylation level is associated with histologic grade and vascular invasion of lung adenocarcinoma. Additionally, LINE-1 hypomethylation is a useful biomarker to predict early recurrence of lung adenocarcinoma.

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[378]
TÍTULO / TITLE: - Assessment of SHOX2 methylation in EBUS-TBNA specimen improves accuracy in lung cancer staging.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Darwiche K; Zarogoulidis P; Baehner K; Welter S; Tetzner R; Wohlschlaeger J; Theegarten D; Nakajima T; Freitag L

INSTITUCIÓN / INSTITUTION: - Department of Interventional Pneumology, Ruhrlandklinik, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) is a well-established method to assess mediastinal lymph nodes for lung cancer. However, a proportion of patients require further investigation, due to the low negative predictive value (NPV). The objective of this study was to determine whether the assessment of short stature homeobox 2 (SHOX2) DNA methylation level in lymph node tissue obtained by EBUS-TBNA improves the accuracy of mediastinal staging. PATIENTS AND METHODS: EBUS-TBNA was carried out for suspicious lymph nodes of 154 patients. Negative or ambiguous histological results were confirmed by surgical means and clinical follow-up over 6 months. EBUS-TBNA was assessed on 80 positive and 85 negative classified lymph nodes and compared with the result of the SHOX2 DNA methylation real-time PCR analysis. Relative methylation measured by delta-delta cycle threshold (DeltaDeltaCt) was used to classify the samples. Clinical performance of the EBUS-TBNA procedure with and without the additional SHOX2 assessment was calculated against the final classification according to the gold standard. RESULTS: Based on data from 105 patients, an average 80-fold increase in the SHOX2 methylation level was measured for positive compared with negative lymph nodes. SHOX2 results with a DeltaDeltaCt value of <6.5 indicate positive lymph nodes. Applying this molecular analysis to EBUS-TBNA cases, not diagnosed by pathologic assessment, the sensitivity of staging was improved by 17%-99%. The NPV increased from 80% to 99%. CONCLUSIONS: The combination of EBUS-TBNA and SHOX2 methylation level strongly improves the assessment of the nodal status by identifying additional malignant lesions and confirming benign nodes and therefore avoiding invasive follow-up procedures.

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TÍTULO / TITLE: - Variability of tumor area measurements for response assessment in malignant pleural mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Darwiche K; Zarogoulidis P; Baehner K; Welter S; Tetzner R; Wohlschlaeger J; Theegarten D; Nakajima T; Freitag L

INSTITUCIÓN / INSTITUTION: - Department of Interventional Pneumology, Ruhrlandklinik, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) is a well-established method to assess mediastinal lymph nodes for lung cancer. However, a proportion of patients require further investigation, due to the low negative predictive value (NPV). The objective of this study was to determine whether the assessment of short stature homeobox 2 (SHOX2) DNA methylation level in lymph node tissue obtained by EBUS-TBNA improves the accuracy of mediastinal staging. PATIENTS AND METHODS: EBUS-TBNA was carried out for suspicious lymph nodes of 154 patients. Negative or ambiguous histological results were confirmed by surgical means and clinical follow-up over 6 months. EBUS-TBNA was assessed on 80 positive and 85 negative classified lymph nodes and compared with the result of the SHOX2 DNA methylation real-time PCR analysis. Relative methylation measured by delta-delta cycle threshold (DeltaDeltaCt) was used to classify the samples. Clinical performance of the EBUS-TBNA procedure with and without the additional SHOX2 assessment was calculated against the final classification according to the gold standard. RESULTS: Based on data from 105 patients, an average 80-fold increase in the SHOX2 methylation level was measured for positive compared with negative lymph nodes. SHOX2 results with a DeltaDeltaCt value of <6.5 indicate positive lymph nodes. Applying this molecular analysis to EBUS-TBNA cases, not diagnosed by pathologic assessment, the sensitivity of staging was improved by 17%-99%. The NPV increased from 80% to 99%. CONCLUSIONS: The combination of EBUS-TBNA and SHOX2 methylation level strongly improves the assessment of the nodal status by identifying additional malignant lesions and confirming benign nodes and therefore avoiding invasive follow-up procedures.

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PURPOSE: The measurement of malignant pleural mesothelioma is critical to the assessment of tumor response to therapy. Current response assessment standards utilize summed linear measurements acquired on three computed tomography (CT) sections. The purpose of this study was to evaluate manual area measurements as an alternate response assessment metric, specifically through the study of measurement interobserver variability. METHODS: Two CT scans from each of 31 patients were collected. Using a computer interface, five observers contoured tumor on three selected CT sections from each baseline scan. Four observers also constructed matched follow-up scan tumor contours for the same 31 patients. Area measurements extracted from these contours were compared using a random effects analysis of variance model to assess relative interobserver variability. The sums of section area measurements were also analyzed, since these area sums are more clinically relevant for response assessment. RESULTS: When each observer’s measurements were compared with those of the other four observers, strong correlation was observed. The 95% confidence interval for relative interobserver variability of baseline scan summed area measurements was [-71%, +240%], spanning 311%. For the follow-up scan summed area measurements, the 95% confidence interval for relative interobserver variability was [-41%, +70%], spanning 111%. At both baseline and follow-up, the variability among observers was a significant component of the total variability in both per-section and summed area measurements (p<0.0001). CONCLUSIONS: Despite the ability of tumor area measurements to capture tumor burden with greater fidelity than linear tumor thickness measurements, manual area measurements may not be a robust means of response assessment in mesothelioma patients.
RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Early detection of local recurrences following stereotactic ablative radiotherapy (SABR) for lung cancer may allow for curative salvage treatment, but recurrence can be difficult to distinguish from fibrosis. We studied the clinical performance of CT imaging high-risk features (HRFs) for detecting local recurrence. MATERIALS AND METHODS: Patients treated with SABR for early stage lung cancer between 2003 and 2012 who developed pathology-proven local recurrence (n=12) were matched 1:2 to patients without recurrences (n=24), based on baseline factors. Serial CT images were assessed by blinded radiation oncologists. Previously reported HRFs were (1) enlarging opacity at primary site; (2) sequential enlarging opacity; (3) enlarging opacity after 12-months; (4) bulging margin; (5) loss of linear margin and (6) air bronchogram loss. RESULTS: All HRFs were significantly associated with local recurrence (p<0.01), and one new HRF was identified: cranio-caudal growth (p<0.001). The best individual predictor of local recurrence was opacity enlargement after 12-months (100% sensitivity, 83% specificity, p<0.001). The odds of recurrence increased 4-fold for each additional HRF detected. The presence of 3 HRFs was highly sensitive and specific for recurrence (both >90%). CONCLUSION: The systematic assessment of post-SABR CT images for HRFs enables the accurate prediction of local recurrence.

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TÍTULO / TITLE: - Characterization of a French series of female cases of mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1002/ajim.22229
AUTORES / AUTHORS: - Camiade E; Gramond C; Jutand MA; Audignon S; Rinaldo M; Imbernon E; Luce D; Galateau-Salle F; Astoul P; Pairon JC; Brochard P; Lacourt A
INSTITUCIÓN / INSTITUTION: - Univ. Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique Equipe sante environnement, F-33000, Bordeaux, France; INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, Equipe sante environnement, F-33000, Bordeaux, France; Univ. Bordeaux, ISPED, Equipe Associee en Sante Travail, F-33000, Bordeaux, France.
RESUMEN / SUMMARY: - BACKGROUND: More than 80% of mesothelioma cases in men are attributable to occupational asbestos exposure compared to only 40% in women. The objective of the study was to characterize a series of female pleural mesotheliomas according to known and suspected risk factors. METHODS: From the exhaustive recording of 318 female mesothelioma cases in the French National Mesothelioma Surveillance Program between 1998 and 2009, multiple correspondence analysis and hybrid clustering were performed to characterize these cases according to expert assessed occupational and non-occupational exposure to asbestos and man-made vitreous fibers, X-ray exposure, and history of cancer and non-
malignant respiratory diseases. RESULTS: Four clusters were identified: (1) occupational exposure to asbestos and man-made vitreous fibers (7.9% of subjects); (2) radiation exposure during radiotherapy (12.9%); (3) increased asbestos exposure (19.8%); and (4) “non-exposure” characteristics (59.4%). CONCLUSION: These results will allow hypotheses to be generated about associations between mesothelioma and non-occupational asbestos exposure, X-ray exposure and history of respiratory disease. Am. J. Ind. Med. © 2013 Wiley Periodicals, Inc.

[382] TÍTULO / TITLE: - WWTR1 promotes cell proliferation and inhibits apoptosis through cyclin A and CTGF regulation in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Wang L; Chen Z; Wang Y; Chang D; Su L; Guo Y; Liu C
INSTITUCIÓN / INSTITUTION: - Nanlou Respiratory Diseases Department, Chinese PLA General Hospital, Beijing, 100853, China.
RESUMEN / SUMMARY: - The Hippo pathway plays a major role in development and organ size control, and its dysregulation contributes to tumorigenesis. WWTR1 is a transcription coactivator acting downstream of the Hippo pathway. Recently, WWTR1 has been reported to be overexpressed in several human cancers including lung cancer. However, the molecular mechanism of WWTR1 regulating lung cancer aggressiveness remains ambiguous. In the present study, we analyzed the expression of WWTR1 in NSCLC cell lines and found that WWTR1 was overexpressed at both the mRNA and protein levels. Knockdown of WWTR1 by siRNA interference in A549 cells significantly inhibited cell proliferation and increased paclitaxel-induced apoptosis. On the other side, WWTR1 overexpression in HBE cell line promoted cell proliferation and inhibited apoptosis. In addition, we found that the decreased proliferation after siRNA treatment was due to cell cycle arrest. Further analysis showed that WWTR1 could induce cyclin A, connective tissue growth factor (CTGF) expression, and inhibit caspase3 cleavage. In conclusion, WWTR1 promotes malignant cell growth and inhibits apoptosis by cyclin A and CTGF regulation.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
BACKGROUND: Concurrent chemoradiotherapy using S-1 containing tegafur, an oral 5-FU prodrug, plus cisplatin has been reported to show promising efficacy against locally advanced non-small cell lung cancer with acceptable toxicity. The purpose of this study is to assess the impact of this induction treatment followed by surgery on survival for those patients. METHODS: Potentially resectable locally advanced non-small cell lung cancer patients were eligible. The concurrent phase consisted of S-1 (orally at 40 mg/m² twice a day on days 1 to 14 and 22 to 36) and cisplatin (60 mg/m² on days 1 and 22) with radiation of 40 Gy/20 fractions beginning on day 1 followed by surgical resection. RESULTS: Forty-two consecutive patients, between June 2005 and February 2011, were retrospectively analyzed. The median age was 59 (42 to 77) years, there were 34 males and 8 females, 26 cStage IIIA and 16 IIIB, each 21 adenocarcinomas and others. There were 26 partial responses and 16 stable disease cases after current induction treatment without uncontrollable toxicity. Of the 42 patients, 39 underwent surgical resection; 27 underwent a lobectomy and 12 pneumonectomies. One patient died due to thoracic empyema 65 days after surgery. The median follow-up time was 32.0 months. Three- and 5-year disease-free survival rates in all 39 resected patients were 52.0% and 44.0%, respectively, and 3- and 5-year overall survival rates were 77.4% and 61.7%, respectively. CONCLUSIONS: Concurrent chemoradiotherapy using S-1 plus cisplatin followed by surgery may provide a better prognosis for locally advanced non-small cell lung cancer patients. Further prospective clinical investigation should be required.
RESUMEN / SUMMARY: BACKGROUND: The purpose of the study was to assess the efficacy of obtaining adequate cytologic specimens by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for molecular testing of lung adenocarcinomas. METHODS: This was an institutional review board-approved study of all patients who had undergone EBUS-TBNA from April 2010 through March 2012 for the diagnosis, staging, or both of lung cancer. Patients with a diagnosis of adenocarcinoma were reflexively tested for molecular markers by polymerase chain reaction, sequencing, and fluorescence in situ hybridization (FISH). All procedures were performed with patients under conscious sedation in the bronchoscopy suite. RESULTS: Of 205 patients who underwent EBUS-TBNA, 56 patients (24 male, 32 female) had a diagnosis of adenocarcinoma warranting molecular analysis. Molecular analysis was available for epidermal growth factor receptor (EGFR), Kirsten rat sarcoma (Kras) mutation, and anaplastic lymphoma kinase (ALK) gene rearrangement. The institution’s clinical protocol involved initial testing for EGFR mutation with a reflex Kras test if the EGFR test result was negative. ALK FISH molecular testing was completed if both EGFR and Kras test results were negative. A total of 52 of 56 (93%) patients had sufficient cytologic material for complete or partial molecular testing, whereas 46 of 56 (82%) patients had sufficient material for all clinically indicated testing. EGFR, Kras, and ALK analysis yielded positive results in 5 (10%), 10 (25%), and 5 (12%) tested specimens, respectively. No complications were associated with EBUS-TBNA. CONCLUSIONS: EBUS-TBNA performed with the patient under moderate sedation can be expected to yield sufficient tissue for sequential molecular analysis in the majority of patients. In an era of targeted therapy for lung adenocarcinomas, EBUS-TBNA is effective in clinical practice for complete diagnosis, staging, and treatment planning in these patients.

TÍTULO / TITLE: Challenges And Opportunities For Cancer Vaccines In The Current NSCLC Clinical Scenario.
RESUMEN / SUMMARY: This review is aimed to focus on NSCLC as an emerging and promising model for active immunotherapy and the challenges for its inclusion in the current clinical scenario. Cancer vaccines for NSCLC have been focused as a therapeutic
option based on the identification of a tumor hallmark and the active immunization with the related molecules that triggers cellular and/or humoral responses that consequently destroy or delay the rate of malignant progression. This therapeutic intervention in an established disease state has been aimed to impact into prolonging patient’s survival with ethically accepted quality of life. Understanding of relationship between structure and function in cancer vaccines is essential to interpret their opportunities to impact into prolonging survival and increasing quality of life in cancer patients. It is widely accepted that the failure of the cancer vaccines in the NSCLC scenario is related with its introduction in the advanced disease stages and poor performance status of the patients due to the combination of the tumor induced immunosuppression with the immune senescence. Despite first, second and emerging third line of onco-specific treatments the life expectancy for NSCLC patients diagnosed at advanced stages is surrounding the 12 months of median survival and in facts the today real circumstances are extremely demanding for the success inclusion of cancer vaccines as therapeutic choice in the clinical scenario. The kinetics of the active immunizations encompasses a sequential cascade of clinical end points: starting by the activation of the immune system, followed by the antitumor response and finalizing with the consequential impact on patients’ overall survival. Today this cascade of clinical end points is the backbone for active immunization assessment and moreover the concept of cancer vaccines, applied in the NSCLC setting, is just evolving as a complex therapeutic strategy, in which the opportunities for cancer vaccines start from the selection of the target cancer hallmark, followed by the vaccine formulation and its platforms for immune potentiating, also cover the successful insertion in the standard of care, the chronic administration beyond progression disease, the personalization based on predictors of response and the potential combination with other targeted therapies.
Osteopontin is associated with decreased apoptosis and alphav integrin expression in lung adenocarcinoma.

**RESUMEN / SUMMARY:** Osteopontin (OPN) is a glycoprotein involved in invasion, progression and metastasis of many carcinomas. It contains several functional domains including binding sites for alphav integrins, cell surface molecules playing a major role in mediating cell migration and adhesion. The aim of the study was to evaluate the expression of osteopontin in human non-small cell lung cancer (NSCLC) and to determine its possible prognostic significance as well as relation to apoptosis and alphav integrin expression. We analyzed 111 surgically resected NSCLC for immunohistochemical expression of OPN and alphav integrin. OPN expression was compared to apoptotic rate and clinicopathological parameters such as tumor size, histological grade, lymph node status, pT, and TNM stage. Apoptotic rate was measured by TUNEL staining method. OPN expression in NSCLC was significantly higher in lung adenocarcinomas (AC) then in squamous cell carcinomas (p<0.001). There was no correlation between OPN expression and clinicopathological parameters. The level of OPN expression in AC was associated with decreased apoptotic activity of tumor cells (p=0.006), and correlated with alphav integrin expression (p=0.048), particularly in low stage tumors (p=0.013). Prolonged tumor cell survival in lung AC due to OPN and alphav integrin overexpression may have an impact on tumor progression and resistance to therapy.

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Dual Intervention to Improve Pathologic Staging of Resectable Lung Cancer.

**RESUMEN / SUMMARY:** We analyzed 111 surgically resected NSCLC for immunohistochemical expression of OPN and alphav integrin. OPN expression was compared to apoptotic rate and clinicopathological parameters such as tumor size, histological grade, lymph node status, pT, and TNM stage. Apoptotic rate was measured by TUNEL staining method. OPN expression in NSCLC was significantly higher in lung adenocarcinomas (AC) then in squamous cell carcinomas (p<0.001). There was no correlation between OPN expression and clinicopathological parameters. The level of OPN expression in AC was associated with decreased apoptotic activity of tumor cells (p=0.006), and correlated with alphav integrin expression (p=0.048), particularly in low stage tumors (p=0.013). Prolonged tumor cell survival in lung AC due to OPN and alphav integrin overexpression may have an impact on tumor progression and resistance to therapy.
INSTITUCIÓN / INSTITUTION: - Thoracic Oncology Research (ThOR) Group, Multidisciplinary Thoracic Oncology Program, Baptist Cancer Center, Memphis, Tennessee. Electronic address: rosarogi@bmg.md.

RESUMEN / SUMMARY: - BACKGROUND: Detection of lymph node metastasis is of immense prognostic value in patients with resectable non-small cell lung cancer (NSCLC), but routine pathologic nodal staging is suboptimal. To determine the impact on the rate of detection of nodal metastasis, we tested dual intervention with a prelabeled lymph node specimen collection kit to improve intraoperative node dissection and a fastidious gross dissection of the lung resection specimen for intrapulmonary lymph nodes. METHODS: We matched dual-intervention cases with controls staged using standard surgical specimen collection and pathologic examination protocols. Controls were hierarchically matched for extent of resection, laterality, surgeon, pathologist, and T stage. All statistical comparisons were made with exact conditional logistic regression, to account for the matched case-control design. RESULTS: One hundred dual-intervention cases were matched with 100 controls. The dual interventions resulted in approximately a 3-fold increase in the number of lymph nodes examined and the number of lymph nodes with metastasis detected; they also increased the proportion of patients with lymph node metastasis from 21% to 35% (p = 0.02). There were strong trends toward higher aggregate stage distribution, and eligibility for postoperative adjuvant chemotherapy in the dual-intervention cases. CONCLUSIONS: The combination of interventions improved the thoroughness and accuracy of pathologic nodal staging. A prospective randomized trial to test the survival impact of the dual interventions is warranted.

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TÍTULO / TITLE: - DCA increases the antitumor effects of capecitabine in a mouse B16 melanoma allograft and a human non-small cell lung cancer A549 xenograft.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zheng MF; Shen SY; Huang WD

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, School of Life Science, Fudan University, Handan Road 220, Shanghai, 200433, China.

RESUMEN / SUMMARY: - PURPOSE: Capecitabine is one of the few chemotherapy drugs with high oral availability. Recently, sodium dichloroacetate (DCA) has shown great potential as an anticancer agent. In the present study, we assessed the anticancer effect of DCA in combination with capecitabine for cancers that modestly expressed TP. METHODS: A mouse B16 melanoma allograft and a human non-small cell lung cancer A549 xenograft were used to assess the effect of DCA and capecitabine combined treatment. Histology and immunohistochemistry were used to detect the
apoptosis and proliferation of cancer cells. Real-time PCR and Western blot were carried out to detect the expression of TP and caspases, respectively. RESULTS: For the first time, we report that DCA increased the antitumor effects of capecitabine in a mouse B16 allograft and a human A549 xenograft by promoting apoptosis of tumor cells. DCA has little effect on the expression of TP. CONCLUSIONS: Our finding suggests that DCA in combination with capecitabine might be potential as a new therapeutic regimen against some cancers.

[390]

**TÍTULO / TITLE**: New positron emission tomography derived parameters as predictive factors for recurrence in resected stage I non-small cell lung cancer.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS**: Melloni G; Gajate AM; Sestini S; Gallivanone F; Bandiera A; Landoni C; Muriana P; Gianolli L; Zannini P

**INSTITUCIÓN / INSTITUTION**: Department of Thoracic Surgery, San Raffaele Scientific Institute, Milan, Italy. Electronic address: giulio.melloni@hsr.it

**RESUMEN / SUMMARY**: BACKGROUND: The recurrence rate for stage I non-small cell lung cancer is high, with 20-40% of patients that relapse after surgery. The aim of this study was to evaluate new F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) derived parameters, such as standardized uptake value index (SUVindex), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as predictive factors for recurrence in resected stage I non-small cell lung cancer.

METHODS: We retrospectively reviewed 99 resected stage I non-small cell lung cancer patients that were grouped by SUVindex, TLG and MTV above or below their median value. Disease free survival was evaluated as primary end point. RESULTS: The 5-year overall survival and the 5-year disease free survival rates were 62% and 73%, respectively. The median SUVindex, MTL and TLG were 2.73, 2.95 and 9.61, respectively. Patients with low SUVindex, MTV and TLG were more likely to have smaller tumors (p ≤ 0.001). Univariate analysis demonstrated that SUVindex (p = 0.027), MTV (p = 0.014) and TLG (p = 0.006) were significantly related to recurrence showing a better predictive performance than SUVmax (p = 0.031). The 5-year disease free survival rates in patients with low and high SUVindex, MTV and TLG were 84% and 59%, 86% and 62% and 88% and 60%, respectively. The multivariate analysis showed that only TLG was an independent prognostic factor (p = 0.014) with a hazard ratio of 4.782. CONCLUSION: Of the three PET-derived parameters evaluated, TLG seems to be the most accurate in stratifying surgically treated stage I non-small cell lung cancer patients according to their risk of recurrence.
Telomerase is a reverse transcriptase ribonucleo-protein (h-TERT) that synthesizes telomeric repeats using its RNA component (h-TERC) as a template. Telomerase dysfunction has been associated with both fibrogenesis and carcinogenesis. In this study, we aimed to evaluate the telomerase mRNA expression levels of both subunits (h-TERT and h-TERC) in lung tissue and bronchoalveolar lavage fluid (BALF) from patients with idiopathic pulmonary fibrosis (IPF) and non-small cell lung cancer (NSCLC), since there are indications of common pathogenetic pathways in these diseases. We prospectively examined lung tissue samples from 29 patients with IPF, 10 patients with NSCLC and 21 controls. Furthermore, we examined BALF samples from 31 patients with NSCLC, 23 patients with IPF and 12 control subjects. The mRNA expression for both h-TERT and h-TERC was measured by real-time RT-PCR. In the lung tissue samples, both h-TERT and h-TERC mRNA expression levels varied among the 3 groups (p=0.036 and p=0.002, respectively). h-TERT mRNA levels in the patients with IPF were lower compared with those in the controls (p=0.009) and patients with NSCLC (p=0.004). h-TERC mRNA levels in the patients with IPF were lower compared with those in the controls (p=0.0005) and patients with NSCLC (p=0.0004). In the BALF samples, h-TERT mRNA expression levels varied among the groups (p=0.012). More specifically, h-TERT mRNA levels in the patients with IPF were higher compared with those in the controls (p=0.03) and patients with NSCLC (p=0.007). The attenuation of telomerase gene expression in IPF in comparison to lung cancer suggests a differential role of this regulatory gene in fibrogenesis and carcinogenesis. Further functional studies are required in order to further elucidate the role of telomerase in these devastating diseases.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Hu M; Wang Y; Zhang Y; Zhi X

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Xuanwu Hospital, Capital Medical University, Beijing, 100053, People’s Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: Lung cancer has been the most common type of cancer in the world for several decades, and by 2008, there were approximately 1.61 million new cases, representing 12.7% of all new cancers. It has been well known for many years that smoking causes lung cancer. Tobacco control measures have been regarded as the principal causes of the declines in smoking-related mortality, including mortality from lung cancer. METHODS: The Joinpoint Regression Program was used to analyze the long-term trends in lung cancer incidence rates from 1983 to 2008 in urban Shanghai. In addition, this study estimates how many fewer cases of lung cancer have occurred in urban Shanghai because of tobacco control activities. RESULTS: The lung cancer incidence rate among males decreased slightly by 0.6% [95% confidence interval (95% CI) -0.1 to 1.3%] from 1983 to 1999 and then declined rapidly at a rate of 3.8% (95% CI 2.1-5.4%). Among females, the cancer incidence rate decreased by 0.1% (95% CI -0.2 to 0.5%) from 1983 to 2008. Overall, we estimated that approximately 2,711 cases of lung cancer were averted among urban men in Shanghai between 2000 and 2008 because of the reduction in tobacco smoking. CONCLUSION: The reduction in tobacco smoking is a major factor in the decrease in the incidence rate of lung cancer. Sustained progress in tobacco control is essential.

[393]

TÍTULO / TITLE: - Perilous potential: The chance to save lives, or lose them, through low dose computed tomography screening for lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Bach PB

INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, New York, New York.

[394]

TÍTULO / TITLE: - Time evolution of regional CT density changes in normal lung after IMRT for NSCLC.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
PURPOSE: This study investigates the clinical radiobiology of radiation induced lung disease in terms of regional computed tomography (CT) density changes following intensity modulated radiotherapy (IMRT) for non-small-cell lung cancer (NSCLC). METHODS: A total of 387 follow-up CT scans in 131 NSCLC patients receiving IMRT to a prescribed dose of 60 or 66Gy in 2Gy fractions were analyzed. The dose-dependent temporal evolution of the density change was analyzed using a two-component model, a superposition of an early, transient component and a late, persistent component. RESULTS: The CT density of healthy lung tissue was observed to increase significantly (p<0.0001) for all dose levels after IMRT. The time evolution and the size of the density signal depend on the local delivered dose. The transient component of the density signal was found to peak in the range of 3-4 months, while the density tends to stabilize at times >12 months. CONCLUSIONS: The radiobiology of lung injury may be analyzed in terms of CT density change. The initial transient change in density is consistent with radiation pneumonitis, while the subsequent stabilization of the density is consistent with pulmonary fibrosis.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
lungs cancer (NSCLC) tumors measured by DCE-CT and metabolic activity from FDG-PET/CT. METHODS: Thirty three NSCLC patients were analyzed prior to treatment. FDG-PET/CT and DCE-CT were co-registered. The tumor was delineated and metabolic activity was segmented on the FDG-PET/CT in two regions: low (<50% maximum SUV) and high (50% maximum SUV) metabolic uptake. Blood flow, blood volume and permeability were calculated using a maximum slope, deconvolution algorithm and a Patlak model. Correlations were assessed between perfusion parameters for the regions of interest. RESULTS: DCE-CT provided additional information on vasculature and tumor heterogeneity that was not correlated to metabolic tumor activity. There was no significant difference between low and high metabolic active regions for any of the DCE-CT parameters. Furthermore, only moderate correlations between maximum SUV and DCE-CT parameters were observed. CONCLUSIONS: No direct correlation was observed between FDG-uptake and parameters extracted from DCE-CT. DCE-CT may provide complementary information to the characterization of primary NSCLC tumors over FDG-PET/CT imaging.

[396]

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TÍTULO / TITLE: Discriminant Analysis between Malignant Mesothelioma and Reactive Mesothelium Using Nuclear Three-Dimensional Analysis Is Useful for Morphologically Suspicious Cases.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Washiya K; Mizuki Y; Nakamura M; Kakinuma H; Saegusa M; Satoh Y; Yoshioka H; Watanabe J

INSTITUCIÓN / INSTITUTION: Hirosaki University Graduate School of Health Sciences, Hirosaki, Japan.

RESUMEN / SUMMARY: Objective: Morphological discrimination between malignant mesothelioma (MM) and reactive mesothelium (RM) is often difficult. Stereological analysis of nuclear luminance using centrifuged smear samples from coelomic fluid and discriminant analysis based on Mahalanobis distance may help to more accurately discriminate between MM and RM. In the present study, discriminant analysis was conducted on cytological specimens using the auto-smear method in a blinded manner with regard to histological results. Study Design: Coelomic fluid samples of 28 cases, cytologically diagnosed using the auto-smear method, were analyzed to determine pixel counts, the number of focus layers, 3-dimensional variation in the coefficient of variation of nuclear luminance between the focus layers as well as roundness in about 30-50 atypical cell nuclei per case. These measurements were employed to determine malignancy based on Mahalanobis distance. Results: Discrimination rates were as high
as 91.7% for MM and 82.7% for RM. The discrimination rates of MM with histology were >80% in 8 of 10 suspicious cases with the initial cytology. Conclusion: Our method allowed accurate discrimination between MM and RM and provides a useful alternative for the diagnosis of suspicious cases where morphological diagnosis of malignancy is difficult. © 2013 S. Karger AG, Basel.

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**TÍTULO / TITLE**: Intensity modulated radiotherapy for stage III non-small cell lung cancer in the United States: Predictors of use and association with toxicities.

**RESUMEN / SUMMARY**: Background: Intensity modulated radiotherapy for stage III lung cancer has become commonplace in the United States in the absence of randomized controlled trials. We used a large, population-based database to determine which factors led to increased utilization of IMRT and to evaluate associations of IMRT with toxicities. Methods: The Surveillance, Epidemiology, and End Results (SEER)-Medicare records identified 3986 individuals aged 66 years or older diagnosed with stage III lung cancer between 2001 and 2007 and treated with IMRT or 3D conformal radiotherapy. Predictors of IMRT use were determined using logistic regression. Associations of IMRT use with diagnosis codes for radiation-related toxicities were evaluated with multivariate proportional hazards regression and propensity-score matching. Results: Among the 3986 patients studied, the median age was 75 years, 54.1% were male, and 62% had IIIA disease. Two hundred and fifty seven (6.5%) patients received IMRT, with use increasing from 0.5% in 2001 to 14.7% in 2007 (P<0.001). Key predictors of IMRT delivery included increasing year of diagnosis and treatment in a freestanding center (odds ratio, 2.10; 95% confidence interval [CI], 1.59-2.77, P<0.001); tumor size, stage, and number of radiotherapy fractions delivered were not associated with IMRT use. IMRT use was not associated with a higher burden of lung or esophagus toxicities when compared to 3DCRT. Conclusion: These findings suggest that practice environment strongly influenced adoption of IMRT for lung cancer. Patient and tumor factors were not significant predictors of IMRT use. Esophagus and lung toxicity rates were similar between IMRT and 3DCRT.
A potential new enriching trial design for selecting non-small-cell lung cancer patients with no predictive biomarker for trials based on both histology and early tumor response: further analysis of a thalidomide trial.

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Lee SM; Hackshaw A

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There are few predictive biomarkers for antiangiogenic trials in lung cancer. We examine a potential treatment strategy in which a patient group is enriched using both histology and an early assessment of response during standard chemotherapy, and where a new agent is given for the remainder of chemotherapy and as maintenance. We performed a retrospective analysis of 722 stage IIIB/IV non-small-cell lung cancer patients from a double-blind placebo-controlled trial of thalidomide or placebo 100-200 mg/day, combined with gemcitabine/carboplatin (for up to four cycles), then given as single agent maintenance therapy. There was a significant statistical interaction between treatment and histology, with a possible benefit among squamous cell cancer (SCC) patients. We examined 150 SCC patients who were “nonprogressors” (stable disease or complete/partial response) after completing the second chemotherapy cycle. Endpoints were progression-free survival (PFS) and overall survival (OS). Among the 150 patients nonprogressors after cycle 2 (thalidomide, n = 72; placebo, n = 78; baseline characteristics were similar), the hazard ratios (HRs) were: OS = 0.76 (95% CI: 0.54-1.07) and PFS = 0.69 (95% CI: 0.50-0.97). In 57 patients who had a complete/partial response, the HRs were: OS = 0.63 (95% CI: 0.34-1.15) and PFS = 0.50 (95% CI: 0.28-0.88). SCC patients who were nonprogressors after 2 cycles of standard chemotherapy showed evidence of a benefit from thalidomide when taken for the remainder of chemotherapy and as maintenance. This strategy based on histology and, importantly, early assessment of tumor response, as a means of patient enrichment, could be examined in other lung cancer studies. Such an approach might be suitable for trials where there are no predictive biomarkers.

Combination of arsenic trioxide and chemotherapy in small cell lung cancer.

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Combination of arsenic trioxide and chemotherapy in small cell lung cancer.
INTRODUCTION: Small cell lung cancer (SCLC) carries high mortality despite standard chemotherapy. Arsenic trioxide (ATO) has demonstrated clinical efficacy in leukemia and in vitro activity in various solid tumors. This study was conducted to determine the in vitro and in vivo combination effects of ATO and chemotherapy in SCLC. MATERIALS AND METHODS: The in vitro model consisted of 5 SCLC cell lines (H187, H526, H69, H841 and DMS79) and the anti-proliferative effects of ATO, cisplatin, etoposide or combinations thereof were measured. Synergism was determined by calculation of the combination index (CI) according to Chou and Talalay. Assays for apoptosis, intracellular glutathione (GSH) content, and mitochondrial membrane depolarization (MMD) were performed. Arsenic content was measured by inductively coupled plasma-mass spectrometry. Expression level of MRP1, MRP2 and pH2AX was detected by Western blot while cellular pH2AX level was monitored by immunofluorescent staining. An in vivo xenograft model in nude mice was established with a H841 cell line to test the effects of drug combinations. RESULTS: All 5 SCLC cell lines were sensitive to ATO, with IC50 values (48h) 1.6-8μM. Synergistic or additive effects were obtained by combining cisplatin with ATO in all 5 cell lines. Combination of etoposide with ATO resulted in antagonistic or barely additive effects. Apoptotic assays and pH2AX immunofluorescent staining corroborated the synergistic combination of ATO and cisplatin. In addition, the ATO/cisplatin combination enhanced MMD, depleted GSH, downregulated MRP2 and elevated intracellular ATO content compared with either ATO or cisplatin alone. In vivo combination of ATO and cisplatin also demonstrated synergism in the H841 xenograft model. CONCLUSIONS: There was clinically relevant in vitro activity of ATO in a panel of 5 SCLC cell lines. Significant synergism was demonstrated with the ATO/cisplatin combination, while antagonism was noted with the ATO/etoposide combination in both in vitro and in vivo models.
BACKGROUND: The aim of this study was to assess the value of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for differentiating cN0 versus cN1 non-small cell lung cancer. METHODS: A retrospective review of EBUS-TBNA results in patients with potentially resectable clinical N0 or N1 non-small cell lung cancer based on computed tomography and positron emission tomography was performed. Systematic mediastinal and hilar lymph node sampling was performed by EBUS-TBNA. Lymph nodes larger than 5 mm in short axis or suspicious nodes were targeted. In the absence of N2 or N3 disease, patients underwent resection with lymph node dissection. RESULTS: A total of 981 patients underwent EBUS-TBNA during the study period, of which 163 patients met the study criteria. There were 94 cN0 and 69 cN1 patients. A total of 453 lymph nodes (338 mediastinal and 115 N1 lymph nodes, average 2.8 nodes/patient) were sampled. Endobronchial ultrasound upstaged 9 (5.5%) patients to N2 disease, but was falsely negative in the mediastinum in 7 (4.3%) patients. In cN0 patients, EBUS confirmed N0 in 87 (53.4%) and upstaged in 7 (4.3%, N1 in 1, N2 in 6). In cN1 patients, EBUS confirmed N1 in 19 (11.7%), downstaged in 47 (28.8%), and upstaged in 3 (1.8%). The sensitivity, specificity, diagnostic accuracy, and negative predictive value of EBUS-TBNA to accurately differentiate between N0 and N1 disease was 76.2%, 100%, 96.6%, and 96.2%, respectively. The accuracy of mediastinal staging was 95.7%. CONCLUSIONS: Endobronchial ultrasound-guided transbronchial needle aspiration can accurately access the hilar and interlobar lymph nodes in patients with potentially resectable lung cancer. Accurate assessment of cN0 versus cN1 by EBUS-TBNA may be used to guide induction therapy before surgery.

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TÍTULO / TITLE: Differential effect of soy isoflavones in enhancing high intensity radiotherapy and protecting lung tissue in a pre-clinical model of lung carcinoma.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Hillman GG; Singh-Gupta V; Hoogstra DJ; Abernathy L; Rakowski J; Yunker CK; Rothstein SE; Sarkar FH; Gadgeel S; Konski AA; Lonardo F; Joiner MC
INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, Wayne State University School of Medicine, Detroit, USA. Electronic address: hillmang@karmanos.org.

RESUMEN / SUMMARY: BACKGROUND: Radiotherapy of locally-advanced non-small cell lung cancer is limited by radiation-induced pneumonitis and fibrosis. We have further investigated the role of soy isoflavones to improve the effect of a high intensity radiation and reduce lung damage in a pre-clinical lung tumor model. METHODS: Human A549 NSCLC cells were injected i.v. in nude mice to generate a large tumor burden in the lungs. Mice were treated with lung irradiation at 10Gy and with oral soy. The therapy effect on the tumor cells and surrounding lung tissue was analyzed on lung sections stained with H&E, Ki-67 and Masson’s Trichrome. Pneumonitis and vascular damage were evaluated by measurements of alveolar septa and immunofluorescent staining of vessel walls. RESULTS: Combined soy and radiation caused a significantly stronger inhibition of tumor progression compared to each modality alone in contrast to large invasive tumor nodules seen in control mice. At the same time, soy reduced radiation injury in lung tissue by decreasing pneumonitis, fibrosis and protecting alveolar septa, bronchioles and vessels. CONCLUSIONS: These studies demonstrate a differential effect of soy isoflavones on augmenting tumor destruction induced by radiation while radioprotecting the normal lung tissue and support using soy to alleviate radiotoxicity in lung cancer.


RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUORES / AUTHORS: Wu M; Xu Y; Fitch WL; Zheng M; Merritt RE; Shrager JB; Zhang W; Dill DL; Peltz G; Hoang CD

INSTITUCIÓN / INSTITUTION: Department of Anesthesia, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA, 94305, USA.

RESUMEN / SUMMARY: RATIONALE: Metabolomic profiling is a promising methodology of identifying candidate biomarkers for disease detection and monitoring. Although lung cancer is among the leading causes of cancer-related mortality worldwide, the lung tumor metabolome has not been fully characterized. METHODS: We utilized a targeted metabolomic approach to analyze discrete groups of related metabolites. We adopted a dansyl [5-(dimethylamino)-1-naphthalene sulfonamide] derivatization with liquid chromatography/mass spectrometry (LC/MS) to analyze changes of metabolites from paired tumor and normal lung tissues. Identification of dansylated dipeptides was confirmed with synthetic standards. A systematic analysis of retention times was
required to reliably identify isobaric dipeptides. We validated our findings in a separate sample cohort. RESULTS: We produced a database of the LC retention times and MS/MS spectra of 361 dansyl dipeptides. Interpretation of the spectra is presented. Using this standard data, we identified a total of 279 dipeptides in lung tumor tissue. The abundance of 90 dipeptides was selectively increased in lung tumor tissue compared to normal tissue. In a second set of validation tissues, 12 dipeptides were selectively increased. CONCLUSIONS: A systematic evaluation of certain metabolite classes in lung tumors may identify promising disease-specific metabolites. Our database of all possible dipeptides will facilitate ongoing translational applications of metabolomic profiling as it relates to lung cancer. Copyright © 2013 John Wiley & Sons, Ltd.
INTRODUCTION: Platinum-based doublets are standard of care for advanced non-small-cell lung cancer (NSCLC). The combination of docetaxel and oxaliplatin has shown acceptable toxicity and encouraging activity. This phase II study aimed to determine the safety and efficacy of this doublet with bevacizumab as first-line treatment for stage IIIB/IV NSCLC. METHODS: Newly diagnosed patients >/=18 years with histologically proven non-squamous NSCLC and Eastern Cooperative Oncology Group performance status (ECOG PS) </=2 received six 21-day cycles of docetaxel, oxaliplatin, and bevacizumab followed by single-agent bevacizumab for a total of 1 year. Primary efficacy end point was radiographically documented progression-free survival (PFS); secondary end points included objective response rate (ORR), overall survival (OS), time to treatment failure, and safety. RESULTS: Fifty-three patients were enrolled. Median age was 62.0 years, 71.7 % male, 79.2 % Caucasian. A total of 88.7 % had stage IV or recurrent disease; 94.3 % adenocarcinoma; and 94.3 % ECOG PS 0 or 1. Efficacy results are as follows: median PFS 5.6 months, ORR 30.2 % (complete response 1.9 %, partial response 28.3 %); 37.7 % stable disease; and OS 14.0 months. At least one adverse event (AE) was reported in all patients (n = 52); 98.1 % of AEs were treatment related. The most common treatment-emergent grade >/=3 AEs were neutropenia (15.4 %), diarrhea (13.5 %), and fatigue (11.5 %). A serious AE was present in 32.7 %; the most common were pneumonia (7.7 %) and abdominal pain (5.8 %). Dehydration, diarrhea, febrile neutropenia, sepsis, and supraventricular tachycardia each occurred in 3.8 %. CONCLUSIONS: The addition of bevacizumab to docetaxel/oxaliplatin is effective with an acceptable safety profile in patients with chemotherapy-naive advanced NSCLC.
Non-small cell lung cancer is susceptible to induction of DNA damage responses and inhibition of angiogenesis by telomere overhang oligonucleotides.

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Exposure of the telomere overhang acts as a DNA damage signal, and exogenous administration of an 11-base oligonucleotide homologous to the 3'-telomere overhang sequence (T-oligo) mimics the effects of overhang exposure by inducing senescence and cell death in non-small cell lung cancer (NSCLC) cells, but not in normal bronchial epithelial cells. T-oligo-induced decrease in cellular proliferation in NSCLC is likely directed through both p53 and its homolog, p73, with subsequent induction of senescence and expression of senescence-associated proteins, p21, p33ING, and p27Kip1 both in vivo and in vitro. Additionally, T-oligo decreases tumor size and inhibits angiogenesis through decreased VEGF signaling and increased TSP-1 expression.

Recurrence of Pulmonary Carcinoid Tumors After Resection: Implications for Postoperative Surveillance.


Enlace al texto completo (gratuito o de pago) 1016/j.athoracsur.2013.05.047
RESUMEN / SUMMARY: - BACKGROUND: The current guidelines for follow-up care after treatment of non-small cell lung cancer recommend continued surveillance for detection of recurrent or metachronous disease. However, carcinoid tumors, especially those with a typical histologic profile, tend to be less aggressive. Our goal was to determine the patterns of relapse and the manner of detection of recurrences, to guide follow-up care after resection. METHODS: Patients who underwent operations for pulmonary carcinoids at our institution were identified from a prospectively maintained database, and their medical records were reviewed for relapse patterns, detection methods, and outcomes. RESULTS: A total of 337 patients who underwent resection between 1993 and 2010 were included, with a median follow-up time of 3.5 years. Typical and atypical carcinoids were present in 291 (86%) and 46 (14%) patients, respectively. Recurrences occurred in 21 patients (6%), with distant metastases in 20 patients (95%) and locoregional recurrence in only 1 patient. Most recurrences (15 [76%]) were not detected through scheduled surveillance imaging but after the presentation of symptoms (7 [33%]) or incidentally by studies performed for unrelated reasons (8 [38%]). The risk of recurrence increased with positive lymph nodes and atypical histologic type. Only 9 of 291 patients (3%) with typical carcinoids experienced recurrences, with a median time to recurrence of 4 years (range, 0.8-12 years). Conversely, 12 of 46 patients (26%) with atypical carcinoids experienced recurrences, with a median time to recurrence of 1.8 years (range, 0.2-7 years). CONCLUSIONS: After complete resection, scheduled surveillance imaging failed to detect most recurrences. Recurrence was rare in patients with node-negative typical carcinoids. Given the low risk of recurrence and the unclear efficacy of surveillance imaging, routine surveillance imaging may not be warranted in this cohort.

[408]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Dong X; Qiu X; Liu Q; Jia J

INSTITUCIÓN / INSTITUTION: - Department of Hematology-Oncology, Tianjin Medical University General Hospital, Tianjin, China.

RESUMEN / SUMMARY: - In this article, we assessed the pooled sensitivity and specificity of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in studies during the last 10 years that have solely used EBUS-TBNA as a minimally invasive technique, with or without computed tomography or positron-emission
tomography screening. The meta-analysis included 1,066 patients from 9 studies who underwent EBUS-TBNA. The results show EBUS-TBNA is a potential technique for the investigation, diagnosis, and staging of non-small cell lung cancer among patients with suspected lung cancer. It has excellent sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. EBUS-TBNA is well tolerated and does not lead to complications in patients.

[409]

RESUMEN / SUMMARY: Efficient tumor volume delineation by the combined use of PET/CT scanning is necessary for the proper treatment of non-small cell lung cancer (NSCLC). To understand the effect of variation in background intensity on PET-based gross tumor volume (GTV) delineation, we determined the background standard uptake values (SUVs) in normal lung, aorta (blood pool), and liver tissues and determined GTVs using different methods.

METHODS: Thirty-seven previously untreated patients with pathologically confirmed NSCLC underwent PET/CT scanning with 18F-fluorodeoxyglucose (18F-FDG). To obtain 18F-FDG uptake values in normal tissues, regions of interest in the lung lobes (left upper, left lower, right upper, right middle, and right lower), aorta, and liver zones (left, intermediate, and right) were measured. The coefficient of variation (CV) of the SUV was measured for each normal structure. The CT-based GTV (GTVCT) was considered as the standard to which all PET-based GTVs were compared, and the correlation coefficient was analyzed to compare GTV obtained by the various delineation methods. Linear and logarithmic regression analyses were used to determine the relationship between GTVCT and GTVPET.

RESULTS: Normal lung tissue showed a significantly lower SUV and less stability than tissue of the aorta or liver. For the lung, aorta, and liver, the maximum SUV (SUVmax) was 0.82+/-0.32, 2.35+/-0.37, and 3.24+/-0.50 (CV: 38.79%, 15.82%, and 15.30%) and average SUV (SUVave) was 0.49+/-0.18, 1.68+/-0.32, and 2.34+/-0.36 (CV: 36.38%, 18.92%, and 15.44%), respectively. The SUVs of the lung varied from lobe to lobe. The GTV delineation method using the SUVave of the lung lobe in which the tumor was found as background in the source-to-background ratio (SBR) method showed the best correlation with the volume of CT-based GTV (r=0.81). CONCLUSIONS: Our results show vast variation in the SUV among normal tissues, as well as in the different lung
lobes. The tumor volume delineated using the SBR method correlated well with the CT-based tumor volume. We conclude that it is reasonable and precise to contour GTV in patients with NSCLC after taking into account the background intensity of the lung lobe in which the tumor is found.

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TÍTULO / TITLE: Prognostic value of metabolic metrics extracted from baseline positron emission tomography images in non-small cell lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Carvalho S; Leijenaar RT; Velazquez ER; Oberije C; Parmar C; van Elmp W; Reymen B; Troost EG; Oellers M; Dekker A; Gillies R; Aerts HI; Lambin P

INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology (MAASTRO), GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center (MUMC +), Maastricht, the Netherlands.

RESUMEN / SUMMARY: Abstract Background. Maximum, mean and peak SUV of primary tumor at baseline FDG-PET scans, have often been found predictive for overall survival in non-small cell lung cancer (NSCLC) patients. In this study we further investigated the prognostic power of advanced metabolic metrics derived from intensity volume histograms (IVH) extracted from PET imaging. Methods. A cohort of 220 NSCLC patients (mean age, 66.6 years; 149 men, 71 women), stages I-IIIB, treated with radiotherapy with curative intent were included (NCT00522639). Each patient underwent standardized pre-treatment CT-PET imaging. Primary GTV was delineated by an experienced radiation oncologist on CT-PET images. Common PET descriptors such as maximum, mean and peak SUV, and metabolic tumor volume (MTV) were quantified. Advanced descriptors of metabolic activity were quantified by IVH. These comprised five groups of features: absolute and relative volume above relative intensity threshold (AVRI and RVRI), absolute and relative volume above absolute intensity threshold (AVAI and RVAI), and absolute intensity above relative volume threshold (AIRV). MTV was derived from the IVH curves for volumes with SUV above 2.5, 3 and 4, and of 40% and 50% maximum SUV. Univariable analysis using Cox Proportional Hazard Regression was performed for overall survival assessment. Results. Relative volume above higher SUV (80%) was an independent predictor of OS (p = 0.05). None of the possible surrogates for MTV based on volumes above SUV of 3, 40% and 50% of maximum SUV showed significant associations with OS [p (AVAI3) = 0.10, p (AVAI4) = 0.22, p (AVRI40%) = 0.15, p (AVRI50%) = 0.17]. Maximum and peak SUV (r = 0.99) revealed no prognostic value for OS [p (maximum SUV) = 0.20, p (peak SUV) = 0.22]. Conclusions. New methods using more advanced imaging features
extracted from PET were analyzed. Best prognostic value for OS of NSCLC patients was found for relative portions of the tumor above higher uptakes (80% SUV).

[411]

**TITULO / TITLE:** - Modulation of peripheral immune responses by paclitaxel-ifosfamide-cisplatin chemotherapy in advanced non-small-cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Koufos N; Michailidou D; Xynos ID; Tomos P; Athanasiadou K; Kosmas C; Tsavaris N

**INSTITUCIÓN / INSTITUTION:** - Oncology Unit, Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Agios Thomas 17, 11527, Athens, Greece.

**RESUMEN / SUMMARY:** - PURPOSE: The aim of this study was to assess systemic immunological responses in non-small-cell lung cancer (NSCLC) patients with stage III/IV disease during treatment with paclitaxel-ifosfamide-cisplatin (TIP) chemotherapy. METHODS: Peripheral blood mononuclear cells (PBMCs) collected from healthy donors (HD) (n = 20) and chemotherapy-naive NSCLC patients treated with TIP (n = 32) were tested for production of IL-1, TNF-alpha, TNF-beta, IL-6, IL-8, IL-10, IL-12 and IL-2 upon polyclonal stimulation with anti-CD3 mAb. They were further assessed over a treatment period of twelve weeks (i.e., four treatment cycles). RESULTS: PBMCs from NSCLC patients produced higher IL-1, TNF-alpha, TNF-beta, IL-6, IL-8, IL-10 and IL-12 levels, whereas IL-2 exhibited lower values compared to HD (p < 0.001 for all parameters). Of interest, patients who responded to treatment had significantly higher increases in IL-2 (p < 0.001) and significantly higher decreases in IL-1 (p < 0.001), TNF-alpha (p < 0.001), TNF-beta (p < 0.001), IL-6 (p = 0.02), IL-8 (p < 0.001), IL-10 (p < 0.001) and IL-12 (p < 0.001) levels. Non-responders revealed post-therapeutically a significantly higher increase in IL-1, TNF-alpha, TNF-beta, IL-6, IL-8, IL-10 and IL-12 secretion and a significantly higher decrease in IL-2 levels (p < 0.001 for all parameters). Patients who responded to treatment and had a significantly higher increase in IL-2 showed a significantly longer median survival (p value < 0.001, 26 vs. 7.5 months). CONCLUSION: Our study indicates that monitoring cytokine dynamics in patients with advanced NSCLC and especially those of IL-2 in peripheral blood components in vitro could be used as a predictor of treatment-related outcome and overall survival in NSCLC.
TÍTULO / TITLE: - Diagnostic method for the detection of KIF5B-RET transformation in lung adenocarcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Go H; Jung YJ; Kang HW; Park IK; Kang CH; Lee JW; Ju YS; Seo JS; Chung DH; Kim YT

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - KIF5B-RET fusions have recently been reported to occur in pulmonary adenocarcinomas, thereby being proposed as a novel genetic alteration in adenocarcinoma of the lung. However, clinically useful methods to detect RET-rearrangement in pulmonary adenocarcinoma have not been well established. 53 cases of lung adenocarcinomas harbored “triple (EGFR, KRAS and ALK)-negative” were tested for KIF5B-RET fusions using whole-transcriptome sequencing, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and long-range PCR. Dual color break-apart probes and KIF5B-RET fusion probes were used for FISH. Three different commercial antibodies against C-terminal RET protein were tested for IHC. Primers designed for 3 different variants of KIF5B-RET fusions were used for long-range PCR. Three patients (5.6%) showed RET rearrangement in whole-transcriptome sequencing, which were used as a gold standard. All those three patients were also positive in FISH for both KIF5B-RET fusion and RET break-apart probes. None of remaining patients showed positive result, resulting in 100% concordance rate of FISH and transcriptome sequencing methods. However, fused RET proteins were not detected by IHC in none of true positive patients. Moreover, 6 patients without RET fusions showed gain of gene copy number of both KIF5B and RET. All those three true positive cases were detected by long-range PCR methods and none with true negative cases were positive. Both FISH and PCR may be useful methods to detect novel KIF5B-RET rearrangements in pulmonary adenocarcinomas rather than IHC. However, as there may be additional variant of fusion mutation, FISH may be better than PCR method in terms of sensitivity.

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TÍTULO / TITLE: - Lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Go H; Jung YJ; Kang HW; Park IK; Kang CH; Lee JW; Ju YS; Seo JS; Chung DH; Kim YT

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea.
AUTORES / AUTHORS: - Gautschi O; Peters S; Zoete V; Aebersold-Keller F; Strobel K; Schwizer B; Hirschmann A; Michielin O; Diebold J
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Luzerner Kantonsspital, Luzern, Switzerland. Electronic address: oliver.gautschi@luks.ch.
RESUMEN / SUMMARY: - BRAF V600E is an emerging drug target in lung cancer, but the clinical significance of non-V600 BRAF mutations in lung cancer and other malignancies is less clear. Here, we report the case of a patient with metastatic lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib. We calculated a structure model of this very rare type of mutated BRAF kinase to explain the molecular mechanism of drug resistance. This information may help to develop effective targeted therapies for cancers with non-V600 BRAF mutations.

[414]
TÍTULO / TITLE: - Usefulness of immunohistochemistry for the detection of the BRAF V600E mutation in Japanese lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Sasaki H; Shimizu S; Tani Y; Shitara M; Okuda K; Hikosaka Y; Moriyama S; Yano M; Fujii Y
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. Electronic address: hisasaki@med.nagoya-cu.ac.jp.
RESUMEN / SUMMARY: - PURPOSE: Mutations in components of the mitogen-activated protein kinase (MAPK) cascade may be a new candidate for target for lung cancer. The usefulness of immunohistochemistry (IHC) as a new approach for the detection of BRAF V600E in cancer patients has been recently reported. METHODS: To increase the sensitivity, we modified BRAF V600E expression detection assay by IHC using mutation specific antibody. From the screening step, we found a novel 599 insertion T BRAF mutation in lung adenocarcinoma. In this study included 26 surgically removed cases with EGFR, Kras, erbB2, EML4-ALK and KIF5B-RET wild-type (wt) lung adenocarcinomas, including 7 BRAF mutants (5 V600E, 1 N581I, and 1 novel 599 insertion T mutation) analyzed by DNA sequencing. Detection of the BRAF V600E mutation was carried out by the Dako EnVision FLEX detection system using the VE1 clone antibody and compared with the results of direct sequencing. RESULTS: The autostainer IHC VE1 assay was positive in 5 of 5 (100%) BRAF V600E-mutated tumors and negative in 20 of 21 (95.2%) BRAF non-V600E tumors, except for a novel 599 insertion T case. CONCLUSION: IHC using the VE1 clone and FLEX linker is a specific method for the detection BRAF V600E and may be an alternative to molecular biology
for the detection of mutations in lung adenocarcinomas. This method might be useful for screening to use molecular target therapy for lung adenocarcinomas.

[415]

**TÍTULO / TITLE:** - Comparative study evaluating the role of color Doppler sonography and computed tomography in predicting chest wall invasion by lung tumors.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Sripathi S; Mahajan A

**INSTITUCIÓN / INSTITUTION:** - Department of Radiodiagnosis and Imaging, Tata Memorial Hospital, Dr E. Borges Road, Parel, Mumbai, Maharashtra 400 012, India.

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**RESUMEN / SUMMARY:** - Objectives- To analyze qualitative and quantitative parameters of lung tumors by color Doppler sonography, determine the role of color Doppler sonography in predicting chest wall invasion by lung tumors using spectral waveform analysis, and compare color Doppler sonography and computed tomography (CT) for predicting chest wall invasion by lung tumors. Methods- Between March and September 2007, 55 patients with pleuropulmonary lesions on chest radiography were assessed by grayscale and color Doppler sonography for chest wall invasion. Four patients were excluded from the study because of poor acoustic windows. Quantitative and qualitative sonographic examinations of the lesions were performed using grayscale and color Doppler imaging. The correlation between the color Doppler and CT findings was determined, and the final outcomes were correlated with the histopathologic findings. Results- Of a total of 51 lesions, 32 were malignant. Vascularity was present on color Doppler sonography in 28 lesions, and chest wall invasion was documented in 22 cases. Computed tomography was performed in 24 of 28 evaluable malignant lesions, and the findings were correlated with the color Doppler findings for chest wall invasion. Of the 24 patients who underwent CT, 19 showed chest wall invasion. The correlation between the color Doppler and CT findings revealed that color Doppler sonography had sensitivity of 95.6% and specificity of 100% for assessing chest wall invasion, whereas CT had sensitivity of 85.7% and specificity of 66.7%. Conclusions- Combined qualitative and quantitative color Doppler sonography can predict chest wall invasion by lung tumors with better sensitivity and specificity than CT. Although surgery is the reference standard, color Doppler sonography is a readily available, affordable, and noninvasive in vivo diagnostic imaging modality that is complementary to CT and magnetic resonance imaging for lung cancer staging.
**TÍTULO / TITLE:** The Role of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in the Diagnosis of Recurrent Non-small Cell Lung Cancer after Surgery.

**RESUMEN / SUMMARY:** Obtaining an accurate histopathological diagnosis is mandatory for the optimal treatment of patients who are suspected of having recurrent lung cancer. The purpose of this retrospective study was to investigate the usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of recurrent non-small cell lung cancer (NSCLC) among patients who undergo curative surgical resection. Methods Consecutive patients who underwent convex probe EBUS-TBNA for mediastinal or hilar lymph node and peribronchial lung parenchymal lesions between May 2009 and May 2011 were included. The diagnostic sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated on a per-lesion and per-patient basis. Results Forty-two patients who were suspected of having recurrent NSCLC underwent EBUS-TBNA to assess 53 mediastinal and hilar lymph nodes and seven peribronchial lung parenchymal lesions. Among the 60 lesions, recurrence of malignancy was confirmed in 41 lesions on EBUS-TBNA (36 lymph nodes and five peribronchial lung lesions). On a per-lesion basis, the diagnostic sensitivity, specificity, accuracy, PPV and NPV of EBUS-TBNA for confirming recurrence were 95.3%, 100%, 96.6%, 100% and 88.9%, respectively. On a per-person basis, the diagnostic sensitivity, specificity, accuracy, PPV and NPV were 94.3%, 100%, 95.2%, 100% and 77.8%, respectively. No serious complications related to the procedures were observed. Conclusion Convex probe EBUS-TBNA is a sensitive method for diagnosing recurrent NSCLC in patients with lymph node and peribronchial lung parenchymal lesions. Therefore, EBUS-TBNA should be considered first for the cytopathological diagnosis of recurrent NSCLC.

**INSTITUCIÓN / INSTITUTION:** Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea.

**RESUMEN / SUMMARY:** Objective Obtaining an accurate histopathological diagnosis is mandatory for the optimal treatment of patients who are suspected of having recurrent lung cancer. The purpose of this retrospective study was to investigate the usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of recurrent non-small cell lung cancer (NSCLC) among patients who undergo curative surgical resection. Methods Consecutive patients who underwent convex probe EBUS-TBNA for mediastinal or hilar lymph node and peribronchial lung parenchymal lesions between May 2009 and May 2011 were included. The diagnostic sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated on a per-lesion and per-patient basis. Results Forty-two patients who were suspected of having recurrent NSCLC underwent EBUS-TBNA to assess 53 mediastinal and hilar lymph nodes and seven peribronchial lung parenchymal lesions. Among the 60 lesions, recurrence of malignancy was confirmed in 41 lesions on EBUS-TBNA (36 lymph nodes and five peribronchial lung lesions). On a per-lesion basis, the diagnostic sensitivity, specificity, accuracy, PPV and NPV of EBUS-TBNA for confirming recurrence were 95.3%, 100%, 96.6%, 100% and 88.9%, respectively. On a per-person basis, the diagnostic sensitivity, specificity, accuracy, PPV and NPV were 94.3%, 100%, 95.2%, 100% and 77.8%, respectively. No serious complications related to the procedures were observed. Conclusion Convex probe EBUS-TBNA is a sensitive method for diagnosing recurrent NSCLC in patients with lymph node and peribronchial lung parenchymal lesions. Therefore, EBUS-TBNA should be considered first for the cytopathological diagnosis of recurrent NSCLC.
OBJECTIVES: To describe our management of complex glottic stenosis in tracheotomy dependent children with severe recurrent respiratory papillomatosis. METHODS: Retrospective chart review at a tertiary care children’s hospital. RESULTS: Three children with complex glottic stenosis secondary to severe recurrent respiratory papillomatosis were treated at our institution since 2011. Two patients had complete stenosis, and the third had near-complete stenosis. Two patients were managed using balloon dilation alone, and the third also underwent laryngotracheal reconstruction with posterior costal cartilage grafting. Two patients have been successfully decannulated and the third has been tolerating continuous tracheotomy capping for greater than twelve months. All three patients underwent aggressive debridement of papillomatosis and balloon dilation every 4-6 weeks until their burden of disease was controlled. In two patients, the glottic airway was patent, and the third continued to have complete restenosis between procedures and required laryngotracheoplasty with multiple post-operative dilation procedures to establish an adequate glottic airway. CONCLUSIONS: Severe laryngeal stenosis is a well-described complication of recurrent respiratory papillomatosis, but its management is not well-defined. Aggressive management of papillomatosis with frequent debridement is critical in successfully managing laryngeal stenosis. Balloon dilation alone may be surprisingly effective in these patients, and laryngotracheoplasty can be used as an adjunct procedure in those patients who fail balloon dilation. Given the quality of life issues and concerns regarding distal spread of disease with tracheotomies in these patients, we feel that aggressive management and early decannulation is in the patient’s best interest.
Telomeres are the end structures of chromosomes in mammalian cells; they play a pivotal role in maintaining the stability of the chromosome and become shorter with each cell division. However, several types of tumor cells express telomerase in very high levels to overcome this crisis and achieve the ability to proliferate endlessly. The telomerase inhibitors can partly inhibit tumor cell proliferation and promote apoptosis, but their roles are only limited. Tankyrase is a poly(ADP-ribose) polymerase which has synergistic effect on telomerase, and is expressed in lung cancer cells in high levels. In the present study, antisense oligonucleotides of telomerase (ashTERT) and tankyrase (asTANKS) were used as specific inhibitors to silence the expression of target genes in A549 human lung adenocarcinoma cells by transfection. The results showed that ashTERT and asTANKS suppressed the expression of telomerase and tankyrase significantly; both inhibited the activity of telomerase and the combination group achieved better effect, but only ashTERT shortened the length of telomeres, asTANKS did not. Further studies showed that ashTERT and asTANKS-promoted A549 apoptosis was not mediated by downregulation of the expression of the antiapoptotic gene BCL-2 or upregulation of the expression of the proapoptotic gene BAX, but by adjusting the two isoforms proportion of myeloid cell leukemia-1 (MCL1) which can interact with tankyrase directly. MCL-1short (MCL1S), a pro-apoptotic gene, increased more than MCL-1Long (MCL1L) which is an anti-apoptotic gene, leading to A549 cell apoptosis and a similar result was obtained in nude mice in vivo. The present study suggests that combination of the inhibitors of telomerase and tankyrase can be used as a strategy for the treatment of lung cancer in humans.

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**Título / Title:** Acute kidney injury following crizotinib administration for non-small-cell lung carcinoma.

**Resumen / Summary:** A case of locally advanced non-small-cell lung carcinoma (NSCLC) was inadequately controlled with cisplatin, bevacizumab and pemetrexed chemotherapy. Following identification of a mutation of the echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase (EML4-ALK) gene, crizotinib was then administered as targeted treatment. Kidney function was normal at diagnosis and...
during the first line therapy. The administration of crizotinib coincided on two occasions with a conspicuous rise in the serum creatinine level. Urinary protein over creatinine ratio was 0.31g/g with 22% albumin and macroscopic hematuria. A kidney biopsy was performed at the time of the second episode of renal impairment which showed acute tubular necrosis (ATN) indicating recent renal injury together with a mononuclear cell infiltrate consistent with ongoing repair related to a previous insult. The renal lesions were closely related temporally to crizotinib administration, supporting a causative role for crizotinib in the acute renal injury and this phenomenon has not previously been described.

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TÍTULO / TITLE: - Extended Sleeve Lobectomy: One More Step Toward Avoiding Pneumonectomy in Centrally Located Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Berthet JP; Paradela M; Jimenez MJ; Molins L; Gomez-Caro A
INSTITUCIÓN / INSTITUTION: - General Thoracic Surgery Department, Hospital Clinic, Universidad de Barcelona, Barcelona, España; U1046, INSERM, Universite Montpellier 1, Universite Montpellier 2, Montpellier, France. Electronic address: jeanphilippe.berthet@gmail.com.
RESUMEN / SUMMARY: - BACKGROUND: The purpose of this study was to evaluate surgical outcomes of extended sleeve lobectomy (ESL) in centrally located non-small-cell lung cancer (NSCLC), sparing lung tissue and aggressively avoiding pneumonectomy. METHODS: Patients who underwent ESL between January 2006 and January 2013 were included prospectively. An atypical bronchial anastomosis was used for sleeve lobectomy involving additional lobes or segments. RESULTS: We included 27 patients, aged 62.7 +/- 8.2 years (range, 49-83 years), with a forced expiratory volume in 1 second (FEV1) of 2.27 +/- 0.6 (range, 1.6-2.7). According to the Okada classification, 16 cases were type A (right upper lobe + middle lobe +/- segment 6), 7 cases were type B (left upper lobe + segment 6), and 2 cases were type C (left lower lobe + segments 4-5); we additionally classified 2 patients with right lower lobe tumors involving the right main bronchus as type D (right lower lobe + middle lobe). Anastomosis was performed between the right superior and right main bronchial stumps. Eleven patients underwent combined pulmonary angioplasties. Complete resection was achieved in all cases. There were no operative deaths. Mean segment reimplantation was 4.5 +/- 0.84 (range, 3-6), resulting in a mean FEV1 improvement of 0.620 +/- 0.16 (right-sided ESL) and 0.393 +/- 0.21 (left-sided ESL). The complication
rate was 25% (no immediate anastomosis-related complications; 1 case of delayed bronchial stenosis). No local recurrence was reported. At 6 months, mean FEV1 was 1.5 +/- 0.4 (right-sided ESL) and 1.4 +/- 0.3 (left-sided ESL). Mean follow-up time was 28 +/- 19 months (range, 7-72 months). Overall 5-year survival was 62%.

CONCLUSIONS: In patients with centrally located NSCLC, lung-sparing ESL, whose safety and reliability rival that of pneumonectomy, should be considered. Functional effectiveness is higher with right-sided than with left-sided ESL.

[TÍTULO / TITLE]: Salvage Stereotactic Ablative Irradiation for Isolated Postsurgical Local Recurrence of Lung Cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Takeda A; Sanuki N; Eriguchi T; Enomoto T; Yokosuka T; Kaneko T; Handa H; Aoki Y; Oku Y; Kunieda E

INSTITUCIÓN / INSTITUTION: Radiation Oncology Center, Ofuna Chuo Hospital, Ofuna, Japan.

RESUMEN / SUMMARY: BACKGROUND: For isolated postsurgical local recurrences (IPSLR) of lung cancer, salvage resection is often unfeasible due to a high risk of morbidity and death. Stereotactic ablative body radiotherapy (SABR) provides excellent therapeutic effects, with mild toxicities, for patients with medically inoperable lung cancer. However, the outcomes of SABR for IPSLR have not been reported. METHODS: Patients with IPSLR who were treated with SABR between 2005 and 2012 were retrospectively identified. The prescribed doses were 40 to 60 Gy per 5 to 10 fractions. Treatment outcomes and toxicities were evaluated. RESULTS: We identified 23 patients with IPSLR, including 21 with bronchial stump or staple line recurrences and 2 with chest wall recurrences. During follow-up, IPSLR occurred at a median of 36.7 months (range, 5.0 to 190 months) after resection. All patients were N0 M0, and the T stages at recurrence were T1a, T1b, T2a, and T4 in 6, 5, 3, and 9 patients, respectively. The initial pathologic diagnoses were adenocarcinoma in 17 patients and squamous cell carcinoma in 6. At a median follow-up duration of 17.0 months (range, 6.0 to 89.6 months) after SABR, there were 2 local recurrences. Local control and overall survival rates at 1 and 2 years were 94.7% and 86.8% and 84.0% and 76.4%, respectively. Grade 3 to 5 radiation pneumonitis occurred in 1 patient each. Grade 3 temporary but repeated obstructive pneumonia occurred in 2 patients.

CONCLUSIONS: SABR for IPSLR achieved high local control with limited toxicities.
may lead to a potential cure and should be considered as a salvage treatment option for IPSLR.

[422]  
TÍTULO / TITLE: Extensive invasion of the left atrium by lung cancer.  
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary  
●● Enlace al texto completo (gratuito o de pago)  
1016/j.athoracsur.2012.12.050  
AUTORES / AUTHORS: Ma Q; Liu D; Liu P; Chen J; Xie Z; D’Amico TA  
INSTITUCIÓN / INSTITUTION: Section of General Thoracic Surgery, Duke University Medical Center, Durham, North Carolina; Department of General Thoracic Surgery, China-Japan Friendship Hospital, Chaoyang, Beijing, China.  
RESUMEN / SUMMARY: A 52-year-old man complained of cough and hemoptysis for 1 month. Chest computed tomography scan revealed a 9 cm x 7 cm right lung mass invading the right inferior pulmonary vein and left atrium extensively, and the inferior pulmonary vein was completely occluded. Transsternal echocardiogram confirmed that the lesion invaded the apex of left atrium adjacent to the right pulmonary inferior vein. Positron emission tomography scan showed no other metastatic disease. Bronchoscopy with endobronchial biopsy demonstrated a low-grade squamous cell carcinoma. After 2 cycles of induction chemotherapy, he underwent resection with cardiopulmonary bypass. Postoperative pathology was sarcoma mixed with squamous carcinoma (10%), without lymph node metastasis. Both the bronchial and atrial margins were negative, pathology stage T4N0M0, IIIA. He recovered without postoperative complications, and went back to work 20 days after surgery. He received four cycles of subsequent chemotherapy, but a solitary brain metastasis was discovered 7 months later, and he died 9 months after surgery.

[423]  
TÍTULO / TITLE: Thoracoscopic lobectomy for synchronous intralobar pulmonary sequestration and lung cancer.  
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary  
●● Enlace al texto completo (gratuito o de pago)  
1016/j.athoracsur.2012.12.063  
AUTORES / AUTHORS: Wang TK; Oh T; Ramanathan T
INSTITUCIÓN / INSTITUTION: - Green Lane Cardiothoracic Surgical Unit, Auckland City Hospital, Grafton, Auckland, New Zealand. twang@adhb.govt.nz

RESUMEN / SUMMARY: - Bronchopulmonary sequestration is a rare congenital pulmonary malformation for which surgical resection is recommended, and several reports have described successful resection by video-assisted thoracoscopic surgery. Coexistence of sequestration with lung malignancy is extremely rare. We report the first case of thoracoscopic resection of synchronous intralobar pulmonary sequestration and non-small cell lung cancer.

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TÍTULO / TITLE: - Intradiaphragmatic bronchogenic cyst.
RESUMEN / SUMMARY: - Bronchogenic cyst (BC) is a rare congenital developmental abnormality. BCs are usually encountered in the mediastinum, but ectopic BCs are rare. We present a case of BC located within the diaphragm in an adult female patient. The lesion was successfully resected via thoracotomy. Diagnosis was confirmed by pathology.

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Nonintubated Thoracoscopic Anatomical Segmentectomy for Lung Tumors.

AUTORES / AUTHORS: - Hung MH; Hsu HH; Chen KC; Chan KC; Cheng YJ; Chen JS

INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan.
RESUMEN / SUMMARY: - BACKGROUND: Intubated general anesthesia with one-lung ventilation is considered mandatory for anatomical pulmonary resections. Nonintubated thoracoscopic segmentectomy for management of lung tumors, which is technically challenging, has not been reported previously. The goal of this study was to evaluate the feasibility and safety of thoracoscopic anatomical segmentectomy without endotracheal intubation. METHODS: From August 2009 to December 2012, 21 patients with lung tumors were treated using thoracoscopic anatomical segmentectomy without endotracheal intubation using a combination of thoracic epidural anesthesia, intrathoracic vagal blockade, and target-controlled sedation. RESULTS: There were 16 patients with primary or metastatic lung cancers and 5 patients with nonmalignant tumors. Left upper lobe apical trisegmentectomy was most commonly performed (n = 6), followed by superior segmentectomy of the right lower lobe (n = 4) and left lower lobe (n = 4). One patient required conversion to intubated single-lung ventilation because of vigorous mediastinal and diaphragmatic movement. No patient required conversion to a thoracotomy or lobectomy. Operative complications developed in 1 patient who had an air leak for more than 3 days postoperatively. The mean duration of postoperative chest tube drainage and mean hospital stay were 2.5 days and 6.0 days, respectively. Anesthetic induction and the operation required a mean 26.5 minutes and 148.0 minutes, respectively. CONCLUSIONS: Nonintubated thoracoscopic segmentectomy is technically feasible and safe. It can be an alternative to intubated single-lung ventilation for management of lung tumors in selected patients.

TÍTULO / TITLE: - Lymph Node Evaluation Achieved by Open Lobectomy Compared With Thoracoscopic Lobectomy for N0 Lung Cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Merritt RE; Hoang CD; Shrager JB

INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, Division of Thoracic Surgery, Stanford University School of Medicine, Stanford, California. Electronic address: rmerritt@stanford.edu.

RESUMEN / SUMMARY: - BACKGROUND: Controversy remains regarding the adequacy of the lymph node evaluation achieved by video-assisted thoracic surgery (VATS) lobectomy for lung cancer. This study compared the completeness of the lymph node dissection or sampling for patients undergoing lobectomy by open thoracotomy vs VATS for clinical N0 lung cancer. METHODS: This study was a retrospective review of
129 patients who underwent lobectomy for clinical N0 lung carcinoma from December 2008 to January 2012. RESULTS: Lobectomy was an open procedure in 69 patients (53.5%) and by VATS in 60 (46.5%). The VATS and open groups were well matched for age (p = 0.50) and forced expiratory volume in 1 second percentage predicted (p = 0.16). The mean pathologic tumor sizes were not significantly different (2.9 +/- 0.26 vs 3.4 +/- 0.25 cm, respectively; p = 0.14). The mean number of nodes dissected in the open group was significantly higher (14.7 +/- 1.3 vs. 9.9 +/- 0.8 nodes; p = 0.003). In the open lobectomy group, 24.6% of the patients were upstaged to pathologic N1 or N2 compared with 10% in the VATS group (p = 0.05). The Kaplan-Meier 3-year survival was similar between the groups. CONCLUSIONS: In our hands, significantly more lymph nodes were dissected, and a higher percentage of patients were upstaged to N1/N2, during open lobectomy compared with VATS lobectomy in patients with clinical stage N0 lung cancer. Although this did not translate into improved survival at 3 years, concern is raised about the adequacy of lymph node dissection during VATS lobectomy.

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**TÍTULO / TITLE:** Up-regulation of pro-angiogenic factors and establishment of tolerance in malignant pleural effusions.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Lieser EA; Croghan GA; Nevala WK; Bradshaw MJ; Markovic SN; Mansfield AS

**INSTITUCIÓN / INSTITUTION:** Mayo Graduate School, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States.

**RESUMEN / SUMMARY:** INTRODUCTION: Malignant pleural effusions (MPEs) are a significant source of cancer morbidity and mortality. Currently there is no cure for MPEs and treatments only palliate the symptoms. The purpose of this study was to determine if there are differences in markers of angiogenesis and immune phenotypes between adenocarcinoma-induced MPEs and benign pleural effusions (BPEs).

**MÉTODOS:** Pleural effusions were collected from patients with MPEs and BPEs. Cells were isolated from effusions and characterized using fluorescent cell sorting (FACS). Pleural effusions were evaluated by ELISA for VEGF-A. An angiogenesis protein array was completed to compare protein expression in malignant and non-malignant effusions. **RESULTAS:** FACS analysis demonstrated lower accumulation of cytotoxic T-cells and significantly higher accumulation of monocytes, dendritic cells, mesothelial and tumor cells in MPEs compared to benign pleural effusions. MPEs were found to have 77-fold higher VEGF-A levels compared to BPEs. The angiogenesis protein array...
demonstrated elevated levels of pro-angiogenic factors VEGF-A, CXCL4 and MMP-8, and low levels of pro-inflammatory cytokines IL-8, MCP-1, and TGF-beta1 in MPEs. CONCLUSIONS: MPE is biased toward a Th2 dominant state. There is an increase in expression of VEGF-A and other pro-angiogenic factors in MPE. These data suggest there is a role for anti-angiogenesis therapy in patients with MPEs.

[428]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Becker M; Muller CB; De Bastiani MA; Klamt F
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, ICBS/UFRGS, and National Institutes for Science and Technology - Translational Medicine (INCT-TM), Porto Alegre (RS), Brazil.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung malignancies. Tumor-associated macrophages (TAM) are abundant components of NSCLC. Although under certain conditions TAM can kill tumor cells, they can also act as tumor promoters secreting a variety of factors that directly stimulate tumor invasion and metastasis. TAM presents two distinct phenotypes: the classically activated (or M1) phenotype, which is highly pro-inflammatory (phagocytic and cytotoxic), and the alternatively activated (or M2) phenotype, which has anti-inflammatory and pro-tumoral properties. The polarization status of TAM depends on stimulating factors from the tumor microenvironment, and some in vitro evidence implies that the phagocytosis of apoptotic bodies derived from tumoral cells is a key factor in M1/M2 modulation, raising the question of whether the evaluation of the apoptotic index (AI) and macrophage polarization have a prognostic role in NSCLC patient survival. The present article systematically reviewed the published series of clinical data that correlated the AI and/or macrophage densities and polarization status (M1/M2) with the outcome of non-small cell lung cancer patients. Even though an overwhelming body of clinical data support that TAM’s density, micro-anatomical localization, phenotype and intra-tumoral AI are independent predictors of survival time, no study to date has been conducted to evaluate the impact of these parameters altogether in NSCLC patient outcome. Joint analysis of these biologic factors in future studies might reveal their prognostic value in the management of NSCLC cases.

[429]
**TÍTULO / TITLE:** The cathelicidin-BF Lys16 mutant Cbf-K16 selectively inhibits non-small cell lung cancer proliferation in vitro.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** Tian Y; Wang H; Li B; Ke M; Wang J; Dou J; Zhou C

**INSTITUCIÓN / INSTITUTION:** State Key Laboratory of Natural Medicines, School of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu 210009, P.R. China.

**RESUMEN / SUMMARY:** The 30-amino acid antimicrobial peptide Cbf-K16 is a cathelicidin-BF (BF-30) Lys16 mutant derived from the snake venom of Bungarus fasciatus. Our previous study found that BF-30 selectively inhibited the proliferation of the metastatic melanoma cell line B16F10 in vitro and in vivo, but had a negligible effect on human lung cells. In the present study, it was demonstrated for the first time that Cbf-K16 selectively inhibits the proliferation of lung carcinoma cells in vitro, with low toxicity to normal cells. The half-maximal inhibitory concentrations (IC50) of Cbf-K16 against H460 human non-small cell lung carcinoma cells and mouse Lewis lung cancer cells were only 16.5 and 10.5 microM, respectively, which were much less compared to that of BF-30 (45 and 40.3 microM). Data using a transmission electron microscope (TEM) assay showed that, at 20 and 40 microM, Cbf-K16 induced the rupture of the cytoplasmic membrane, which was consistent with data obtained from lactate dehydrogenase (LDH) release assays. The LDH release increased from 17.8 to 52.9% as the duration and dosage of Cbf-K16 increased. Annexin V-fluorescein and propidium iodide staining assays indicated that there were no obvious apoptotic effects at the different dosages and times tested. In H460 cells, the rate of genomic DNA binding increased from 51.9 to 86.8% as the concentration of Cbf-K16 increased from 5 to 10 microM. These data indicate that Cbf-K16 selectively inhibits the proliferation of lung carcinoma cells via cytoplasmic membrane permeabilization and DNA binding, rather than apoptosis. Although Cbf-K16 displayed significant cytotoxic activity (40 microM) against tumor cells, in splenocytes no significant inhibitory effect was observed and hemolysis was only 5.6%. These results suggest that Cbf-K16 is a low-toxicity anti-lung cancer drug candidate.

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**TÍTULO / TITLE:** Evaluation of Amrubicin as a Third or Later Line of Chemotherapy for Advanced Non-Small Cell Lung Cancer.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** Chemotherapy. 2013 Sep 10;59(2):99-105.

**AUTORES / AUTHORS:** Tian Y; Wang H; Li B; Ke M; Wang J; Dou J; Zhou C

**INSTITUCIÓN / INSTITUTION:** State Key Laboratory of Natural Medicines, School of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu 210009, P.R. China.

**RESUMEN / SUMMARY:** The 30-amino acid antimicrobial peptide Cbf-K16 is a cathelicidin-BF (BF-30) Lys16 mutant derived from the snake venom of Bungarus fasciatus. Our previous study found that BF-30 selectively inhibited the proliferation of the metastatic melanoma cell line B16F10 in vitro and in vivo, but had a negligible effect on human lung cells. In the present study, it was demonstrated for the first time that Cbf-K16 selectively inhibits the proliferation of lung carcinoma cells in vitro, with low toxicity to normal cells. The half-maximal inhibitory concentrations (IC50) of Cbf-K16 against H460 human non-small cell lung carcinoma cells and mouse Lewis lung cancer cells were only 16.5 and 10.5 microM, respectively, which were much less compared to that of BF-30 (45 and 40.3 microM). Data using a transmission electron microscope (TEM) assay showed that, at 20 and 40 microM, Cbf-K16 induced the rupture of the cytoplasmic membrane, which was consistent with data obtained from lactate dehydrogenase (LDH) release assays. The LDH release increased from 17.8 to 52.9% as the duration and dosage of Cbf-K16 increased. Annexin V-fluorescein and propidium iodide staining assays indicated that there were no obvious apoptotic effects at the different dosages and times tested. In H460 cells, the rate of genomic DNA binding increased from 51.9 to 86.8% as the concentration of Cbf-K16 increased from 5 to 10 microM. These data indicate that Cbf-K16 selectively inhibits the proliferation of lung carcinoma cells via cytoplasmic membrane permeabilization and DNA binding, rather than apoptosis. Although Cbf-K16 displayed significant cytotoxic activity (40 microM) against tumor cells, in splenocytes no significant inhibitory effect was observed and hemolysis was only 5.6%. These results suggest that Cbf-K16 is a low-toxicity anti-lung cancer drug candidate.

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Background: Currently, there are no standard cytotoxic treatments for non-small-cell lung cancer (NSCLC) patients beyond third-line therapy. The purpose of this study was to evaluate the efficacy of amrubicin monotherapy as a salvage treatment in heavily pretreated NSCLC patients. Methods: The records of NSCLC patients who received amrubicin monotherapy as a third or later line of chemotherapy at a Kitasato University Hospital between January 2009 and December 2012 were retrospectively reviewed. Amrubicin was administered to patients by intravenous injection at a dose of 35 or 40 mg/m² daily on 3 consecutive days, and cycles were repeated at 3-week intervals. Results: There were 36 patients who met the inclusion criteria. Their median number of prior chemotherapy treatments was 4 (range 2-7), and the median number of chemotherapy cycles per patient was 4 (range 1-9). Grade 3 or 4 hematologic toxicities included neutropenia (61.1%), leukopenia (58.3%), thrombocytopenia (22.2%) and anemia (11.1%). Febrile neutropenia occurred in 8 patients (22.2%). Nonhematologic toxicities were mild. The overall response rate, median progression-free survival time and median survival time were 8.3%, 1.7 months, and 6.3 months, respectively. Progression-free survival time was the same, i.e. 1.7 months in both groups i.e. the 35- and the 40-mg/m²-dose groups. Conclusion: Amrubicin exhibits modest activity and acceptable toxicity when used as a third or later line of chemotherapy for advanced NSCLC.

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TÍTULO / TITLE: - A rare occurrence of biphasic pulmonary blastoma in an elderly male.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Sharma A; O’Gorman K; Aman C; Rassl D; Mohamid W; Polychronis A

RESUMEN / SUMMARY: - Pulmonary Blastoma (PB) is a rare primary lung malignancy usually occurring in young to middle aged adults. Surgery is the primary mode of treatment, but survival is poor with the mean 5-year survival being approximately 16%. We report on a case of PB arising in a 63-year-old man. Computed tomography, magnetic resonance imaging and positron emission tomography confirmed the mass to be of pulmonary origin. The morphological appearance combined with the immunoprofile of the tumour was consistent with a poorly-differentiated biphasic
pulmonary blastoma. Two months after the surgical resection the patient relapsed with multiple sites of metastasis. The patient was treated with four cycles of cyclophosphamide-, doxorubicin- and vincristine-(CAV)-based chemotherapy, achieving a partial response to treatment. He is currently on a two-monthly review and is recovering from chemotherapy-related toxicities.
The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society grading system has limited prognostic significance in advanced resected pulmonary adenocarcinoma.

Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1097/PAT.0b013e32836532ae

AUTORES / AUTHORS: - Westaway DD; Toon CW; Farzin M; Sioson L; Watson N; Brady PW; Marshman D; Mathur MM; Gill AJ

INSTITUCIÓN / INSTITUTION: - *Sydney Medical School, Sydney daggerCancer Diagnosis and Pathology Research Group, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards double daggerHistoPath Pathology, North Ryde section signDepartments of Anatomical Pathology, and Cardiothoracic Surgery, Royal North Shore Hospital, St Leonards, New South Wales, Australia paragraph signthese two authors contributed equally.

RESUMEN / SUMMARY: - INTRODUCTION: The International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society (IASLC/ATS/ERS) system which subclassifies lung adenocarcinoma into five distinct types has been widely adopted. We assessed the prognostic value of subclassifying adenocarcinoma in this way in consecutive patients undergoing surgery. METHODS: All patients at our institution undergoing surgery for lung carcinoma between 2000 and 2010 were identified. The original pathology slides were independently reviewed and reclassified according to the 2011 IASLC/ATS/ERS grading and the American Joint Committee on Cancer (AJCC) 7 edition 2009 staging systems. RESULTS: We identified 270 patients including 152 with adenocarcinoma histology with long-term follow-up. Using the Kaplan-Meier method, the calculated 5 year survival for each of the adenocarcinoma categories were papillary-predominant 80%, lepidic-predominant 71%, micropapillary-predominant 55%, acinar-predominant 43%, solid-predominant 39% and invasive mucinous adenocarcinoma 38%. The AJCC stage was a very strong predictor of survival (p < 0.001). The IASLC/ATS/ERS subclassification of adenocarcinoma demonstrated a trend as a prognostic marker but failed to reach statistical significance in univariate or multivariate analysis. CONCLUSION: Although the IASLC/ATS/ERS classification has been validated by several studies in stage I tumours, further studies of larger cohorts will be required to show prognostic value in unselected lung carcinoma undergoing surgery with curative intent.
El objetivo de la hoja de ruta anatómica del Instituto Internacional para el Estudio del Cáncer de Pulmón (IASLC) es proporcionar descripciones anatómicas de las estaciones de ganglios linfáticos del tórax utilizadas para estadiar a los pacientes con cáncer de pulmón. La TC se utiliza en el estadiado clínico de pacientes con cáncer de pulmón. Es importante poder identificar correctamente y clasificar el adenopatía torácica presente en la TC, lo que permite la muestreando quirúrgica de las estaciones de ganglios linfáticos adecuadas para diagnosticar y estadiar el cáncer. Este artículo revisita la hoja de ruta anatómica del IASLC y muestra la apariencia de las estaciones de ganglios linfáticos del IASLC en la imagen de TC.

[435]

**Título / Title:** Histological evaluation of preoperative mediastinoscopy lymph node biopsies in non-small cell lung cancer.

**Resumen / Summary:** Enlace al Resumen / Link to its Summary


**Autores / Authors:** Dhaliwal CA; Andrews TD; Walker WS; Wallace WA

**Institución / Institution:** Department of Pathology, Royal Infirmary of Edinburgh, Edinburgh, UK.

**Resumen / Summary:** INTRODUCTION: A pesar del avance de la PET y las técnicas endoscópicas mínimamente invasivas para muestrear ganglios linfáticos mediastínicos, el examen quirúrgico, particularmente mediante mediastinoscopia, sigue siendo una herramienta importante para el estadiado del cáncer de pulmón no pequeñocelular. METHODS: Realizamos una revisión retrospectiva de las biopsias de ganglios linfáticos mediastínicos realizadas en el Royal Infirmary de Edimburgo entre 1996 y 2006, y realizamos investigaciones histológicas adicionales en selectos casos. RESULTS: En total, 89/802 (11%) pacientes tuvieron una mediastinoscopia negativa pero un estadiado final de N2/N3. En este grupo, 41/89 (46%) pacientes tenían ganglios linfáticos resecados positivos en estaciones potencialmente accesibles a la biopsia mediante mediastinoscopia. De estos, 30 (34%) pacientes habían tenido la estación metastásica muestreada mediante mediastinoscopia. Adicionalmente, la historioprófuturo examinación (niveles múltiples y pancitokeratin inmunohistoquímica) de estas biopsias originales detectó micrometástasis en dos casos, uno de los cuales, retrospectivamente, había sido pasado por alto en la sección original al momento de informar. Isolados tumores células fueron detectadas por inmunohistoquímica en otros dos casos. CONCLUSIONES: El examen rutinario
additional levels and immunohistochemical staining of mediastinal lymph nodes biopsies is not required and would not improve the overall negative predictive value of the procedure.

[436]

**TÍTULO / TITLE**: - Synaptic acetylcholinesterase targeted by microRNA-212 functions as a tumor suppressor in non-small cell lung cancer.

**RESUMEN / SUMMARY**: - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS**: - Lu L; Zhang X; Zhang B; Wu J; Zhang X

**INSTITUCIÓN / INSTITUTION**: - State Key Laboratory of Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China.

**RESUMEN / SUMMARY**: - Acetylcholinesterase expression is modulated in various types of tumor, which suggests it is associated with tumor development; however, the mechanism of acetylcholinesterase gene regulation in tumors remains unclear. Here, we report that acetylcholinesterase is aberrantly expressed in non-small cell lung cancer and is an evolutionarily conserved functional target of miR-212. Acetylcholinesterase expression was negatively regulated by miR-212 in vitro and was inversely correlated with miR-212 expression in vivo. In addition, acetylcholinesterase levels were increased, and miR-212 levels decreased, in non-small cell lung cancer cells during cisplatin-induced apoptosis. We further determined that acetylcholinesterase acted as a pro-apoptotic gene in non-small cell lung cells; and attenuated the growth of xenografts in nude mice when upregulated. In contrast, elevated miR-212 levels preserved the protective effect of acetylcholinesterase silencing by RNA interference against cisplatin-induced apoptosis, whereas restoration of miR-212-resistant synaptic acetylcholinesterase expression inhibited the miR-212 anti-apoptotic function. The results demonstrated that miR-212 exerted an anti-apoptotic effect through direct repression of synaptic acetylcholinesterase expression in non-small cell lung cancer cells. Taken together, our study revealed that synaptic acetylcholinesterase may be a tumor suppressor and is modulated by miR-212 in non-small cell lung cancer.

[437]


**RESUMEN / SUMMARY**: - [Enlace al Resumen / Link to its Summary](#)
OBJECTIONS: Comparative long-term survival and oncological outcomes for patients with non-small-cell lung cancer (NSCLC) who undergo video-assisted thoracic surgery (VATS) or conventional open lobectomy remain uncertain. We conducted a multi-institutional propensity-matched study to stratify potential differences in these outcomes. METHODS: We established a multi-institutional registry for 4312 patients with NSCLC who underwent lobectomy between 2001 and 2008 from eight institutions in the People’s Republic of China. Age, gender, histological type and tumour staging were entered into a non-parsimonious multivariable logistic regression model to assess long-term survival outcomes. The predicted probability derived from the logistic equation was used as the propensity score for each individual. Based on similar propensity scores, we matched 1458 of the 1700 patients who underwent VATS lobectomy with 1458 of the 2612 patients who underwent open lobectomy and compared their long-term survival outcomes. RESULTS: The mean age of the 2916 matched patients was 59 (standard deviation = 11) years. After propensity-matching, VATS and open lobectomy patients were similar in regards to important prognostic variables. Three prognostic factors were independently associated with improved survival in the multivariate analysis: age < 60 (P < 0.001), female gender (P = 0.013) and pathological staging (P < 0.001). Patients who underwent VATS vs open lobectomy had similar long-term survival (P = 0.07). CONCLUSIONS: The current propensity score analysis suggests that well-matched patients with NSCLC who underwent standardized VATS lobectomy had similar long-term survival outcomes when compared with those who underwent open lobectomy.
ILEI drives epithelial to mesenchymal transition and metastatic progression in the lung cancer cell line A549.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Song Q; Sheng W; Zhang X; Jiao S; Li F

INSTITUCIÓN / INSTITUTION: Department of Oncology, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing, 100853, China.

RESUMEN / SUMMARY: Transforming growth factor beta (TGF-beta) induces epithelial-mesenchymal transition (EMT) accompanied by cellular differentiation and migration. Despite extensive transcriptomic profiling, identification of TGF-beta-inducible, EMT-specific genes during metastatic progression of lung cancer remains elusive. Here, we functionally validate a previously described post-transcriptional pathway by which TGF-beta modulates expression of interleukin-like EMT inducer (ILEI), and EMT itself. We show that poly r©-binding protein 1 (PCBP1) binds ILEI transcript and repress its translation. TGF-beta activation leads to phosphorylation at serine-43 of PCBP1 by protein kinase Bbeta/Akt2, inducing its release from the ILEI transcript and translational activation. Modulation of hnRNP E1 expression modification altered TGF-beta-mediated reversal of translational silencing of ILEI transcripts and EMT. Furthermore, ILEI could induce, as well as maintain, CD24lowCD44high subpopulation in A549 cells treated with TGF-beta, which might explain its capability to induce metastatic progression. These results thus validate the existence of an evolutionary conserved TGF-beta-inducible post-transcriptional regulon that controls EMT and subsequent metastatic progression of lung cancer.

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Functional MUC4 suppress epithelial-mesenchymal transition in lung adenocarcinoma metastasis.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Gao L; Liu J; Zhang B; Zhang H; Wang D; Zhang T; Liu Y; Wang C

INSTITUCIÓN / INSTITUTION: Department of Lung Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, 300060, China, gaoliuwei198719@sina.com.

RESUMEN / SUMMARY: The mucin MUC4 is a high molecular weight membrane-bound transmembrane glycoprotein that is frequently detected in invasive and metastatic cancer. The overexpression of MUC4 is associated with increased risks for several types of cancer. However, the functional role of MUC4 is poorly understood in lung adenocarcinoma. Using antisense-MUC4-RNA transfected adenocarcinoma cells, we
discovered that the loss of MUC4 expression results in epithelial-mesenchymal transition (EMT). We found morphological alterations and the repression of the epithelial marker E-cadherin in transfected cells. Additionally, the loss of MUC4 caused the upregulation of the mesenchymal marker vimentin compared to control cells. Using a MUC4-knockdown versus control LTEP xenograft mice model (129/sv mice), we also found that EMT happened in lung tissues of MUC4-knockdown-LTEP xenograft mice. Moreover, antisense-MUC4-RNA transfected cells had a significantly increased cellular migration ability in vitro. The loss of MUC4 also occurred in lung adenocarcinoma patients with lymph node metastases. We further investigated MUC4 and found that it plays a critical role in regulating EMT by modulating beta-catenin. Taken together, our study reveals a novel role for MUC4 in suppressing EMT and suggests that the assessment of MUC4 may function as a prognostic biomarker and could be a potential therapeutic target for lung adenocarcinoma metastasis.

[441]

TÍTULO / TITLE: High cofillin-1 levels correlate with cisplatin resistance in lung adenocarcinomas.
RESUMEN / SUMMARY: High cofillin-1 levels have been shown to be an accurate prognostic biomarker in non-small cell lung cancer (NSCLC) and a predictive factor in drug resistance. Herein we explore the role of cofillin-1 in cis-diamminedichloroplatinum(II) (cisplatin) resistance. We evaluated cofillin-1 levels in intrinsically cisplatin-resistant A549 (ICR-A549) cells and determined the cisplatin toxicity in A549 cells transiently transfected and overexpressing CFL1 plasmid. Moreover, expression levels (activity) of the CFL1 gene network were analyzed in a cisplatin-resistant human lung adenocarcinoma cell panel. ICR-A549 cells, selected by challenging parental cells with 10-fold drug GI50 value, presented a sixfold increase in cisplatin GI50 value and an increased cofillin-1 immunocontent (P < 0.01). In addition, cells transfected with cofillin-1 became more resistant to cisplatin (P < 0.01). High activity of the CFL1 gene network was found in a cisplatin-resistant adenocarcinoma cell panel (P < 0.01). In vitro evidences suggest that cofillin-1 is a biological predictor of cisplatin resistance, supporting new treatment initiatives based on cofillin-1 levels to guide chemotherapeutic interventions in NSCLC patients.
**TÍTULO / TITLE:** Prognostic significance of serum microRNA-210 levels in nonsmall-cell lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Li ZH; Zhang H; Yang ZG; Wen GQ; Cui YB; Shao GG

**INSTITUCIÓN / INSTITUTION:** Department of Thoracic Surgery, The First Hospital, Jilin University, Changchun, Jilin Province, China.

**RESUMEN / SUMMARY:** OBJECTIVE: To investigate the levels of microRNA-210 (miR-210) in the serum of patients with nonsmall-cell lung cancer (NSCLC) and to determine whether there was a correlation with the prognosis of NSCLC patients following cisplatin-based chemotherapy. METHODS: Quantitative real-time reverse transcription-polymerase chain reaction was used to measure the serum levels of miR-210 in patients with NSCLC and healthy age-matched control subjects. Correlations between serum miR-210 levels and clinicopathological factors and prognosis were investigated. RESULTS: Serum miR-210 was significantly upregulated in 60 patients with NSCLC compared with 30 healthy control subjects. Higher serum miR-210 levels were significantly correlated with the clinical stage and the presence of regional lymph node metastasis in patients with NSCLC. Serum miR-210 levels in patients that achieved a partial response following cisplatin-based chemotherapy were significantly lower than in patients with stable or progressive disease, and were similar to those in healthy control subjects. CONCLUSIONS: These findings suggest that serum miR-210 levels might be a novel diagnostic and prognostic marker of NSCLC.

**TÍTULO / TITLE:** TTF-1 and napsin A do not differentiate metastatic lung adenocarcinomas from primary esophageal adenocarcinomas: proposal of a novel staining panel.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Aulakh KS; Chisholm CD; Smith DA; Speights VO

**INSTITUCIÓN / INSTITUTION:** Department of Pathology, Scott & White Healthcare, Temple, Texas, USA.
RESUMEN / SUMMARY: - CONTEXT: When adenocarcinomas arise within the esophagus, particularly when located away from the gastroesophageal junction, it may be important in some patients to differentiate between a primary esophageal adenocarcinoma and metastasis from another site. Lung adenocarcinoma is one tumor that has been reported to frequently metastasize to the esophagus. OBJECTIVES: To create a panel of immunohistochemical markers that can reliably distinguish between an esophageal and pulmonary primary; within the gastrointestinal pathology literature, including published articles and textbooks, common lung immunohistochemical markers, such as TTF-1, are assumed to be negative in esophageal adenocarcinoma, yet, to our knowledge, no study has yet investigated the veracity of that presumption. DESIGN: In this study, 24 cases each of pulmonary and esophageal adenocarcinomas were stained with TTF-1, napsin A, CDX2, 34betaE12, N-cadherin, and IMP3 in an attempt to define an optimal panel for differentiation. Esophageal adenocarcinomas occurring at the gastroesophageal junction were excluded in this study because a gastric primary tumor cannot be excluded in those cases. RESULTS: Surprisingly, TTF-1 and napsin A were positive in similar proportions of tumors from both sites. Those markers that differentiated statistically between esophageal and pulmonary adenocarcinoma were IMP3, CDX2, and N-cadherin. CONCLUSIONS: When differentiating the origin of a tumor as either esophageal or pulmonary, an immunohistochemical panel consisting of IMP3, CDX2, and N-cadherin is superior to either TTF-1 or napsin A.

[444]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kim MJ; Yun HS; Hong EH; Lee SJ; Baek JH; Lee CW; Yim JH; Kim JS; Park JK; Um HD; Hwang SG
INSTITUCIÓN / INSTITUTION: - Division of Radiation Cancer Biology, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea.
RESUMEN / SUMMARY: - Although end-binding protein 1 (EB1) is well known to regulate microtubule dynamics, the role of EB1 in apoptosis of non-small cell lung cancer (NSCLC) is poorly understood. Here, we investigated the molecular mechanism by which EB1 regulates apoptosis in H460, A549, and H1299 cells. Depletion of EB1 in A549 and H1299 cells, which express high levels of EB1, induced cell death in a p53-independent manner through over-production of reactive oxygen species (ROS) and Bax induction. This phenomenon was potentiated in radiation-treated EB1-knockdown cells and was largely blocked by N-acetyl-L-cysteine, a scavenger of ROS. ROS accelerated the activation of nuclear factor-kappa B (NF-kappaB) to promote
transcriptional activity of Bax, an action that was accompanied by cytochrome c translocation and apoptosis-inducing factor (AIF) release. The NF-kappaB inhibitor, BAY 11-7082, potently inhibited the apoptosis induced by EB1 knockdown and radiation treatment, in association with diminished activity of the mitochondrial death pathway. Conversely, ectopic overexpression of EB1 in H460 cells, which express low levels of EB1, remarkably abrogated radiation-induced apoptosis and NF-kappaB-mediated mitochondrial dysfunction. Our data provide the first demonstration that down-regulation of EB1 promotes NSCLC cell death by inducing ROS-mediated, NF-kappaB-dependent Bax signaling cascades, a process in which cytochrome c and AIF play important roles, indicating a potential therapeutic benefit of EB1 in lung cancer.

[445]

TÍTULO / TITLE: Systematic combination screening reveals synergism between rapamycin and sunitinib against human lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Li X; Tong LJ; Ding J; Meng LH
INSTITUCIÓN / INSTITUTION: Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China.
RESUMEN / SUMMARY: Mammalian target of rapamycin (mTOR) acts as a hub integrating signals from nutrient availability and growth factors and plays central roles in regulating protein synthesis and cell growth, which has been validated as a promising target for cancer therapy. Rapamycin and its analogues have emerged as the first generation of mTOR inhibitors, but their efficacy is modest in clinical settings. Combinatorial use of rapamycin with other drugs is a promising strategy to improve its anticancer activity. Here we developed an unbiased systematic binary screening platform aiming to discover new remedy for rapamycin-based cancer therapy. We found that sunitinib emerged as one of the clinically available anticancer drugs screened that displayed significant synergy with rapamycin in NSCLC cells. Combination of rapamycin with sunitinib resulted in enhanced cell cycle arrest in G1 phase, which was accompanied with enhanced suppression of mTOR signaling and disruption of the negative feedback loop that activate AKT upon mTORC1 inhibition. Furthermore, sunitinib and rapamycin displayed synergistic activity against tube formation by human microvessel endothelial cells as well as outgrowth of endothelial tubes and microvessels both in vitro and in vivo, which is associated with down-regulation of VEGF secretion and HIF1alpha expression. Our study demonstrated that new combinatorial regimen could be identified via systematic drug combination
screening and established a mechanistic rationale for a combination approach using rapalogs and sunitinib in the treatment of human NSCLC.

[446]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhao B; Han H; Chen J; Zhang Z; Li S; Fang F; Zheng Q; Ma Y; Zhang J; Wu N; Yang Y
INSTITUCIÓN / INSTITUTION: - Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital and Institute, Beijing 100142, People’s Republic of China.
RESUMEN / SUMMARY: - MicroRNAs play an important regulatory role in carcinogenesis and cancer metastasis. Different members of let-7 family have been reported to be decreased in human lung tumors. However, the effect of specific let-7 member on metastasis of NSCLC remains undefined. Our current study detected the expression of let-7 members in 94 cases of NSCLC and a significant association was noticed between low levels of let-7c expression and metastasis, venous invasion, advanced TNM stages and poor survival of NSCLC patients. Consistently, ectopic expression of let-7c in relatively highly metastatic cells remarkably suppressed their migration and invasion. Inhibition of let-7c in cells with relatively low metastatic potential promoted their motility and invasion. We then analyzed the potential targets of let-7c and found that ITGB3 and MAP4K3 were directly repressed by let-7c. Upon restoring the expression of ITGB3 and MAP4K3, the effects of let-7c on tumor metastasis were partially reversed, and more importantly, the expression levels of ITGB3 and MAP4K3 were inversely correlated with let-7c in 64 NSCLC tissues. Collectively, our results suggest that let-7c, by degrading ITGB3 and MAP4K3, prevents NSCLC metastasis.

[447]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Shin J; Lee J; Baek KH
RESUMEN / SUMMARY: - The incidence of most solid tumors is remarkably reduced in individuals with Down syndrome. Using mouse models of Down syndrome, we have previously shown that this decrease in tumor incidence is due in part to suppression of tumor angiogenesis as a consequence of attenuated calcineurin signaling in endothelial cells. Our prior studies utilized xenografted tumors in a transgenic mouse model with three copies of the Down syndrome critical region-1 (Dscr1) gene, a chromosome 21-encoded endogenous calcineurin inhibitor. These data indicate that upregulated Dscr1 contributes to broad cancer protection by suppressing tumor angiogenesis through inhibiting the calcineurin pathway in the vascular endothelium. However, it still remains to be confirmed whether a single extra copy of Dscr1 is also sufficient to suppress tumor angiogenesis in slow growing spontaneous tumors that more accurately recapitulate molecular features of human malignancies. In this study, utilizing LSL-KrasG12D mice, an inducible and autochthonous model of human lung adenocarcinoma, on a Dscr1 transgenic mouse background, we show that a single extra transgenic copy of Dscr1 provides a survival advantage in these mice developing spontaneous lung tumors driven by oncogenic KrasG12D without affecting either initiation or progression of spontaneous lung tumors. Furthermore, we show that Dscr1 trisomy significantly reduces microvessel density in lung tumors and thus limits the growth of lung tumors through decreased proliferation and increased apoptosis of lung tumor cells. These data provide evidence that a single extra copy of Dscr1 is sufficient to suppress tumor angiogenesis during spontaneous lung tumorigenesis and further support our hypothesis that suppression of tumor angiogenesis by an additional copy of Dscr1 contributes to the reduced cancer incidence in individuals with Down syndrome and the calcineurin pathway in the tumor vasculature is a potential target for cancer treatment.

Enlace al Resumen / Link to its Summary


van Reij EJ; Dahele M; van de Ven PM; de Haan PF; Verbakel WF; Smit EF; Slotman BJ; Senan S

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands.

Background. Concurrent chemo-radiotherapy (CON-CRT) is recommended for selected patients with stage III non-small cell lung cancer (NSCLC), but utilization varies. We assessed the response to national guidelines introduced in 2004 and the impact on outcomes. Material and methods. Retrospective study of stage III NSCLC patients treated with radical intent non-surgical treatment during 2003-2010 in a university medical center characterized by multidisciplinary assessment, routine use of four-dimensional computed tomography for radiotherapy planning, and rapid implementation of radiotherapy advances. Results. Between 2003 and 2010, 319/435 (73%) patients with stage III NSCLC received (chemo) radiotherapy. The number receiving CON-CRT in successive two-year periods increased from 13/48 (27%) - 40/80 (50%) - 63/90 (70%), to 74/101 (73%). Median overall survival (OS) from start of radiotherapy was 18.6 months for CON-CRT (190/319) and 17.4 months for sequential (SEQ), typically hypofractionated, CRT (90/319) (p = 0.78). Eleven months OS with radiotherapy alone (39/319) was significantly shorter (p = 0.006). OS did not differ between the four periods (p = 0.87). CON-CRT was not over-represented in the 16% of patients dying within five months of starting radiotherapy. Conclusions. Between 2003 and 2010, CON-CRT for stage III NSCLC was rapidly and safely increased. However, OS did not increase and, as practiced, did not differ between CON- or SEQ-CRT.

Reduced folate carrier (RFC) as a predictive marker for response to pemetrexed in advanced non-small cell lung cancer (NSCLC).

Enlace al Resumen / Link to its Summary


Alvarez-Fernandez C; Perez-Arnillas Q; Ruiz-Echeverria L; Rodriguez-Rubi D; Sanchez-Lorenzo L; Li-Torres W; Izquierdo-Manuel M; Berros JP; Luque-Cabal M; Jimenez-Fonseca P; Villanueva-Palicio N; Esteban-Gonzalez E

Enlace al texto completo (gratuito o de pago) 1007/s10637-013-9992-1
**RESUMEN / SUMMARY:** Introduction RFC is the major transport system in mammalian cells for folate cofactors and antifolate therapeutics. The aim of this study was to assess the predictive value of RFC expression in patients receiving pemetrexed for advanced NSCLC. Methods The study was carried out in a population of 48 patients with advanced NSCLC which have received pemetrexed monotherapy in second and third line. RFC expression was assessed using a two-step model of immunohistochemical staining in paraffin-embedded tissue samples. Results RFC expression was detected in 16 (33 %) patients. In the global population, the median progression free survival (PFS) and the median overall survival (OS) were 3.3 and 6.5 months respectively. The subgroup of patients with expression of RFC had a tendency to better median PFS (4.5 vs 2.8 months; p = 0.926) and median OS (11.7 vs 4.8; p = 0.150). In patients with adenocarcinoma histology and RFC expression median OS after treatment with pemetrexed was 14.4 months versus 5.0 in those with adenocarcinoma but without RFC expression (p = 0.039). Conclusions These results suggest the possible relation between RFC expression and response to treatment with antifolates (pemetrexed) independently of the tumor histology. Further studies are required to confirm these results.

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**TÍTULO / TITLE:** Small cell carcinoma of the head and neck: report of three cases.

**RESUMEN / SUMMARY:**


**AUTORES / AUTHORS:** Matsuyama H; Yamazaki K; Tomita M; Takahashi S

**INSTITUCIÓN / INSTITUTION:** Department of Otolaryngology, Faculty of Medicine, Niigata University, Japan.

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**TÍTULO / TITLE:** Second primary non-small-cell lung cancer: implications of the new adenocarcinoma classification in the challenging decision of the best surgical strategy.

**RESUMEN / SUMMARY:**


**AUTORES / AUTHORS:** Lococo F; Cesario A; Leuzzi G; Apolone G
Maine has among the highest rates of lung cancer in the United States (US). Maine serves as a geographical representation of US rural communities, and their associated health disparities. As the key risks of tobacco use decrease and radon abatement increases, previously obscured environmental exposures may measurably contribute to the attributable risk fraction of lung cancer. To generate hypotheses of novel environmental exposures associated with lung cancer, we investigated if there was non-random spatial distribution of lung cancer in Maine. Case data (n=14,038) between 1995 and 2006 were obtained from the Maine Cancer Registry. Population data were obtained from the 2000 US Census. We assessed the spatial distribution of lung cancers among white cases by histopathology subtype [non-small cell lung carcinoma (NSCLC): adenocarcinoma (n=3680), squamous cell (n=2801) and large cell (n=1195); and small cell lung carcinoma (SCLC) (n=1994)], using spatial scan statistic, assuming a discrete Poisson distribution adjusted for age and population density. Because of time-dependent trends in lung cancer differential diagnostic criteria, we repeated our analyses, limiting it to 2002-2006. While SCLC rates were equivalent across the state, we identified discrete regions with elevated rates of adenocarcinoma among females and squamous cell carcinoma among males. Independent of gender, the most striking geospatial observation was elevated large cell lung cancer specifically in one of the poorest counties in the US. A selective spatial distribution of large cell lung cancer has not been previously reported. More research is needed to identify factors inducing large cell carcinoma pathology, and to determine if in rural communities health disparities are associated with increased risk for this diagnosis.
Monitoring of exhaled carbon monoxide and carbon dioxide during lung cancer operation.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Khasag N; Sakiyama S; Toba H; Yoshida M; Nakagawa Y; Takizawa H; Kawakami Y; Kenzaki K; Ali AH; Kondo K; Tangoku A

INSTITUCIÓN / INSTITUTION: Department of Thoracic, Endocrine Surgery and Oncology, Institute of Health Bioscience, The University of Tokushima Graduate School, Tokushima, Japan.

RESUMEN / SUMMARY: OBJECTIVE: Carbon monoxide (CO) is expelled mainly via the lungs, so that exhaled carbon monoxide (Ex-CO) concentration reflects endogenous production. Recent reports have shown that Ex-CO levels are increased in critically ill patients and after anaesthesia and surgery. However, there has been no investigation of the changes in Ex-CO level during a lung operation. We continuously monitored Ex-CO and exhaled carbon dioxide (Ex-CO2) concentrations during surgery for lung cancer. METHODS: Eighteen lung cancer patients who underwent elective lung cancer lobectomy were enrolled in this study. All patients were endotracheally intubated and ventilated under general anaesthesia. Ex-CO and Ex-CO2 concentrations were separately monitored and recorded continuously using two sets of Carbolyzer® breath analysers (Taiyo Inc., Osaka, Japan). RESULTS: Ex-CO concentration increased rapidly in response to changes in body position from supine to decubitus and was significantly decreased when patients were once again lying back (supine 2). Upon restarting bilateral ventilation, Ex-CO concentration in the operated lung was significantly higher than that in the breathing lung. In the lateral decubitus position, Ex-CO2 concentration showed the same pattern of increase as seen for Ex-CO. In the operated lung, the Ex-CO2 concentrations changed significantly at clamping, declamping and supine 2. In the re-ventilated, operated lung, the Ex-CO2 concentration was significantly lower than in the breathing lung. In the breathing lung, the Ex-CO2 concentration did not exhibit any significant changes over the course of the operation. CONCLUSIONS: When breathing was restarted, the Ex-CO level of the target lung was significantly higher than that of the breathing lung. The Ex-CO concentration was also affected by the surgical body position and this change was marked and transient.

[455]

Localized Intrasplenic Mesothelioma: A Case Report.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Giansanti M; Bellezza G; Guerriero A; Pireddu A; Sidoni A
Malignant mesothelioma is a primary neoplasm of the serosal membranes that usually presents with a diffuse pattern of growth. However, cases of localized mesotheliomas have been described. The predominant localization is the pleura; peritoneum and pericardium being rarer localizations. Only few cases of true intraparenchymal mesothelioma arising in organs such as liver, gonads, lung, and pancreas have been described. We report a case of an otherwise healthy 48-year-old man without asbestos exposure with a nodule of 3 cm in diameter, localized in the spleen, discovered incidentally at the ultrasonographic examination, for which histopathological and immunohistochemical findings were consistent with epithelioid mesothelioma: large round cells with eosinophil dense cytoplasm and macronucleoli and with immunohistochemical positivity for pancytokeratins, calretinin, Wilms tumor-1, and others markers of mesothelial differentiation. The diagnosis of localized intrasplenic epithelioid malignant mesothelioma was carried out. To the best of our knowledge, this is the first case of a localized intrasplenic mesothelioma published in the indexed literature.

[456]

**TÍTULO / TITLE:** - Lung cancer biomarkers: present status and future developments.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 5858/arpa.2013-0319-CR

**AUTORES / AUTHORS:** - Cagle PT; Olsen RJ

**INSTITUCIÓN / INSTITUTION:** - From the Department of Pathology and Genomic Medicine, The Methodist Hospital, Houston, Texas, and the Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, New York (Drs Cagle and Olsen); and.

**RESUMEN / SUMMARY:** - The publication of the “Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology” has now provided a guideline for biomarker testing for first-generation lung cancer tyrosine kinase inhibitors. Biomarker testing has forever altered the role of pathologists in the management of patients with lung cancer. Current, unresolved issues in the precision medicine of lung cancer will be addressed by the development of new biomarker tests, new drugs, and new test technologies and by improvement in the cost to benefit ratio of biomarker testing.

[457]
Downregulation of miR-145 contributes to lung adenocarcinoma cell growth to form brain metastases.

The development of metastases involves the dissociation of cells from the primary tumor, penetrating the basement membrane, invasion and exiting from the vasculature to seed, and finally colonizing in distant tissues. The formation of brain metastasis (BM) in lung adenocarcinoma remains poorly understood. We examined the differential microRNA (miRNA) expression profiles of 5 primary and 3 brain metastatic lung adenocarcinoma samples by Agilent miRNA Microarrays. Five upregulated miRNAs (miRs-9*, -1471, 718, 3656, 720) and 3 downregulated miRNAs (miRs-214, -145 and -23*) were detected. The 4 most significantly deregulated miRNAs (miR-145, miR-214, miR-9* and miR-1471) were validated in the additional 43 samples (35 primary and 8 brain metastatic lung adenocarcinoma samples) using TaqMan quantitative PCR. By functional assay, we found that the expression of miR-145 can regulate the ability of proliferation of A549 and SPC-A1 cells in vitro, but is not related to lymph node metastasis, migration and invasion. These results suggest that miR-145 may have a cell type-specific function and play important roles in the process of BM from lung adenocarcinoma.

Investigating strategies to reduce toxicity in stereotactic ablative radiotherapy for central lung tumors.

Background. Stereotactic radiotherapy for central lung tumors has a narrower therapeutic index than that for peripheral tumors. Tumor tracking strategies have been proposed to reduce treatment volumes and toxicity, however they need to consider uncertainties in tumor size and shape change throughout respiration to ensure optimal local control. We quantified these uncertainties and explored strategies to account for them. Material and methods. Ten patients with
central tumors, PTV > 100 cm³, motion > 5 mm and a 10-phase 4DCT without significant artifact in the tumor region were evaluated. Uncertainties were quantified using GTV size in different phases, and the Hausdorff distance (HD) between the phase 50% GTV and other phases after soft-tissue rigid registration. An individualized internal target volume for tracking (ITVT) was generated from the union of the GTVs in all phases after rigid registration. This was compared to ITVs generated for tracking based on the phase 50% GTV alone or with isotropic margins of 3 or 5 mm for size and volume overlap. Results. Median free-breathing PTV size and motion were 162.1 cm³ (110-210) and 8.9 mm (6.1-14.1). Overall, median GTV size variation and HD were 4.7% (0.2-22.3) and 6.3 mm (3.9-17.6). Tracking using GTV 50% alone resulted in median volume overlap with ITVT of 71.7% (range 56.8-85.1). Isotropic margins of 3 or 5 mm always resulted in a volume overlap less than 95% or a volume larger than the ITVT. Conclusions. Changes in size and shape of central lung tumors are substantial during respiration. These limit the ability to reduce treatment volumes with tracking, especially if isotropic margins are used. An individualized ITV for tracking, such as the ITVT is preferred.

[459]
TÍTULO / TITLE: - The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Iyer S; Roughley A; Rider A; Taylor-Stokes G
RESUMEN / SUMMARY: - PURPOSE: Disease symptom management in patients with advanced non-small cell lung cancer (NSCLC) is a critical aspect of therapy. The main objective of our study was to assess patient-reported outcomes and the degree of concordance between physician and patient perceptions of symptom severity in advanced NSCLC in the USA. METHODS: Patients with advanced (stage IIIB/IV) NSCLC (N = 450) were recruited in a nationwide (USA) lung cancer study. Patients and their oncologists completed patient and physician versions of the Lung Cancer Symptom Scale (LCSS). Patient-reported lung cancer-specific quality of life was assessed with the Functional Assessment of Cancer Therapy-Lung (FACT-L). Concordance was assessed using the kappa-statistic. Regression analysis was performed with FACT-L total score as the dependent variable and patient-reported LCSS symptom scores as predictors. RESULTS: A high proportion of patients experienced lung cancer symptoms: fatigue (100 %), loss of appetite (97 %), shortness of breath (95 %), cough (93 %), pain (92 %), and blood in sputum (63 %). Concordance between physician and patients was lowest
for loss of appetite (kappa 0.1701) and greatest for hemoptysis (kappa 0.4586). Loss of appetite (beta = -0.204; p < 0.001), cough (beta = -0.145; p < 0.01), pain (beta = -0.265; p < 0.001), and shortness of breath (beta = -0.145; p < 0.01) were found to be significant predictors of the quality of life. CONCLUSIONS: Symptom burden in patients with advanced NSCLC is high and has a negative impact on the quality of life. Patient-reported outcomes data could help optimize disease outcomes and therapy management in NSCLC.

[460]
TÍTULO / TITLE: - Intrapleural hyperthermic perfusion using distilled water at 48 degrees C for malignant pleural effusion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ba M; Long H; Wang Y; Tang Y; Wu Y; Zhang X; Cui S
INSTITUCIÓN / INSTITUTION: - Intracelom Hyperthermic Perfusion Therapy Center, Cancer Hospital of Guangzhou Medical College, Guangzhou, 510095, China, bamingchen2011@126.com.
RESUMEN / SUMMARY: - BACKGROUND: To evaluate the feasibility, safety and preliminary efficacy of B-ultrasound-guided continuous circulatory intrapleural hyperthermic perfusion (IHP) with distilled water (DW) at 48 degrees C, for the treatment of malignant pleural effusion (MPE). METHODS: Prospective, randomized interventional study in China (from December 2008 to December 2011) in adults with MPE originating from disseminated pleural tumor. Exclusion criteria: thoracotomy or surgical resection, limited encapsulated pleural effusion or extensive pleural adhesions. Patients were randomly divided into DW (12 patients; B-ultrasound-guided IHP with 48 degrees C DW) and PSS-C (11 patients; B-ultrasound-guided IHP with 45 degrees C physiological saline solution and cisplatin) groups. Patients were followed up for assessment of objective MPE remission rate, Karnofsky performance scale (KPS) scores and survival duration. RESULTS: Pleural effusion was controlled in 100 % of patients, and mean KPS score was increased by 40 % after therapy. Patients’ median survival times in the DW and PSS-C groups were 13.0 and 12.9 months, respectively. No serious clinical complications were observed. There were no significant differences between groups in the total objective MPE remission rate, mean KPS score change or median survival time, demonstrating the achievement of significant clinical efficacy with our modified IHP. CONCLUSION: Intrapleural hyperthermic perfusion with 48 degrees C DW is feasible, easy to perform and relatively safe. This method may offer excellent local control for patients with MPE secondary to disseminated pleural lesions.
We report a case of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). We performed immunohistochemical analysis of 17 neuropeptides and human gonadotropin-alpha (hCGalpha), a trophoblastic peptide that promotes the proliferation of neuroendocrine cells. A 51-year-old woman with no history of smoking was found to have a nodule in the right middle lobe. Upon examination, the nodule was found to comprise diffuse linear and nodular neuroendocrine cell hyperplasia (NECH), numerous pulmonary tumorlets merging with one peripheral carcinoid, and an additional central carcinoid. Immunohistochemical analysis revealed diffuse but intense expression of the general neuroendocrine markers CD56, synaptophysin, and chromogranin A, together with gastrin-releasing peptide (GRP), calcitonin, and hCGalpha throughout the carcinoids, tumorlets, and NECH. Positive staining was also noted for adrenocorticotropic hormone, corticotropin-releasing hormone, met-enkephalin, vasoactive intestinal polypeptide, neurotensin, and growth hormone-releasing hormone in a few isolated cells of the carcinoids and the tumorlets, but staining for these proteins was entirely negative in the NECH lesions. The presence of these neuropeptides in neuroendocrine tumors might explain the presence of neuropeptide-producing tumors of the lungs, cases of which have been reported over the last 30 years. The preoperative serum proGRP level was high but returned to normal after surgical intervention, indicating that GRP was produced and secreted by carcinoids, tumorlets, and/or NECH lesions. It is also probable that neuroendocrine cells secreted GRP into the interstitium in a paracrine manner, leading to the development of dense fibrosis around the tumorlets. During the preoperative and postoperative periods, no evidence of bronchiolitis obliterans was noted, in contrast to some previously reported cases of DIPNECH.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   - Enlace al texto completo (gratuito o de pago) 1053/j.ro.2013.05.001
AUTORES / AUTHORS: - Rakheja R; Ko JP; Friedman K
INSTITUCIÓN / INSTITUTION: - Division of Nuclear Medicine, New York University Langone Medical Center, New York, NY.

[463]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   - Enlace al texto completo (gratuito o de pago) 1002/jso.23391
AUTORES / AUTHORS: - Midthun DE; Jett JR
INSTITUCIÓN / INSTITUTION: - Mayo Clinic, Rochester, Minnesota.
RESUMEN / SUMMARY: - Efforts in lung cancer screening with chest X-ray (CXR) and sputum cytology in the 1970s and 1980s were negative. In the ensuing decade, the early lung cancer action project (ELCAP), and the Mayo screening study showed the promise of low-dose CT. These and other studies led to the National lung screening study (NLST), which showed definitively that low-dose spiral computed tomography had a measurable impact on mortality and could be justified as a tool for lung cancer screening. This review examines the results of past and recent studies of lung cancer screening. J. Surg. Oncol. 2013 108:275-279. © 2013 Wiley Periodicals, Inc.

[464]

TÍTULO / TITLE: - Left main bronchial obstruction caused by a mediastinal bronchogenic cyst.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   - Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt456
AUTORES / AUTHORS: - Suh JH; Park CB; Kim CK; Yoon JS
INSTITUCIÓN / INSTITUTION: - Department of Thoracic and Cardiovascular Surgery, Incheon St Mary’s Hospital, The Catholic University of Korea, Incheon, Republic of Korea.

[465]
- The association between red cell distribution width and non-small-cell lung cancer.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** Balta S; Arslan Z; Unlu M; Demirkol S

**INSTITUCIÓN / INSTITUTION:** Department of Cardiology, Gulhane Medical Academy, Ankara, Turkey.

Minimizing over-diagnosis in lung cancer screening.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** Grannis FW Jr

**INSTITUCIÓN / INSTITUTION:** Thoracic Surgery Section, City of Hope National Medical Center, Duarte, California.

Overestimation of the frequency and impact of over-diagnosis bias in lung cancer screening has contributed to long delays in implementation of lung cancer screening programs. Literature review reveals little evidence of substantial numbers of over-diagnosed non-lethal lung cancer. There is now strong evidence that lung cancers that would not cause symptoms or kill during normal anticipated survival are uncommon and mostly limited to in situ adenocarcinomas, identifiable as CT non-solid nodules. Prevention of overtreatment is possible within well-constructed diagnostic algorithms.

FDG-PET/CT IMAGING FOR ADRENAL MASSES IN PATIENTS WITH LUNG CANCER: REVIEW AND DIAGNOSTIC ALGORITHM.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** Stone WZ; Wymer D; Canales BK

**INSTITUCIÓN / INSTITUTION:** University of Florida, Urology, Gainesville, Florida, United States; wzstone@ufl.edu.

Background and Purpose: Positron-emission tomography/computed tomography (PET/CT) with fluorine-18 fluorodeoxyglucose (FDG) is used as first-line staging for patients with newly diagnosed non-small cell lung
cancer (NSCLC). Our purpose was to review the accuracy of FDG-PET/CT to predict adrenal gland metastasis, explain the causes for false positive PET, and provide a diagnostic algorithm. Patients and Methods: Two patients with incidentally discovered lung masses were found to have hypermetabolic adrenal activity by FDG-PET/CT with maximal standard uptake value (SUV) of 4.5 and 6.5. A MEDLINE search was performed on the topic of FDG-PET/CT, adrenal gland metastasis, and NSCLC. Literature was reviewed with regard to diagnosis, accuracy, outcomes, and alternative imaging or diagnostic strategies. Results: Both patients underwent transabdominal laparoscopic adrenalectomy and were found to have nodular hyperplasia without evidence of adrenal tumor. A total of 7 articles containing 366 patients were identified as containing pertinent oncologic information for NSCLC patients with adrenal lesions. Sensitivity and specificity of PET/CT for distant metastasis was 94% and 85% respectively but only 12% (44/366) of these patients had histologically confirmed adrenal diagnoses. Based on this, a diagnostic algorithm was created to aid in decision-making. Conclusions: Although PET/CT has high sensitivity and specificity for adrenal metastasis in the setting of NSCLC, adrenal biopsy or other secondary imaging should be considered to confirm the finding. Adrenalectomy in lieu of biopsy may have both diagnostic and therapeutic benefit in cases where the adrenal mass is \( \geq 10 \) mm in size with high PET maximum SUV (\( \geq 3.1 \)) and SUV ratios (\( > 2.5 \)), where washout CT or chemical shift MRI is positive, or where percutaneous biopsy is deemed too difficult or unsafe.

[468]

**TÍTULO / TITLE:** Antitumor Activity of Elacytarabine Combined with Bevacizumab, Cetuximab and Trastuzumab in Human NSCLC Xenografts.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Anticancer Res. 2013 Sep;33(9):3615-21.

**AUTORES / AUTHORS:** Bruheim S; Sandvold ML; Maelandsmo GM; Fodstad O

**INSTITUCIÓN / INSTITUTION:** Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Montebello, N-0310 Oslo, Norway. Skjalg.Bruheim@rr-research.no.

**RESUMEN / SUMMARY:** Aim: The objective of the present study was to determine the in vivo antitumor activity of elacytarabine, the 5′-elaidic acid ester of arabinofuranosyl cytidine, alone and in combination with bevacizumab, cetuximab and trastuzumab in Vascular endothelial growth factor (VEGF), Epidermal growth factor receptor (EGFR)- and Human epidermal growth factor receptor 2 (HER2)-expressing non-small cell lung cancer xenografts. MATERIALS AND METHODS: The antitumor activity of elacytarabine, was tested at the maximal tolerable dose (MTD; 50 mg/kg) and half MTD (25 mg/kg), alone and in combination with the antibodies bevacizumab (5 mg/kg), cetuximab (20 mg/kg) and trastuzumab (4 mg/kg) in two human non-small cell lung cancer
xenografts. RESULTS: Elacytarabine exhibited very high activity in the EKVX xenograft at both dose levels, but was inactive in MAKSAE. Neither of the two xenografts were sensitive to bevacizumab or trastuzumab, but the MAKSAE xenograft showed intermediate response to cetuximab. The high sensitivity of EKVX to elacytarabine precluded the assessment of a potential benefit of the combinations with the antibodies. In the elacytarabine-, bevacizumab- and trastuzumab-insensitive MAKSAE xenograft, the combination of either bevacizumab or trastuzumab with elacytarabine at the MTD or half MTD resulted in intermediate activity, suggesting a beneficial effect of the combinations, whereas for cetuximab, the effect was enhanced when combined with elacytarabine given at the MTD, but not half-MTD. CONCLUSION: The results suggest that elacytarabine could be active in some cases of non-small cell lung cancer, and that the combination of elacytarabine and tyrosine kinase inhibitors may exert important additive or possibly synergistic effects of potential clinical benefit.

[469]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Harders SW; Madsen HH; Nellemann HM; Rasmussen TR; Thygesen J; Hager H; Andersen NT; Rasmussen F
INSTITUCIÓN / INSTITUTION: - Aarhus University Hospital Resident Radiologist Department of Radiology Noerrebrogade 44, bld. 6 DENMARK Aarhus DK 8000 (45) 7845 4478 Aarhus University Hospital.

[470]
TÍTULO / TITLE: - High T790M Detection Rate in TKI-Naive NSCLC with EGFR Sensitive Mutation: Truth or Artifact?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ye X; Zhu ZZ; Zhong L; Lu Y; Sun Y; Yin X; Yang Z; Zhu G; Ji Q
INSTITUCIÓN / INSTITUTION: - *Innovation Center China of AstraZeneca Research & Development, Shanghai, China; daggerDepartment of Oncology, No. 113 Hospital of People’s Liberation Army, Ningbo, China; and double daggerDepartment of Thoracic Surgery, Changzheng Hospital, Shanghai, China.
The lignan arctigenin (ARG) from the herb Arctium lappa L. possesses anti-cancer activity, however the mechanism of action of ARG has been found to vary among tissues and types of cancer cells. The current study aims to gain insight into the ARG mediated mechanism of action involved in inhibiting proliferation and inducing apoptosis in lung adenocarcinoma cells. This study also delineates the cancer cell specificity of ARG by comparison with its effects on various normal cell lines. ARG selectively arrested the proliferation of cancer cells at the G0/G1 phase through the down-regulation of NPAT protein expression. This down-regulation occurred via the suppression of either cyclin E/CDK2 or cyclin H/CDK7, while apoptosis was induced through the modulation of the Akt-1-related signaling pathway. Furthermore, a GSH synthase inhibitor specifically enhanced the cytotoxicity of ARG against cancer cells, suggesting that the intracellular GSH content was another factor influencing the susceptibility of cancer cells to ARG. These findings suggest that specific cytotoxicity of ARG against lung cancer cells was explained by its selective modulation of the expression of NPAT, which is involved in histone biosynthesis. The cytotoxicity of ARG appeared to be dependent on the intracellular GSH level.

The role of PTPN13 in invasion and metastasis of lung squamous cell carcinoma.

ARG selectively arrested the proliferation of cancer cells at the G0/G1 phase through the down-regulation of NPAT protein expression. This down-regulation occurred via the suppression of either cyclin E/CDK2 or cyclin H/CDK7, while apoptosis was induced through the modulation of the Akt-1-related signaling pathway. Furthermore, a GSH synthase inhibitor specifically enhanced the cytotoxicity of ARG against cancer cells, suggesting that the intracellular GSH content was another factor influencing the susceptibility of cancer cells to ARG. These findings suggest that specific cytotoxicity of ARG against lung cancer cells was explained by its selective modulation of the expression of NPAT, which is involved in histone biosynthesis. The cytotoxicity of ARG appeared to be dependent on the intracellular GSH level.
INSTITUCIÓN / INSTITUTION: - The Helmholtz Sino-German Research Laboratory for Cancer, Department of Pathology, Tangdu Hospital, Fourth Military Medical University, Xi’an, People’s Republic of China.

RESUMEN / SUMMARY: - OBJECTIVES: PTPN13 is a new candidate tumor-suppressing gene. To investigate the PTPN13 expression and its potential function in the invasion and metastasis of lung squamous cell carcinoma (LSCC), we performed this study in 91 primary LSCC tissues and the adjacent non-cancerous tissues. METHODS: The mRNA expression of PTPN13 and FAK was quantitated by reverse transcription polymerase chain reaction. The protein expression of PTPN13, focal adhesion kinase (FAK) and phosphorylated FAK (P-FAK) was evaluated using immunohistochemical staining and western blotting. The association among PTPN13 expression, FAK expression and the clinicopathological parameters were analyzed. RESULTS: PTPN13 expression was down-regulated in LSCC, and was negatively correlated with the cancer grade and stage. FAK mRNA, as well as FAK protein level was elevated in LSCC tissues. P-FAK level, also found increased, had no association with FAK mRNA and FAK protein expression, but had a negative correlation with the PTPN13 expression. P-FAK level had a significant positive correlation with the TNM classification. CONCLUSION: The over-expression of FAK and increased FAK phosphorylation plays an important role in the invasion and metastasis of LSCC. PTPN13 may function as an antioncogene via inhibiting the phosphorylation of FAK.

[473]
TÍTULO / TITLE: - CT Screening for Lung Cancer: Filling in the Gaps.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Boiselle PM

[474]
TÍTULO / TITLE: - Thin-section CT findings in peripheral lung cancer of 3 cm or smaller: are there any characteristic features for predicting tumor histology or do they depend only on tumor size?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Jiang B; Takashima S; Miyake C; Hakucho T; Takahashi Y; Morimoto D; Numasaki H; Nakanishi K; Tomita Y; Higashiyama M
INSTITUCIÓN / INSTITUTION: - Department of Diagnostic Radiological Imaging, Division of Allied Health Sciences, Osaka University Graduate School of Medicine, Osaka, Japan.
BACKGROUND: Ground-glass opacity (GGO) is reported to be characteristic to lepidic growth of neoplasm in subsolid nodules. In solid nodules of lung cancer, however, there is no characteristic feature to be reported. PURPOSE: To study if there are any thin-section CT findings characteristic to tumor histology or if they are only related to tumor size in solid nodules of the lung cancer. MATERIAL AND METHODS: This study included 106 solid peripheral lung cancers of 3 cm or smaller (56 adenocarcinomas, 33 squamous cell carcinomas, and 17 small cell carcinomas) in which 16-slice CT with 1 mm collimation was performed before surgery. Six morphologic findings (presence or absence of lobulation, coarse spiculation, air bronchogram, cavity, pleural tag, and pleural-based lesion) and four measurements (ratio of the greatest transverse and vertical diameter to the shortest transverse diameter and density of lobulation and coarse spiculation) on thin-section CT images were evaluated. Density of lobulation (coarse spiculation) was defined as the ratio of lobulation (coarse spiculation) number to the greatest transverse diameter of a nodule. RESULTS: Air bronchogram (P < 0.01) was the only significant factor for predicting lung adenocarcinoma. The prevalence of air bronchogram was significantly greater in adenocarcinoma than in squamous cell carcinoma (P < 0.01) or small cell carcinoma (P < 0.01). As the tumor size advanced, significantly positive linear trends were seen in the prevalence of lobulation (P < 0.01), coarse spiculation (P < 0.01), and pleural tag (P < 0.01), and the mean values of density of lobulation (P < 0.01) and coarse spiculation (P < 0.01), while the significant negative linear trend was seen in the ratio of vertical diameter to the shortest transverse (P = 0.02). CONCLUSION: Air bronchogram on thin-section CT is characteristic feature of solid adenocarcinoma of the lung. However, other thin-section CT findings are irrelevant to tumor histology and related only to tumor size.
changes during intensity-modulated radiotherapy (IMRT) of patients with NSCLC.

Material and methods. Sixteen NSCLC patients received IMRT with concomitant chemotherapy. The tumor and lymph node targets were delineated in the mid-ventilation phase of a planning 4DCT scan (CT1). Typically 66 Gy was delivered in 33 fractions using daily CBCT with bony anatomy match for patient setup. The daily baseline shifts of the mean tumor position relative to the spine were extracted from the CBCT scans. A second 4DCT scan (CT2) was acquired halfway through the treatment course and the respiratory tumor motion was extracted. The plan was recalculated on CT2 with and without inclusion of the respiratory tumor motion and baseline shifts in order to investigate the impact of tumor motion and anatomical changes on the tumor dose. Results. Respiratory tumor motion was largest in the cranio-caudal (CC) direction (range 0-13.1 mm). Tumor baseline shifts up to 18 mm (CC direction) and 24 mm (left-right and anterior-posterior) were observed. The average absolute difference in CT mean dose to the primary tumor (CTV-t) between CT1 and CT2 was 1.28% (range 0.1-4.0%) without motion. Respiratory motion and baseline shifts lead to average absolute CTV-t mean dose changes of 0.46% (0-1.9%) and 0.65% (0.0-2.1%), respectively. For most patients, the changes in the CTV-t dose were caused by anatomical changes rather than internal target motion. Conclusion. Anatomical changes had larger impact on the target dose distribution than internal target motion. Adaptive radiotherapy could be used to achieve better target coverage throughout the treatment course.

[476]

TÍTULO / TITLE: Detecting lung cancer relapse using self-evaluation forms weekly filled at home: the sentinel follow-up.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Denis F; Viger L; Charron A; Voog E; Letellier C

INSTITUCIÓN / INSTITUTION: Jean Bernard Center/Victor Hugo Clinic, 9 rue Beauverger, Le Mans, France, f.denis@cjb72.org.

RESUMEN / SUMMARY: PURPOSE: We aimed to assess if patients’ ratings of symptoms can be used to provide an early indication of disease recurrence or progression in lung cancer. We proposed a simple self-evaluation form made of six clinical parameters weekly scored by patients at home as a follow-up here named sentinel-to improve relapse detection. Its performances were compared to those of a routine imaging follow-up. METHODS: Patients with lung cancer were prospectively recruited to weekly fill a form at home for self-assessing weight, fatigue, pain, appetite, cough, and breathlessness during at least 4 months. Each patient reported weight and assessed the severity of each symptom by grading it from 0 (no symptom) to 3 (major
symptom). A score was retrospectively designed for discriminating patients with relapse from those without. Accuracy of relapse detection was then compared to values of the routine planned imaging. RESULTS: Forty-three patients were included in our center and recruited for 16 weeks or more follow-up during which at least one tumor imaging assessment was performed (CT scan or PET-CT). Forty-one completed the form weekly. Sensitivity, specificity, and positive and negative predictive values of sentinel were high (86, 93, 86 % and 93 vs 79, 96, 92, and 90 % for routine imaging-p = ns) and well correlated with relapse (p<0.001). Moreover, relapses were detectable with sentinel on average 6 weeks earlier than the planned imaging. CONCLUSION: This study suggests that a personalized cancer follow-up based on a weekly self-evaluation of six symptoms is feasible and may be accurate for earlier detection of lung cancer relapse, allowing integration in electronic devices for real-time patient outcome follow-up.

[477]
TÍTULO / TITLE: - Effects of Epigallocatechin-3-gallate (EGCG) on A549 Lung Cancer Tumor Growth and Angiogenesis.
RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary]
AUTORES / AUTHORS: - Sakamoto Y; Terashita N; Muraguchi T; Fukusato T; Kubota S
INSTITUCIÓN / INSTITUTION: - Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo.
RESUMEN / SUMMARY: - Epigallocatechin 3-gallate (EGCG) has cytotoxic effects in many cancer cells. It has been reported that A549 lung cancer cells are markedly resistant to cell death induced by EGCG. In the present study, the effects of EGCG on A549 lung cancer cell growth and angiogenesis were studied. We found that EGCG dose-dependently suppressed A549 cell growth, while A549 cells were markedly resistant to cell death in vitro. Next we found that EGCG increased endostatin expression and suppressed vascular endothelial growth factor (VEGF) expression. We further studied to determine whether EGCG would suppress A549 tumor growth in nude mouse and angiogenesis. EGCG in drinking water significantly suppressed A549 tumor growth in nude mice. Histological analysis revealed that the number of CD34 positive vessels had a tendency to decrease in the tumor. In sum, EGCG had anti-proliferative effects of A549 on tumor growth and showed a tendency to suppress angiogenesis.

[478]
TÍTULO / TITLE: - The role of genotoxicity in asbestos-induced mesothelioma: an explanation for the differences in carcinogenic potential among fiber types.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Barlow CA; Lievense L; Gross S; Ronk CJ; Paustenbach DJ

INSTITUCIÓN / INSTITUTION: - Cardno ChemRisk, Boulder, CO 80301, USA. christy.barlow@cardno.com

RESUMEN / SUMMARY: - The mechanism(s) underlying asbestos toxicity associated with the pathogenesis of mesothelioma has been a challenge to unravel for more than 60 years. A significant amount of research has focused on the characteristics of different fiber types and their potential to induce mesothelioma. These mechanistic studies of fiber toxicity have proceeded along two lines: those demonstrating biochemical mechanisms by which fibers induce disease and those investigating human susceptibility. Most recent studies focused on in vitro genotoxic effects induced by asbestos as the mechanism responsible for asbestos-induced disease. Although asbestos exerts a genotoxic effect at certain concentrations in vitro, a positive response in these tests does not indicate that the chemical is likely to produce an increased risk of carcinogenesis in exposed human populations. Thus far, findings from studies on the effects of fiber type in mesothelial cells are seriously flawed by a lack of a dose response relationship. The common limitation of these in vitro experiments is the lack of attention paid to the complexities of the human anatomy, biochemistry and physiology, which make the observed effects in these experimental systems difficult to extrapolate to persons in the workplace. Mechanistic differences between carcinogenic and genotoxic processes indicate why tests for genotoxicity do not provide much insight regarding the ability to predict carcinogenic potential in workers exposed to asbestos doses in the post-Occupational Safety and Health Administration era. This review discusses the existing literature on asbestos-induced genotoxicity and explains why these studies may or may not likely help characterize the dose-response curve at low dose.

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[479]

TÍTULO / TITLE: - Hyperamylasemia and dual paraneoplastic syndromes in small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Akinosoglou K; Siagris D; Geropoulou E; Kosmopoulou O; Velissaris D; Kyriazopoulou V; Gogos C

INSTITUCIÓN / INSTITUTION: - Division of Internal Medicine, University General Hospital of Patras, Patras, Greece.
RESUMEN / SUMMARY: - We hereby describe the rare case of a 59-year-old patient presenting with marked hyperamylasemia mimicking acute pancreatitis upon admission. Investigation of co-existent hypokalemia revealed the presence of ectopic adrenocorticotropic hormone secretion, leading to the final diagnosis of small cell lung cancer, exhibiting dual paraneoplastic syndromes including Cushing Syndrome and hyperamylasemia. Although, paraneoplastic syndromes occur commonly, paraneoplastic hyperamylasemia especially in the context of dual paraneoplastic syndromes occurring simultaneously, is extremely rare. Such misleading manifestations require a high index of suspicion on behalf of the physician, so that an underlying malignancy is not missed, and a final diagnosis combining all clinical and laboratory findings is reached. In turn, in rare cases common biochemical markers such as amylase can be used as a useful follow up index driving further management.

TÍTULO / TITLE: - Arsenic Trioxide Co-exposure Potentiates Benzo(a)pyrene Genotoxicity by Enhancing the Oxidative Stress in Human Lung Adenocarcinoma Cell.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Chen C; Jiang X; Ren Y; Zhang Z

INSTITUCIÓN / INSTITUTION: - Department of Environmental Health, West China School of Public Health, Sichuan University, No. 16, Section 3, Renmin Nan Road, Chengdu, 610041, People’s Republic of China.

RESUMEN / SUMMARY: - Although both arsenic trioxide (As2O3) and benzo(a)pyrene (BaP) are well-established human carcinogens, the interaction between As2O3 and BaP is synergistic or antagonistic remains controversial in terms of the existing studies. In addition, the mechanisms responsible for the combined effects are still unclear. In this study, we examined the potential interactive effects between As2O3 (1, 5, and 10 μM) and BaP (5, 10, and 20 μM) in cultured A549 cells by treating with BaP and As2O3 alone or in combination at various concentrations for 24 h. The single and combined effects of As2O3 and BaP on the cytotoxicity, DNA/chromosomal damage, and oxidative stress were examined by using tetrazolium (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) dye colorimetric assay, colony formation assay, fluorescence probe, chemical colorimetry, comet assay as well as micronucleus test. Our results showed that As2O3 synergistically enhanced the cytotoxicity, genotoxicity, and level of oxidative stress induced by BaP at various tested concentrations. Also, our experimental results showed that intracellular glutathione (GSH) contents were increased by various doses of BaP, but single or cotreatment with As2O3 significantly decreased the GSH level in the cells at all tested concentrations. Taken together, our results suggest that As2O3 may exert its synergistic cyto- and genotoxic effects with
BaP mainly via elevated intracellular reactive oxygen species and reduced GSH contents and superoxide dismutase activities, thus promoting high level of oxidative stress, which may be a pivotal mechanism underlying As2O3 cocarcinogenic action.

[481] TÍTULO / TITLE: - Intralesional cidofovir as adjuvant for the successful management of aggressive respiratory papillomatosis in an infant.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Durvasula VS; Richter GT
INSTITUCIÓN / INSTITUTION: - Arkansas Children’s Hospital, United States. Electronic address: phanidurvasula@hotmail.co.uk.
RESUMEN / SUMMARY: - Recurrent respiratory papillomatosis (RRP) in young children is frequently characterized by a recalcitrant course and need for multiple surgeries. Periodic surgical debulking and ablation is the mainstay of therapy as a cure for RRP rarely occurs. Benefits of adjuvant treatment with local injection of cidofovir in aggressive cases of RRP have been reported in both children and adults. However, a consensus on initiation, dosage, or scheduling of this drug has not been established in the very young patient. Literature on successful remission in children less than 1 year of age is not available. One such case of an infant with aggressive RRP treated with local adjuvant cidofovir is described herein.

[482] RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kunimasa K; Korogi Y; Okamoto Y; Ishida T
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Kurashiki Central Hospital, Japan.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - 
INSTITUCIÓN / INSTITUTION: - 
RESUMEN / SUMMARY: - 

●● Enlace al texto completo (gratuito o de pago) 1007/s12032-013-0676-7
RESUMEN / SUMMARY: Vascular endothelial growth factor (VEGF) is involved in non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE), but little is known regarding the efficacy of bevacizumab (Bev) with carboplatin-paclitaxel (CP) for NSCLC with MPE. Chemotherapy-naive non-SQ NSCLC patients with MPE were eligible to participate. Pleurodesis before chemotherapy was not allowed. In the first cycle, the treated patients received only CP to prevent Bev-induced wound healing delayed after chest drainage. Subsequently, they received 2-6 cycles of CP with Bev. Patients who completed more than 4 cycles of CP and Bev without disease progression or severe toxicities continued to receive Bev alone as a maintenance therapy. The primary end point was overall response, although an increase in MPE was allowed in the first cycle. The VEGF levels in plasma and MPE were measured at baseline, and the VEGF levels in plasma were measured after 3 cycles of chemotherapy. Between September 2010 and June 2012, 23 patients were enrolled. The overall response rate was 60.8%; the disease control rate was 87.0%. Sixteen patients received maintenance therapy, following a median of 3 cycles. Median progression-free and overall survival times were 7.1 months (95% confidence interval [CI], 5.6-9.4 months) and 11.7 months (95% CI, 7.4-16.8 months), respectively. Most patients experienced severe hematological toxicities, including >/=grade 3 neutropenia; none experienced severe bleeding events. The MPE control rate improved on combining CP with Bev (CP, 78.3%; CP with Bev, 91.3%; P = 0.08). The median baseline VEGF level in MPE was 1798.6 (range 223.4-35,633.4) pg/mL. Plasma VEGF levels significantly decreased after 3 chemotherapy cycles (baseline, 513.6 +/- 326.4 pg/mL, post-chemotherapy, 25.1 +/- 14.1 pg/mL, P < 0.01). CP plus Bev was effective and tolerable in chemotherapy-naive non-squamous NSCLC patients with MPE.
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Bao Di Hospital, Bao Di Clinical College of Tianjin Medical University, Guang Chuan road, Bao Di, Tianjin, People’s Republic of China.

RESUMEN / SUMMARY: - Lung cancer is a heterogeneous disease with currently still unknown mechanisms of development. Besides genetic and epigenetic mechanisms, microRNAs (miRNAs) have recently been discovered as one of the crucial players in lung carcinogenesis through posttranscriptional regulation of tumor suppressor and oncogenes. A substantial number of deregulated miRNAs have been revealed in lung cancer, and the biological significance of those miRNAs has been confirmed in multiple functional experiments. A growing number of studies suggest involvement of miRNAs in various steps of lung carcinogenesis. Great biological stability of miRNAs opens novel fields in biomarker research with potential clinical implementation in screening, diagnosis and prediction of prognosis. In this review, we provide the basic knowledge of miRNA biogenesis and discuss extensively the role of miRNAs in lung carcinogenesis, including potential translational clinical implementations.

[485]

TÍTULO / TITLE: - Sweet syndrome preceding a carcinoid lung tumor and multiple myeloma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Tewari A; Chandrakumar A; Macdonald D; Staughton R; Bunker CB

[486]

TÍTULO / TITLE: - Effects of selenium on Pteridium aquilinum and urethane-induced lung carcinogenesis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Nakahara SB; Sanches DS; Caniceiro BD; Wysochi HL Jr; da Silva GB; Latorre AO
INSTITUCIÓN / INSTITUTION: - Department of Pathology, School of Veterinary Medicine and Animal Sciences, University of Sao Paulo, Sao Paulo, Brazil.
RESUMEN / SUMMARY: - Abstract The results of our previous study demonstrated that ptaquiloside, the main toxic agent found in Pteridium aquilinum, suppresses natural killer (NK) cell-mediated cytotoxicity. However, the ability of ptaquiloside to suppress the cytotoxicity of NK cells was prevented by selenium supplementation. NK cells play
an important role in the innate immune response and have the ability to kill tumor cells. Therefore, we hypothesized that selenium may prevent the higher susceptibility to urethane-induced lung carcinogenesis that has been observed in mice treated with P. aquilinum. The immunosuppressive effects of ptaquiloside have been associated with a higher number of urethane-induced lung nodules in mice. Hence, we assessed the effects of P. aquilinum-induced immunosuppression on urethane-induced lung carcinogenesis in C57BL/6 mice that had been supplemented with selenium. For these experiments, mice were treated with both an aqueous extract of P. aquilinum (20 g/kg/day) and selenium (1.3 mg/kg) by gavage once daily for 14 days followed by a once-weekly intraperitoneal injection of urethane (1 g/kg) for 10 weeks that was accompanied by gavage 5 days a week. Lung adenomas in mice that had been treated with P. aquilinum plus urethane occurred with a frequency that was 44% higher than that in mice that had been treated with only urethane. In mice that had been supplemented with selenium and treated with P. aquilinum plus urethane, the occurrence of lung adenomas was reduced to 26%. These results suggest that selenium prevents the immunosuppressive effects of P. aquilinum on urethane-induced lung carcinogenesis.
screen/diagnose lung cancers. As the isolation of circulating exosomes is a minimally invasive procedure, this technique opens new possibilities for diagnostic applications.

METHODS:: We used a first set of 30 plasma samples from as many patients, including 10 patients affected by lung adenocarcinomas, 10 with lung granulomas, and 10 healthy smokers matched for age and sex as negative controls. Wide-range microRNAs analysis (742 microRNAs) was performed by quantitative real time polymerase chain reaction. Data were compared on the basis of lesion characteristics, using WEKA software for statistics and modeling. Subsequently, selected microRNAs were evaluated on an independent larger group of samples (105 specimens: 50 lung adenocarcinomas, 30 lung granulomas, and 25 healthy smokers). RESULTS:: This analysis led to the selection of four microRNAs to perform a screening test (miR-378â¸, miR-379, miR-139-5p, and miR-200b-5p), useful to divide population into two groups: nodule (lung adenocarcinomas + carcinomas) and non-nodule (healthy former smokers). Six microRNAs (miR-151âµ-5p, miR-30âµ-3p, miR-200b-5p, miR-629, miR-100, and miR-154-3p) were selected for a second test on the nodule population to discriminate between lung adenocarcinoma and granuloma. CONCLUSIONS:: The screening test showed 97.5% sensitivity, 72.0% specificity, and area under the curve receiver operating characteristic of 90.8%. The diagnostic test had 96.0% sensitivity, 60.0% specificity, and area under the curve receiver operating characteristic of 76.0%. Further evaluation is needed to confirm the predictive power of these models on larger cohorts of samples.
combination approaches that combine debulking surgery and chemotherapy with IP genetic immunotherapy.

[489]
TÍTULO / TITLE: - EBUS-TBNA/Staging of Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fielding DI; Kurimoto N
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Medicine, Royal Brisbane and Women’s Hospital, Butterfield Street, Herston, Queensland 4029, Australia. Electronic address: david_fielding@health.qld.gov.au.
RESUMEN / SUMMARY: - In the staging of mediastinal lymph nodes before lung cancer surgery, endobronchial ultrasound transbronchial needle aspirations (EBUS-TBNA) have proven to be highly sensitive and specific as well as safe. Although positron emission tomography/computed tomography (PET/CT) has been a major development in the preoperative workup of patients with lung cancer, EBUS-TBNA has superior test performance and PET/CT cannot be regarded as a substitute for tissue sampling with EBUS-TBNA. In general, EBUS-TBNA staging is needed for any patient with CT nodes greater than 1 cm in short axis, or PET-positive mediastinal nodes.

[490]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Nakajima T; Yasufuku K
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Toronto General Hospital, University Health Network, University of Toronto, 200 Elizabeth Street, 9N-957, Toronto, Ontario MSG 2C4, Canada.
RESUMEN / SUMMARY: - Early detection and surgical resection are essential for the treatment of lung cancer. It would be ideal to be able to detect and treat preinvasive bronchial lesions, defined as dysplasia and carcinoma in situ before progressing to invasive cancer. Advanced airway-assessment techniques have opened an avenue for early detection and surveillance of endobronchial malignancy. This article reviews currently available advanced imaging techniques for early detection of lung cancer, including autofluorescence bronchoscopy, narrow-band imaging, high-magnification
bronchovideoscopy, endobronchial ultrasonography, and optical coherence tomography. Also discussed are the more recently developed endocytoscopy system and confocal fluorescence microendoscopy, currently used only for research purposes.

[491]

**TÍTULO / TITLE**: - Lung cancer screening: past, present and future.
**RESUMEN / SUMMARY**: - Enlace al Resumen / Link to its Summary

**AUTORES / AUTHORS**: - Finigan JH; Kern JA
**INSTITUCIÓN / INSTITUTION**: - Division of Oncology, Department of Medicine, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA; Division of Pulmonary and Critical Care Medicine, Department of Medicine, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA; Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado, 12700 East 19th Avenue, Aurora, CO 80045, USA. Electronic address: FiniganJ@NJHealth.org.
**RESUMEN / SUMMARY**: - Lung cancer is the leading cause of cancer death for men and women. Most lung cancer cases are diagnosed at an advanced stage, when cure is no longer an option; this heavily influences mortality. Historically, attempts at lung cancer screening using chest x-rays and sputum cytology have failed to influence lung cancer mortality. However, the recent National Lung Screening Trial demonstrated that low-dose computed tomography screening for lung cancer decreases mortality. This article outlines the history of lung cancer screening, the current state of screening and possible future adjuncts to screening.

[492]

**TÍTULO / TITLE**: - Classic Biphasic Pulmonary Blastoma Demonstrated by 18F-FDG PET/CT.
**RESUMEN / SUMMARY**: - Enlace al Resumen / Link to its Summary

**AUTORES / AUTHORS**: - Keu KV; Berry GJ; Quon A
**INSTITUCIÓN / INSTITUTION**: - From the *Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, and daggerDepartment of Pathology, Stanford University Medical Center, Stanford, CA.
**RESUMEN / SUMMARY**: - A 75-year-old nonsmoker woman was referred for the evaluation of a nonsecretory left adrenal lesion. An abdominal contrast-enhanced CT showed an incidental left lower lobe mass, which was confirmed on a chest contrast-
enhanced CT. A F-FDG PET/CT showed a hypermetabolic tumor without nodal or distant metastasis. She underwent a lobectomy, and the final pathology reported a classic biphasic pulmonary blastoma, which is an uncommon histological form of malignant lung neoplasm. This case highlighted the glucose avidity of this rare and aggressive cancer.
OBJECTIVES: To evaluate the agreements of unidimensional, bidimensional, area and volume measurements of pulmonary tumors on multidetector computed tomography (MDCT), and to determine which method is the most reliable one. MATERIALS AND METHODS: Thirty patients with pulmonary tumors were enrolled in this study, which referred to undergo thoracic MDCT in our hospital. Four radiologists evaluated dimensions of pulmonary tumor independently, including length, width, height, area and volume. The intraclass correlation coefficient (ICC) and concordance correlation coefficient (CCC) were both used to evaluate the variability between the repeat readings of the same scan. RESULTS: The ICCs and CCCs of the intraobserver were both higher than interobserver’s (ICC intra vs. inter: 0.984 vs. 0.947 and CCC intra vs. inter: 0.993 vs. 0.943). Area of intraobserver ICC (ICC=0.992, P<.001) and CCC (CCC=0.997, P<.001) both had the best agreements of the six methods. Among the interobserver ICCs and CCCs, area (ICC=0.981, P<.001 and CCC=0.982, P<.001) was also the best of the six methods. CONCLUSIONS: Area measurement on MDCT is the most reproducible method that measures tumor dimension accurately.
Lung cancer screening programs for high-risk populations using low-dose computed tomography (LDCT) have been shown by a class I clinical trial to reduce lung cancer mortality by 20%. We present an overview of randomized and nonrandomized lung cancer screening trials and review some of the arguments advocating for or against the widespread implementation of such a screening program. Concerns regarding the use of LDCT screening for lung cancer include increased risk from radiation exposure, overdiagnosis of indolent tumors, and high numbers of false-positive results, which may increase patient anxiety and result in unnecessary procedures with potential complications. Current recommendations regarding diagnostic criteria and workup of positive screens as well as the risks and benefits of using LDCT for lung cancer screening are provided.
OBJECTIVE: To investigate the expression of the stem cell marker Nanog in lung cancer tissues and the correlations between Nanog expression and clinic-pathologic characteristics as well as prognosis of lung cancer. METHODS: 163 patients with lung cancers enrolled in the study. The expression of Nanog in the cell lines and lung cancers were evaluated by RT-PCR, immunofluorescence and immunohistochemistry. Then, the correlations between Nanog expression status and clinic-pathologic characteristics and prognosis of lung cancer patients were analyzed. RESULTS: It showed that Nanog are higher expressed in lung cancer tissues compared to their normal counterparts in both mRNA and protein levels, and Nanog expression was observed to be positively correlated with tumor differentiation and clinical stages of lung cancer patients (P = 0.001 and 0.001). Nanog were mainly localized at the cytoplasm in the brown color in the lung cancers. In addition, nuclear staining of Nanog was more observed in poorly differentiated lung cancers compared to others (P = 0.01). Furthermore, survival analyses showed that over-expression of Nanog protein predicted a worse prognosis for lung cancer patients (P = 0.001). CONCLUSION: Nanog can be an important prognostic marker for lung cancer, which may present a new therapeutic target for lung cancer patients in the future.
has been linked to development, progression, and prognosis of non-small-cell lung cancer (NSCLC). We sought to investigate the underlying mechanism of WT1 and metastasis in NSCLC. METHODS: Real-time polymerase chain reaction was applied to detect WT1 and CDH1 mRNA in 159 NSCLC samples and corresponding adjacent tissues. Stable clones with overexpression and knockdown of WT1 were generated with plasmid and shRNA via lentivirus technology in H1568 and H1650 NSCLC cell lines. Wound-healing assay, transwell assays, and polymerase chain reaction array were carried out for invasion evaluation. Dual luciferase reporter assay was performed to validate the effect of WT1 on CDH1. RESULTS: The level of the WT1 mRNA was negatively correlated with that of E-cadherin (CDH1) and associated with pathological stage, metastasis, and survival rate of 159 NSCLC patients. A series of genes were regulated by WT1, and WT1 could suppress CDH1 transcription via direct binding to its promoter and may enhance the invasive ability of H1568 and H1650 NSCLC cell lines. CONCLUSIONS: WT1 expression was correlated with clinical stage, metastasis, and survival rate in 159 NSCLC patients. Via direct binding to the promoter, WT1 could suppress CDH1 and promote NSCLC invasion.
is currently lacking, as are prospective studies of lung cancer therapy. SUMMARY: There is an urgent need for prospective clinical trials in HIV-associated lung cancer to improve understanding of lung cancer pathogenesis and to optimize patient care. Several clinical trials are in progress to address questions in cancer biology, screening, and treatment for this significant cause of mortality in persons with HIV infection.

[502]
and a median progression-free survival of 6.2 months (95% CI 1.3-11.1) and a median overall survival of 10.7 months (0.0-21.9). 27 patients (93%) had at least one grade 1-2 treatment-emergent adverse event (mainly cutaneous rash, pruritus, colitis, or diarrhoea), and four patients (14%) had at least one grade 3-4 treatment-emergent adverse event (two gastrointestinal, one neurological, two hepatic, and one pancreatic). INTERPRETATION: Although the effect size was small in our phase 2 trial, tremelimumab seemed to have encouraging clinical activity and an acceptable safety and tolerability profile in previously treated patients with advanced malignant mesothelioma. FUNDING: Associazione Italiana per la Ricerca sul Cancro, Istituto Toscano Tumori, Pfizer, and Fondazione Buzzi Unicem.

[503]
TÍTULO / TITLE: - Reaction of plasma adiponectin level in non-small cell lung cancer patients treated with EGFR-TKIs.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Umekawa K; Kimura T; Kudoh S; Suzumura T; Nagata M; Mitsuoka S; Matsuura K; Oka T; Yoshimura N; Kira Y; Hirata K
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Osaka City University, Graduate School of Medicine, Japan. m2043009@med.osaka-cu.ac.jp
RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are routinely used to treat advanced non-small cell lung cancer (NSCLC) patients with activated EGFR mutations, and are associated with excellent response and improvement of performance status. Adipose tissue produces and releases substances called adipokines, which include adiponectin, leptin, resistin, and hepatocyte growth factor (HGF), etc. Previously, we reported that high levels of plasma HGF at diagnosis indicated intrinsic resistance to EGFR-TKIs. EGFR-TKIs have been hypothesized to affect these adipokines. METHODS: This prospective study, to evaluate the correlation between plasma adiponectin and insulin levels and non-hematological adverse effects in advanced NSCLC following EGFR-TKIs administration, was conducted at the Osaka City University Hospital. Plasma adiponectin and insulin levels were determined at diagnosis and on treatment day 30. RESULTS: Overall 33 patients were enrolled. We obtained plasma samples for analyses from all patients at diagnosis and from 26 patients on day 30. Increased adiponectin (13.69 to 14.42 microg/mL, p = 0.0092), and decreased insulin (404.0 to 351.2 pg/mL, p = 0.022) were observed after EGFR-TKI treatments. High levels of adiponectin at diagnosis were associated with severities of skin rash (p = 0.035). CONCLUSIONS: The adiponectin was affected by EGFR-TKI treatments for NSCLC. Besides, the adverse events by EGFR-TKIs were influenced by the plasma adipokines at diagnosis. Our study may provide useful
information regarding patient outcomes to EGFR-TKI treatments. A prospective large clinical trial is warranted to clarify these results.

[504]

[505]
INTRODUCTION: The National Comprehensive Cancer Network and the American Cancer Society recently released lung screening guidelines that include smoking cessation counseling for smokers undergoing screening. Previous work indicates that smoking behaviors and risk perceptions of the National Lung Screening Trial (NLST) participants were relatively unchanged. We explored American College of Radiology Imaging Network (ACRIN)/NLST former and current smokers’ risk perceptions specifically to (a) determine whether lung screening is a cue for behavior change, (b) elucidate risk perceptions for lung cancer and smoking-related diseases, and (c) explore postscreening behavioral intentions and changes. METHODS: A random sample of 35 participants from 4 ACRIN sites were qualitatively interviewed 1-2 years postscreen. We used a structured interview guide based on Health Belief Model and Self-Regulation Model constructs. Content analyses were conducted with NVivo 8.

RESULTS: Most participants endorsed high-risk perceptions for lung cancer and smoking-related diseases, but heightened concern about these risks did not appear to motivate participants to seek screening. Risk perceptions were mostly attributed to participants’ heavy smoking histories; former smokers expressed greatly reduced risk. Lung cancer and smoking-related diseases were perceived as very severe although participants endorsed low worry. Current smokers had low confidence in their ability to quit, and none reported quitting following their initial screen. CONCLUSIONS: Lung screening did not appear to be a behavior change cue to action, and high-risk perceptions did not translate into quitting behaviors. Cognitive and emotional dissonance and avoidance strategies may deter engagement in smoking behavior change. Smoking cessation and prevention interventions during lung screening should explore risk perceptions, emotions, and quit confidence.
RESUMEN / SUMMARY: Lung cancer is one of the most frequent causes of malignant tumors. In recent years, it has been documented that statins have anticancer and cancer chemopreventive properties. However, the mechanism of simvastatin on lung cancer is still unclear. In this study, the human lung cancer cell line A549 cells were incubated with simvastatin. Simvastatin inhibited the survival of A549 cells in a dose-dependent manner, decreased Bcl-2 protein expression, and increased Bax protein expression time and dose dependently. In addition, simvastatin blocked cells in the G1 phase of the cell cycle, downregulated cyclin D1 and CDKs protein expression, mediated the mitochondria-dependent caspase cascade by increasing caspase-3, -8, and -9 mRNA and protein expression, downregulated Xiap levels to induce cells apoptosis. Importantly, simvastatin suppressed decreased MMP-9 protein expression and suppressed NF-kappaB activation in A549 cells. Taken together, these results showed that the anticancer effect of simvastatin in lung cancer A549 cells via the inhibiting cell proliferation, influencing the cell cycle, downregulating cyclin D1 and CDKs expression, inducing apoptosis, and decreasing MMP-9 levels, possibly by inhibiting the activation of NF-kappaB. Statins contribute to lung cancer therapy and may be an ideal anticancer and cancer chemopreventive agent for lung cancer.

TÍTULO / TITLE: Immediate and Late Outcomes of Bronchial and Systemic Artery Embolization for Palliative Treatment of Patients With Nonsmall-Cell Lung Cancer Having Hemoptysis.

RESUMEN / SUMMARY: Background: Hemoptysis in patients with advanced lung cancer can be a life threatening. Objectives: To evaluate immediate outcomes and late outcomes of bronchial artery embolization (BAE) for palliative treatment in patients with advanced nonsmall-cell lung cancer (NSCLC) having hemoptysis. METHODS: The BAE was performed in 28 patients with NSCLC. Hemoptysis was defined as follows: massive bleeding greater than 300 mL within 24 hours (n = 8), moderate bleeding of 100 to 300 mL within 24 hours (n = 12), and slight bleeding less than 100 mL within 24 hours (n = 8). RESULTS: Success rate was 96%. Immediate clinical success within 24 hours after BAE was achieved in 22 of the 27 patients who underwent embolization.
CONCLUSIONS: The BAE with gelatin sponge particles can provide good management of hemoptysis as a palliative treatment in patients with advanced NSCLC.

[508]
TÍTULO / TITLE: Glyceraldehyde-3-phosphate dehydrogenase gene over expression correlates with poor prognosis in non small cell lung cancer patients.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1186/1476-4598-12-97
AUTORES / AUTHORS: Puzone R; Savarino G; Salvi S; Dal Bello MG; Barletta G; Genova C; Rijavec E; Sini C; Esposito Al; Truini M; Grossi F; Pfeffer U
RESUMEN / SUMMARY: BACKGROUND: Glycolysis in presence of oxygen with high glucose consumption is known to be the metabolism of choice in many tumors. In lung cancer this phenomenon is routinely exploited in diagnostic PET imaging of fluorodeoxyglucose uptake, but not much is known about the prognostic capabilities of glycolysis level assessment in resected lung tumor samples. METHODS: In this retrospective study, we used real time polymerase chain reaction(RQ-PCR) to assess the expression level of the gene for Glyceraldehyde 3-phosphate dehydrogenase(GAPDH), key enzyme for glucose breakdown, in tumor samples from 82 consecutive early stages resected non small cell lung cancer(NSCLC) patients. We then compared our results in six large publicly available NSCLC microarray datasets collecting data from over 1250 total patients. RESULTS: In our study GAPDH gene over expression was found to be an adverse prognostic factor in early stages NSCLC (n = 82 HR = 1.30 p = 0.050). This result was confirmed in 5 of 6 public datasets analyzed: Shedden et al. 2008: n = 442 HR = 1.54 p < 0.0001; Lee et al. 2008: n = 138 HR = 1.31 p = 0.043; Tomida et al. 2009: n = 117 HR = 1.59 p = 0.004; Roepman et al. 2009: n = 172 (TPI1 gene) HR = 1.51 p = 0.009; Okayama et al. 2012: n = 226 HR = 3.19 p < 0.0001; Botling et al. 2013: n = 196 HR = 1.00 p = 0.97). Furthermore, in the large and clinically well annotated Shedden et al. microarray dataset, GAPDH hazard ratio did not change whether calculated for the whole dataset or for the subgroup of adjuvant naive patients only (n = 330 HR = 1.49 p < 0.0001). CONCLUSION: GAPDH gene over expression in resected tumor samples is an adverse prognostic factor in NSCLC. Our results confirm the prognostic value of glucose metabolism assessment in NSCLC.

[509]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
RT0G 0839 es un estudio de fase II de quimioradioterapia preoperatoria con o sin panitumumab en pacientes con cáncer de pulmón avanzado no pequeño (NSCLC) potencialmente operables. El agente investigacional, panitumumab, es una antígeno-epitelial de crecimiento factor receptor (EGFR) que mejora la supervivencia libre de progresión en pacientes con cáncer colorrectal inmune-refractario (mCRC). Recientemente, tanto el estado mutacional KRAS (i.e., mutado o no) como el subtipo (i.e., activante o inactivante) han demostrado ser predictores de respuesta a la terapia anti-EGFR en mCRC. Sin embargo, en el NSCLC, es desconocido si el estado mutacional KRAS o el subtipo predicen beneficio a terapias anti-EGFR debido a factores genéticos y epigenéticos únicos a cada cáncer. Presentamos un paciente con NSCLC de estadio III que contenía una mutación activante KRAS G12D y tenía una respuesta parcial patológica, con desaparición de un clone mutante minoritario KRAS. Este caso sugiere posible erradicación de las clones de G12D de cáncer de pulmón KRAS por tratamiento concurrente con quimioradioterapia y panitumumab.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Skirecki T; Hoser G; Kawiak J; Dziedzic D; Domagala-Kulawik J
INSTITUCIÓN / INSTITUTION: - Laboratory of Flow Cytometry, Medical Center of Postgraduate Education, Warsaw, Poland.
RESUMEN / SUMMARY: - Lung tumors are characterized by their high metastatic potential, which is the main cause of therapeutic failure. However, the exact cellular origin of metastasis remains unknown. Since the introduction of the cancer stem cell theory, lung cancer stem cells (LCSCs) have been thought to represent metastasis-founding cells. The current study aimed to evaluate whether LCSCs could be found in the circulation. Expression of the stem cell markers CD133 and EpCAM was confirmed in tumor and normal lung tissue by flow cytometry. Then, this technique was further used to investigate the expression of CD133 and EpCAM in the peripheral blood of 41 patients with primary lung cancer. Putative LCSCs (CD133+EpCAM+) were present in 6/7 tumor samples, and CD133+EpCAM+ cells were identified in the blood samples of 15 patients at a median level of 40/ml of blood. EpCAM+ cells were detected in 60 % of the patients, and the number of these cells was higher in patients with adenocarcinoma than patients with squamous cell carcinoma and was also higher in...
patients with less advanced disease. Moreover, the frequency of this subpopulation significantly correlated with the circulating level of SSEA-4+ cells. Additionally, CD133+EpCAM- cells were found in 87% of the patients, and the numbers of these cells were significantly higher in patients with distant metastases and correlated with disease stage. This study confirmed the presence of an LCSC subpopulation with a CD133+EpCAM+ phenotype in the tumors and blood of patients with lung cancer, and these results suggest an important role for CD133 and EpCAM in lung cancer progression and their potential application as novel biomarkers of the disease.

[511]
TÍTULO / TITLE: - Chemotherapy agents induced immunoresistance in lung cancer cells could be reversed by trop-2 inhibition in vitro and in vivo by interaction with MAPK signaling pathway.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wang X; Long M; Dong K; Lin F; Weng Y; Ouyang Y; Liu L; Wei J; Chen X; He T; Zhang HZ
INSTITUCIÓN / INSTITUTION: - Department of Clinical Diagnosis; Tangdu Hospital; Fourth Military Medical University; Xi’an, PR China.
RESUMEN / SUMMARY: - Chemotherapy has been widely used in cancer treatment, but the prognosis of the cancer patients following chemotherapy has not been substantially improved. Alternative strategies such as immunotherapy and their combinations with chemotherapy are now being considered; however, the effects of chemotherapy on the immune responses of cancer cells are not fully understood. In the present studies, we reveal a potential link between chemotherapy and cancer immunoresistance, we first examined the effects of chemopreventive agent DDP on the expression of a cell surface glycoprotein Trop-2 in lung cancer cells, and found that DDP not only induce Trop-2 surface expression in human lung cancer cells, but also induce T cell apoptosis effectively. In order to investigate the relationship between DDP induced Trop-2 expression and T cell apoptosis, we stably transfected A549 and PC14 lung cancer cells with Trop-2 shRNA, the DDP induced Trop-2 surface expression was effectively decreased in stably transfected cell lines, but chemotherapeutic reagent induced cell proliferation inhibition and apoptosis were increased through inhibition of the MAPK signaling pathway. In vivo animal experiments showed that Trop-2 knockdown tumors displayed a slower growth rate than the control xenografts. Importantly, DDP treatment exhibited a strong antitumor activity in the mice with Trop-2 knockdown tumors, but only a marginal effect in the control group. Taken together, our data show that DDP resistance in lung cancer cells could be induced through increased surface expression of Trop-2, which at least partially by interfering with MAPK pathway. These results provide novel insight into
the function of Trop-2 and encourage the design and testing of approaches targeting this protein and its partners.

[512]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Hyun SH; Ahn HK; Kim H; Ahn MJ; Park K; Ahn YC; Kim J; Shim YM; Choi JY
INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea.
RESUMEN / SUMMARY: - PURPOSE: We evaluated the prognostic impact of volume-based assessment by 18F-FDG PET/CT in patients with stage III non-small-cell lung cancer (NSCLC). METHODS: We reviewed 194 consecutive patients with stage IIIA NSCLC treated with surgical resection (surgical group) and 115 patients treated with nonsurgical therapy (nonsurgical group: 50 stage IIIA, 65 stage IIIB). Metabolic tumour volume (MTV), total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax) of primary tumours were measured using pretreatment 18F-FDG PET/CT. Overall survival was assessed using the Kaplan-Meier method. The prognostic significance of PET parameters and other clinical variables was assessed using Cox proportional hazards regression analyses. To evaluate and compare the predictive performance of PET parameters, time-dependent receiver operating characteristic (ROC) curve analysis was used. RESULTS: In the Cox proportional hazards models, MTV (HR = 1.27 for a doubling of MTV, P = 0.008) and TLG (HR = 1.22 for a doubling of TLG, P = 0.035) were significantly associated with an increased risk of death after adjusting for age, gender, histological cell type, T stage, N stage, and treatment variables in the surgical group. SUVmax was not a significant prognostic factor in either the surgical or nonsurgical group. In the time-dependent ROC curve analysis, volume-based PET parameters predicted survival better than SUVmax. CONCLUSION: The volume-based PET parameters (MTV and TLG) are significant prognostic factors for survival independent of tumour stage and better prognostic imaging biomarkers than SUVmax in patients with stage IIIA NSCLC after surgical resection.

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TÍTULO / TITLE: - Non-small cell lung cancer cells survived ionizing radiation treatment display cancer stem cell and epithelial-mesenchymal transition phenotypes.
Ionizing radiation (IR) is used for patients diagnosed with unresectable non small cell lung cancer (NSCLC), however radiotherapy remains largely palliative due to radioresistance. Cancer stem cells (CSCs), as well as epithelial-mesenchymal transition (EMT), may contribute to drug and radiation resistance mechanisms in solid tumors. Here we investigated the molecular phenotype of A549 and H460 NSCLC cells that survived treatment with IR (5Gy) and are growing as floating tumor spheres and cells that are maintained in a monolayer after irradiation. Non-irradiated and irradiated cells were collected after one week, seeded onto ultra low attachment plates and propagated as tumor spheres. Bulk NSCLC cells which survived radiation and grew in spheres express cancer stem cell surface and embryonic stem cell markers and are able to self-renew, and generate differentiated progeny. These cells also have a mesenchymal phenotype. Particularly, the radiation survived sphere cells express significantly higher levels of CSC markers (CD24 and CD44), nuclear beta-catenin and EMT markers (Snail1, Vimentin, and N-cadherin) than non-irradiated lung tumor sphere cells. Upregulated levels of Oct-4, Sox2 and beta-catenin were detected in H460 cells maintained in a monolayer after irradiation, but not in radiation survived adherent A459 cells. PDGFR-beta was upregulated in radiation survived sphere cells and in radiation survived adherent cells in both A549 and H460 cell lines. Combining IR treatment with axitinib or dasatinib, inhibitors with anti-PDGFR activity, potentiates the efficacy of NSCLC radiotherapy in vitro. Our findings suggest that radiation survived cells have a complex phenotype combining the properties of CSCs and EMT. CD44, SNAIL and PDGFR-beta are dramatically upregulated in radiation survived cells and might be considered as markers of radiotherapy response in NSCLC.
AUTORES / AUTHORS: - Zhang H; Liu D; Li S; Zheng Y; Yang X; Li X; Zhang Q; Qin N; Lu J; Ren-Heidenreich L; Yang H; Wu Y; Zhang X; Nong J; Sun Y

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Beijing Chest Hospital, Capital Medical University, Beijing, China.

RESUMEN / SUMMARY: - Somatic DNA mutations affecting the epidermal growth factor receptor (EGFR) signaling pathway are known to predict responsiveness to EGFR-tyrosine kinase inhibitor drugs in patients with advanced non-small-cell lung cancers. We evaluated a sensitive liquidchip platform for detecting EGFR, KRAS (alias Ki-ras), proto-oncogene B-Raf, and phosphatidylinositol 3-kinase CA mutations in plasma samples, which were highly correlated with matched tumor tissues from 86 patients with advanced non-small-cell lung cancers. Either EGFR exon 19 or 21 mutations were detected in 36 patients: 23 of whom had identical mutations in both their blood and tissue samples; whereas mutations in the remaining 13 were found only in their tumor samples. These EGFR mutations occurred at a significantly higher frequency in females, never-smokers, and in patients with adenocarcinomas (P <= 0.001). The EGFR exon 20 T790M mutation was detected in only one of the paired samples [100% (95% CI, 96% to 100%) agreement]. For KRAS, proto-oncogene B-Raf, and phosphatidylinositol 3-kinase CA mutations, the overall agreements were 97% (95% CI, 90% to 99%), 98% (95% CI, 92% to 99%), and 97% (95% CI, 90% to 99%), respectively, and these were not associated with age, sex, smoking history, or histopathologic type. In conclusion, mutations detected in plasma correlated strongly with mutation profiles in each respective tumor sample, suggesting that this liquidchip platform may offer a rapid and noninvasive method for predicting tumor responsiveness to EGFR-tyrosine kinase inhibitor drugs in patients with advanced non-small-cell lung cancers.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.07.32

AUTORES / AUTHORS: - Passaro A; Gori B; de Marinis F

INSTITUCIÓN / INSTITUTION: - 1 Oncological Pulmonary Unit, San Camillo, High Specialization Hospital, Rome, Italy.

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Combining Erlotinib and Cetuximab Is Associated with Activity in Patients with Non-Small Cell Lung Cancer (Including Squamous Cell Carcinomas) and Wild-Type EGFR or Resistant Mutations.

Preclinical data suggest that combined EGF receptor (EGFR) targeting with an EGFR tyrosine kinase inhibitor and an anti-EGFR monoclonal antibody may be superior over single-agent targeting. Therefore, as part of a phase I study, we analyzed the outcome of 20 patients with non-small cell lung cancer treated with the combination of erlotinib and cetuximab. EGFR mutation status was ascertained in a Clinical Laboratory Improvement Amendment-approved laboratory. There were 10 men; median number of prior therapies was five. Overall, two of 20 patients (10%) achieved partial response (PR), one of whom had a TKI-resistant EGFR insertion in exon 20, time to treatment failure (TTF) = 24+ months, and the other patient had squamous cell histology (EGFR wild-type), TTF = 7.4 months. In addition, three of 20 patients (15%) achieved stable disease (SD) >/=6 six months (one of whom had wild-type EGFR and squamous cell histology, and two patients had an EGFR TKI-sensitive mutation, one of whom had failed prior erlotinib therapy). Combination therapy with erlotinib plus cetuximab was well tolerated. The most common toxicities were rash, diarrhea, and hypomagnesemia. The recommended phase II dose was erlotinib 150 mg oral daily and cetuximab 250 mg/m2 i.v. weekly. In summary, erlotinib and cetuximab treatment was associated with SD >/= six months/PR in five of 20 patients with non-small cell lung cancer (25%), including individuals with squamous histology, TKI-resistant EGFR mutations, and wild-type EGFR, and those who had progressed on prior erlotinib after an initial response. This combination warrants further study in select populations of non-small cell lung cancer. Mol Cancer Ther; 12(10); 1-9. ©2013 AACR.
Global analyses of DNA methylation contribute important insights into biology and the wide-ranging role of DNA methylation. We describe the use of online solid-phase extraction and isotopic-dilution liquid chromatography/tandem mass spectrometry (LC-MS/MS) for the simultaneous measurement of 5-methyl-2′-deoxycytidine (5-medC) and 2′-deoxycytidine (dC) in DNA. With the incorporation of isotope internal standards and online enrichment techniques, the detection limit of this method was estimated to be as low as 0.065 pg which enables human global DNA methylation detection using only picogram amounts of DNA. This method was applied to assess the optimal amounts of enzymes required for DNA digestion regarding an accurate global DNA methylation determination and completeness of digestion and to determine global methylation in human tumor adjacent lung tissue of 79 lung cancer patients. We further determined methylated (N7-methylguanine (N7-meG), O 6-methylguanine (O 6-meG), and N3-methyladenine (N3-meA)) and oxidized DNA lesions (8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG)) in lung cancer patients by LC-MS/MS. Optimization experiments revealed that dC was liberated from DNA much more readily than 5-medC by nuclease P1 and alkaline phosphatase (AP) in DNA, which could lead to an error in the global DNA methylation measurement following digestion with insufficient enzymes. Nuclease P1 showed more differential activity for 5-medC and dC than AP. Global DNA methylation levels in adenocarcinoma and squamous cell carcinoma patients were similar in the range of 3.16-4.01 %. Global DNA methylation levels were not affected by smoking and gender and were not correlated with N7-meG or 8-oxodG in lung cancer patients. Levels of O 6-meG and N3-meA were however found to be undetectable in all lung tissue samples.

Treatment of Brain Metastases in Lung Cancer: Strategies to Avoid/Reduce Late Complications of Whole Brain Radiation Therapy.

**RESUMEN / SUMMARY:** brain metastases occur in 20-40 % of lung cancer patients. The use of whole brain radiation therapy (WBRT) has been shown...
to ameliorate many neurological symptoms, facilitate corticosteroid reduction, enhance quality of life (QOL), and prolong survival. The acute and early delayed side effects of WBRT are generally mild and inconsequential, whereas late complications often are progressive, irreversible, and may have a profound effect on neurocognitive function and QOL. Nevertheless, WBRT remains the cornerstone for treatment of multiple brain metastases due to its efficacy and the paucity of other treatment options. In avoidance of WBRT and its potential toxicity, patients of good performance status and \( \leq 3 \) metastases may be treated reasonably with focal therapy alone (surgery or radiosurgery) without a compromise in survival. In patients with multiple brain metastases and those undergoing prophylactic cranial irradiation (PCI), established methods to mitigate the late complications of WBRT include total dose observation, dose per fraction restrictions, and avoidance of concomitant chemotherapy. Current areas of active research that hold great potential for benefit include hippocampal-sparing radiotherapy and the use of neuroprotective agents.

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**TÍTULO / TITLE:** - Lung cancer stem cells: Molecular features and therapeutic targets.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Singh S; Chellappan S

**INSTITUCIÓN / INSTITUTION:** - National Institute of Biomedical Genomics (NIBMG), TB Hospital Building, 2nd floor, Kalyani, West Bengal, India.

**RESUMEN / SUMMARY:** - Lung cancers are highly heterogeneous and resistant to available therapeutic agents, with a five year survival rate of less than 15%. Despite significant advances in our knowledge of the genetic alterations and aberrations in signaling pathways, it has been difficult to determine the basis of lung cancer heterogeneity and drug resistance. Cancer stem cell model has attracted a significant amount of attention in recent years as a viable explanation for the heterogeneity, drug resistance, dormancy and recurrence and metastasis of various tumors. At the same time, cancer stem cells have been relatively less characterized in lung cancers. This review summarizes the current understanding of lung cancer stem cells, including their molecular features and signaling pathways that drive their stemness. This review also discusses the potential strategies to inhibit the signaling pathways driving stemness, in an effort to eradicate these cells to combat lung cancer.

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Clinicopathological significance of combined analysis of cytokeratin19 expression and preoperative serum CYFRA21-1 levels in human lung squamous cell carcinoma.

BACKGROUND: To identify a useful biomarker for human lung squamous cell carcinoma (SCC), the expression of cytokeratin19 (CK19) in human SCC tissue was investigated. In addition, we examined the significance of CK19 expression levels by immunostaining and CYFRA21-1 levels in preoperative serum, and their correlation with the clinicopathologic features of human lung SCC. METHODS: To identify proteins in cancerous and non-cancerous tissues for the diagnosis and prognosis of SCC, QSTAR Elite LC-MS/MS was used. Immunostaining for CK19 was classified as either “CK19-strong” or “CK19-weak”. Correlations between prognosis and both CK19 expression in tumor tissues and serum concentrations of CYFRA 21-1 were analyzed in 107 cases of lung SCC. RESULTS: The upregulation of CK19 in human squamous cell carcinoma tissues was observed by LCMS/MS. The weak expression of CK19, as determined by immunostaining intensity, was a significant predictor of poorer disease-specific survival (p = 0.032). The prognosis was significantly poorer for patients with weak CK19 immunostaining in tumor tissues and a high serum concentration of CYFRA21-1 compared with the other groups (p = 0.003). CONCLUSIONS: The combination of weak CK19 expression and high serum CYFRA21-1 levels is a predictor of poorer prognosis for patients with human lung SCC.

Detection of Chronic Obstructive Pulmonary Disease in Community-Based Annual Lung Cancer Screening: Chiba COPD Lung Cancer Screening Study Group.

BACKGROUND AND OBJECTIVE: Detection of chronic obstructive pulmonary disease (COPD) is crucial in the management of COPD. The aim of this study was to establish the utility of a community-based lung cancer screening for detecting
COPD. METHODS: In Japan, community-based lung cancer screening for residents who are 40 years or older using chest radiography is well established. A screening system in Chiba City, Japan, was used to detect COPD. Criteria to consider COPD at screening included age of 60 years or older, a smoking history, and chronic respiratory symptoms. Participants fulfilling these criteria were referred for diagnostic evaluation consisting of pulmonary function testing (PFT) and chest computed tomography (CT).

RESULTS: Of 89,100 Chiba City residents who underwent lung cancer screening, 72,653 residents were 60 years or older. Among them, 878 (1.0%) were identified with suspected COPD and referred for further evaluation. Of those identified, a total of 567 residents (64.6%, 567/878) underwent further evaluations, and 161 (28.4%) were reported to have COPD, with 38.5% of them requiring COPD treatment. To verify the diagnoses from the secondary evaluation centers, PFT and CT data were collected from 228 study participants, and 24.9% were diagnosed with COPD. CT findings classified according to the Goddard classification revealed that 20.1% of these participants had moderate to severe emphysema. CONCLUSIONS: COPD screening added to a community-based lung cancer screening program may be effective in detection of patients with COPD.

[522]

TÍTULO / TITLE: - Non-canonical IKKs, IKK and TBK1, as novel therapeutic targets in the treatment of non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Kim JY; Beg AA; Haura EB

INSTITUCIÓN / INSTITUTION: - H. Lee Moffitt Cancer Center and Research Institute, Department of Thoracic Oncology and Chemical Biology and Molecular Medicine Program, 12902 Magnolia Dr. Tampa, FL 33612, USA eric.haura@moffitt.org.

RESUMEN / SUMMARY: - It is well known that non-canonical IккаB kinases (IKK), IKK and Tank-binding kinase 1 (TBK1), play a key role in anti-viral responses. Interestingly, they have recently emerged as novel survival kinases in several human cancers including lung cancer, given their roles in maintaining cancer cell survival and promoting oncogenic transformation. However, the molecular mechanisms by which IKK/TBK1 are activated and IKK/TBK1 mediate survival signal in cancer cells are still controversial. This article will briefly describe signaling pathways mediated by these non-canonical IKKs, especially focusing in lung cancer, and discuss their potential as molecular targets for lung cancer treatment.
Antagonism of adenosine A2A receptor expressed by lung adenocarcinoma tumor cells and cancer associated fibroblasts inhibits their growth.

Recently it has become clear that the cost associated with the Warburg effect, which is inefficient production of ATP, is offset by selective advantages that are produced by resultant intracellular metabolic alterations. In fact tumors may be addicted to the Warburg effect. In addition these alterations result in changes in the extracellular tumor microenvironment that can also produce selective advantages for tumor cell growth and survival. One such extracellular alteration is increased adenosine concentrations that have been shown to impair T cell mediated rejection and support angiogenesis. The expression of the A2A receptor in non-small cell cancer (NSCLC) tissues, cell lines and cancer associated fibroblasts (CAF) was determined by performing immunohistrochemistry and immunoblot analysis. The efficacy of the A2A receptor antagonists in vivo was evaluated in a PC9 xenograft model. To determine the mode of cell death induced by A2A receptor antagonists flow cytometry, immunoblot and cytotoxic analysis were performed. We found that a significant number of lung adenocarcinomas express adenosine A2A receptors. Antagonism of these receptors impaired CAF and tumor cell growth in vitro and inhibited human tumor xenograft growth in mice. These observations add to the rationale for testing adenosine A2A receptor antagonists as anticancer therapeutics. Not only could there be prevention of negative signaling in T cells within the tumor microenvironment and inhibition of angiogenesis, but also an inhibitory effect on tumor-promoting, immunosuppressive CAFs and a direct inhibitory effect on the tumor cells themselves.

Rare and complex mutations of epidermal growth factor receptor, and efficacy of tyrosine kinase inhibitor in patients with non-small cell lung cancer.

Enlace al texto completo (gratuito o de pago) 1007/s10147-013-0602-1

Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 110-744, Korea.
RESUMEN / SUMMARY: - BACKGROUND: There are many complex and rare mutations in the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) other than the two classical mutations of L858R and exon 19 deletional mutation. The purpose of this study was to investigate the clinical significance of rare and complex mutations, and the efficacy of EGFR tyrosine kinase inhibitors (TKIs).

METHODS: We analyzed 1,431 NSCLC patients who were treated with either gefitinib or erlotinib. Exons 18 to 21 of EGFR were analyzed by PCR and subjected to direct sequencing methods.

RESULTS: Of 306 patients who had EGFR mutation, 24 patients (7.3%) had complex mutations. The frequency of rare mutations was 10.3%. Four groups were categorized [group A (N = 269): classical mutation alone; group B (N = 16): complex mutation with classical mutation; group C (N = 16): rare mutation alone or complex mutation with rare mutation; group D (N = 5): classical mutation with T790M]; the response rate (RR) to TKI was significantly different between each group (RR = 74.8 % in group A vs. 68.8 % in group B vs. 25.0 % in group C vs. 80.0 % in group D, P < 0.001). Progression-free survival (PFS) was also poorer in rare mutations (median PFS: 11.9 vs. 8.1 vs. 1.4 vs. 8.0 months, respectively, P < 0.001).

CONCLUSIONS: NSCLC patients harboring rare mutations did not show consistent and favorable responses to EGFR TKI compared with those harboring classical mutations. However, complex mutations with classical mutations showed similar treatment efficacy toward EGFR TKI to that with classical mutations alone.

[525]

TÍTULO / TITLE: - RET fusion gene: translation to personalized lung cancer therapy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Kohno T; Tsuta K; Tsuchihara K; Nakao K; Yoh K; Goto K

INSTITUCIÓN / INSTITUTION: - Division of Translational Research, Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center; Division of Genome Biology, National Cancer Center Research Institute.

RESUMEN / SUMMARY: - Development of lung adenocarcinoma (LADC), the most frequent histological type of lung cancer, depends in many cases on the activation of “driver” oncogenes such as KRAS, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Inhibitors that target the EGFR and ALK tyrosine kinases show therapeutic effects against LADCs containing EGFR gene mutations and ALK gene fusions, respectively. Recently, we and others identified the RET fusion gene as a new targetable driver gene in LADC. RET fusions occur in 1-2% of LADCs. Existing FDA-approved inhibitors of RET tyrosine kinase show promising therapeutic effects both in vitro and in vivo, as well as in a few patients. Clinical trials are underway to investigate the therapeutic effects of RET tyrosine kinase inhibitors, such as vandetanib.
(ZD6474) and cabozantinib (XL184), in patients with RET fusion-positive non-small cell lung cancer. This article is protected by copyright. All rights reserved.

[526]

**TÍTULO / TITLE:** - Cigarette smoking and lung cancer risk according to histologic type in Japanese men and women.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Seki T; Nishino Y; Tanji F; Maemondo M; Takahashi S; Sato I; Kawai M; Minami Y

**INSTITUCIÓN / INSTITUTION:** - Division of Community Health, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8575, Japan.

**RESUMEN / SUMMARY:** - Although cigarette smoking is a well-known risk factor for lung cancer, histology-specific risk has not been fully clarified in Japan. This case-control study evaluated the associations between smoking and lung cancer risk according to sex and histologic type. From among patients aged 30 yrs and over admitted to a single hospital in Japan between 1997 and 2009, 1,670 lung cancer cases and 5,855 controls were selected. History of smoking, quantity and duration of smoking, and passive smoking from spouses were assessed using a self-administered questionnaire. Odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure were estimated by unconditional logistic regression. Ever-smoking was significantly associated with a higher risk of squamous cell and small cell carcinoma. The OR for these two histologic types combined was larger in women (OR = 24.98, 95% CI: 13.50-46.23) than in men (OR = 9.43, 95% CI: 5.73-15.51). Analysis of the quantity and duration of smoking showed that the OR for each exposure level tended to be larger in women than in men. For adenocarcinoma, clear positive associations with quantity and duration-related factors were observed among men, and a significant positive association with passive smoking from spouses was found among non-smoking women (OR = 1.44, 95% CI: 1.06-1.95). These results suggest sex- and histologic type- differences in the association of smoking with lung cancer risk. Although smoking control should be continued to prevent lung cancers, further studies are required to better clarify differences in smoking-related lung cancer risk between the sexes and histologic types. This article is protected by copyright. All rights reserved.

[527]

**TÍTULO / TITLE:** - Downregulation of LIMK1 Level Inhibits Migration of Lung Cancer Cells and Enhances Sensitivity to Chemotherapy Drugs.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
LIM kinase 1 (LIMK1) is a member of a novel class of serine-threonine protein kinases, which plays an important role in malignant transformation. High expression of LIM kinase 1 (LIMK1) has been detected in various invasive cancers. Here, we showed that LIMK1 was overexpressed in non-small cell lung cancer tissues (NSCLC) and cell lines. Expression of LIMK1 was detected in 115 of 150 lung cancer tissues, the frequency being more significant than in lung tissues. In addition, overexpression of LIMK1 was also associated with high TNM stage and lymph node metastasis in NSCLC patients. Moreover, RNAi-mediated suppression of LIMK1 expression markedly inhibited migration and invasion of 801D lung cancer cells. Furthermore, silencing of LIMK1 sensitized 801D cells to chemotherapeutic drugs of cisplatin and gemcitabine. These results indicate that the overexpression of LIMK1 is tightly associated with an aggressive phenotype of lung cancer cells, knockdown of LIMK1 suppressed cell migration and invasion, enhanced chemosensitivity, suggesting a potential therapeutic target for lung cancer.
dyspnea, insomnia, hemoptysis, cough, thoracic pain, pain in the arm/shoulder, and financial difficulty. There was a worsening on the functional scale which assesses role performance and symptoms of fatigue, nausea and vomiting, sensory neuropathy, pain in other parts, constipation, loss of appetite and alopecia. CONCLUSION: although the patients have an improvement of their QLRH and symptoms related to the lung cancer after the chemotherapy treatment, there was a worsening of the symptoms which resulted from the toxicity of the chemotherapy medications.

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**TÍTULO / TITLE:** Short Hydration in Chemotherapy Containing Cisplatin (>=75 mg/m2) for Patients with Lung Cancer: A Prospective Study.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Jpn J Clin Oncol. 2013 Sep 4.

**AUTORES / AUTHORS:** Horinouchi H; Kubota K; Itani H; Taniyama TK; Nakamichi S; Wakui H; Kanda S; Nokihara H; Yamamoto N; Sekine I; Tamura T

**INSTITUCIÓN / INSTITUTION:** Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan.

**RESUMEN / SUMMARY:** OBJECTIVE: We previously reported that 22% of lung cancer patients experienced a Grade 2 or 3 elevation in creatinine after chemotherapy containing cisplatin. We conducted a Phase II trial to evaluate the safety and efficacy of short hydration. METHODS: The major eligibility criteria included patients with lung cancer for whom a >=75 mg/m2 cisplatin-based regimen was indicated and adequate organ function. Cisplatin was administered with pre- and post-hydration containing 10 mEq of potassium chloride in 500 ml of fluid over a 60-min period. Immediately before the administration of cisplatin, mannitol (20%, 200 ml) was administered as forced diuresis over 30 min. And magnesium sulfate (8 mEq) was added to pre-hydration. RESULTS: Forty-four patients were enrolled between April and December 2011. The patients included 29 men and 15 women with a median (range) age of 64 (42-74) years. Twenty patients received cisplatin and pemetrexed as their most frequent regimen and 38 patients received three to four cycles of chemotherapy. The median (range) duration and volume of the chemotherapies were 4.0 (3.3-6.8) h and 1600 (1550-2050) ml, respectively. Of the 44 patients, 43 (97.8%) completed the cisplatin-based chemotherapy without Grade 2 or higher renal dysfunction. The only patient who had Grade 2 elevation in creatinine (maximum value 1.7 mg/dl) had prompt improvement in creatinine levels and completed four cycles of chemotherapy. CONCLUSIONS: The short hydration is safe without severe renal toxicities in regimens containing cisplatin (>=75 mg/m2) for patients with lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Shimada K; Serada S; Fujimoto M; Nomura S; Nakatsuka R; Harada E; Iwahori K; Tachibana I; Takahashi T; Kumanogoh A; Kishimoto T; Naka T
INSTITUCIÓN / INSTITUTION: Laboratory for Immune Signal, National Institute of Biomedical Innovation, Osaka, Japan; Department of Respiratory Medicine, Allergy, and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka, Japan.
RESUMEN / SUMMARY: Lung cancer (LC) is the major cause of death by cancer and the number of LC patients is increasing worldwide. This study investigated the therapeutic potential of gene delivery using suppressor of cytokine signaling 1 (SOCS-1), an endogenous inhibitor of intracellular signaling pathways, for the treatment of LC. To examine the anti-tumor effect of SOCS-1 overexpression on non-small cell lung cancer (NSCLC) cells, NSCLC cells (A549, LU65 and PC9) were infected with adenovirus-expressing SOCS-1 vector. The cell proliferation assay showed that A549 and LU65, but not PC9, were sensitive to SOCS-1-gene mediated suppression of cell growth. While JAK inhibitor I also could inhibit proliferation of A549 and LU65, SOCS-1 gene delivery appeared to be more potent since SOCS-1 could suppress the FAK and EGFR as well as the JAK/STAT3 signaling pathway. Enhanced phosphorylation of the p53 protein was detected by means of phospho-kinase array in SOCS-1 overexpressed A549 cells compared with control cells, while no phosphorylation of p53 was observed when JAK inhibitor I was used. Furthermore, treatment with AdSOCS-1 in vivo significantly suppressed NSCLC proliferation in a xenograft model. These results suggest that the overexpression of SOCS-1 gene is effective for anti-tumor therapy by suppressing the JAK/STAT, FAK and EGFR signaling pathways and enhancing p53-mediated anti-tumor activity in NSCLC. This article is protected by copyright. All rights reserved.

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TÍTULO / TITLE: Negative modulation of mitochondrial oxidative phosphorylation by epigallocatechin-3 gallate leads to growth arrest and apoptosis in human malignant pleural mesothelioma cells.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Valenti D; de Bari L; Manente GA; Rossi L; Mutti L; Moro L; Vacca RA

[530]
INSTITUCIÓN / INSTITUTION: - Institute of Biomembranes and Bioenergetics, National Council of Research, Bari, Italy. Electronic address: d.valenti@ibbe.cnr.it.
RESUMEN / SUMMARY: - Increasing evidence reveals a large dependency of epithelial cancer cells on oxidative phosphorylation (OXPHOS) for energy production. In this study we tested the potential of epigallocatechin-3-gallate (EGCG), a natural polyphenol known to target mitochondria, in inducing OXPHOS impairment and cell energy deficit in human epithelioid (REN cells) and biphasic (MSTO-211H cells) malignant pleural mesothelioma (MMe), a rare but highly aggressive tumor with high unmet need for treatment. Due to EGCG instability that causes H2O2 formation in culture medium, the drug was added to MMe cells in the presence of exogenous superoxide dismutase and catalase, already proved to stabilize the EGCG molecule and prevent EGCG-dependent reactive oxygen species formation. We show that under these experimental conditions, EGCG causes the selective arrest of MMe cell growth with respect to normal mesothelial cells and the induction of mitochondria-mediated apoptosis, as revealed by early mitochondrial ultrastructure modification, swelling and cytochrome c release. We disclose a novel mechanism by which EGCG induces apoptosis through the impairment of mitochondrial respiratory chain complexes, particularly of complex I, II and ATP synthase. This induces a strong reduction in ATP production by OXPHOS, that is not adequately counterbalanced by glycolytic shift, resulting in cell energy deficit, cell cycle arrest and apoptosis. The EGCG-dependent negative modulation of mitochondrial energy metabolism, selective for cancer cells, gives an important input for the development of novel pharmacological strategies for MMe.

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TÍTULO / TITLE: - Unusual cause of severe anaemia in a patient with metastatic haemangiopericytoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Vanhaudenarde V; Duck L; Mazzeo F; Graux C; Jamar F; Coche E; Galant C; Machiels JP
INSTITUCIÓN / INSTITUTION: - Centre du Cancer, Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Universite Catholique de Louvain, Brussels, Belgium.
RESUMEN / SUMMARY: - Haemangiopericytoma is a rare tumor of vascular origin. We report the case of patient with severe refractory anaemia due to peripheral destruction of red blood cells by spleen metastases. Anaemia was successfully treated by splenectomy. Afterwards, our patient developed liver and lung metastases and was treated, in a clinical trial, with gefitinib that stabilised the disease during nine years. These interesting features are discussed.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 1186/1476-4598-12-88

AUTORES / AUTHORS: - Porcu G; Parsons AB; Di Giandomenico D; Lucisano G; Mosca MG; Boone C; Ragnini-Wilson A

INSTITUCIÓN / INSTITUTION: - Department of Translational Pharmacology, Consorzio Mario Negri Sud, S, Maria Imbaro, Italy. ragnini@negrisud.it.

RESUMEN / SUMMARY: - BACKGROUND: Farnesyltransferase inhibitors (FTIs) are anticancer agents with a spectrum of activity in Ras-dependent and independent tumor cellular and xenograph models. How inhibition of protein farnesylation by FTIs results in reduced cancer cell proliferation is poorly understood due to the multiplicity of potential FTase targets. The low toxicity and oral availability of FTIs led to their introduction into clinical trials for the treatment of breast cancer, hematopoietic malignancy, advanced solid tumor and pancreatic cancer treatment, and Hutchinson-Gilford Progeria Syndrome. Although their efficacy in combinatorial therapies with conventional anticancer treatment for myeloid malignancy and solid tumors is promising, the overall results of clinical tests are far below expectations. Further exploitation of FTIs in the clinic will strongly rely on understanding how these drugs affect global cellular activity. METHODS: Using FTase inhibitor I and genome-wide chemical profiling of the yeast barcoded deletion strain collection, we identified genes whose inactivation increases the antiproliferative action of this FTI peptidomimetic. The main findings were validated in a panel of cancer cell lines using FTI-277 in proliferation and biochemical assays paralleled by multiparametric image-based analyses. RESULTS: ABC transporter Pdr10 or p-21 activated kinase (PAK) gene deletion increases the antiproliferative action of FTase inhibitor I in yeast cells. Consistent with this, enhanced inhibition of cell proliferation by combining group I PAK inhibition, using IPA3, with FTI-277 was observed in melanoma (A375MM), lung (A549) and colon (HT29), but not in epithelial (HeLa) or breast (MCF7), cancer cell lines. Both HeLa and A375MM cells show changes in the nuclear localization of group 1 PAKs in response to FTI-277, but up-regulation of PAK protein levels is observed only in HeLa cells. CONCLUSIONS: Our data support the view that group I PAKs are part of a pro-survival pathway activated by FTI treatment, and group I PAK inactivation potentiates the antiproliferative action of FTIs in yeast as well as in cancer cells. These findings open new perspectives for the use of FTIs in combinatorial strategies with PAK inhibitors in melanoma, lung and colon malignancy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Sun Q; Teong B; Chen IF; Chang SJ; Gao J; Kuo SM
INSTITUCIÓN / INSTITUTION: - Zhejiang Provincial Key Laboratory of Medical Genetics, School of Life Sciences, Wenzhou Medical College, Wenzhou, China.

RESUMEN / SUMMARY: - Recent studies suggest that dihydroartemisinin (DHA), a derivative of artemisinin isolated from the traditional Chinese herb Artemisia annua L., has anticancer properties. Due to poor water solubility, poor oral activity, and a short plasma half-life, large doses of DHA have to be injected to achieve the necessary bioavailability. This study examined increasing DHA bioavailability by encapsulating DHA within gelatin (GEL) or hyaluronan (HA) nanoparticles via an electrostatic field system. Observations from transmission electron microscopy show that DHA in GEL and HA nanoparticles formed GEL/DHA and HA/DHA aggregates that were approximately 30-40 nm in diameter. The entrapment efficiencies for DHA were approximately 13 and 35% for the GEL/DHA and HA/DHA aggregates, respectively. The proliferation of A549 cells was inhibited by the GEL/DHA and HA/DHA aggregates. Fluorescent annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) staining displayed low background staining with annexin V-FITC or PI on DHA-un-treated cells. In contrast, annexin V-FITC and PI stains dramatically increased when the cells were incubated with GEL/DHA and HA/DHA aggregates. These results suggest that DHA-aggregated GEL and HA nanoparticles exhibit higher anticancer proliferation activities than DHA alone in A549 cells most likely due to the greater aqueous dispersion after hydrophilic GEL or HA nanoparticles aggregation. These results demonstrate that DHA can aggregate with nanoparticles in an electrostatic field environment to form DHA nanosized aggregates. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2013.
**INSTITUCIÓN / INSTITUTION:** - Master’s Program in Environmental Sciences, Graduate School of Life and Environmental Sciences, University of Tsukuba.

**RESUMEN / SUMMARY:** - 1,2-Naphthoquinone (1,2-NQ) is found to be an electrophile contaminated in the atmosphere. Although we found that 1,2-NQ activates epidermal growth factor receptor (EGFR) coupled to inhibition of protein tyrosine phosphatase 1B (PTP1B) activity through covalent modification of Cys121 in human epithelial A431 cells, modulation of its downstream signal transduction pathway caused by 1,2-NQ remains to be elucidated. In the present study, we examined whether 1,2-NQ could affect such cellular signaling in human pulmonary A549 cells. Exposure of A549 cells to 1,2-NQ increased EGFR phosphorylation, resulting in activation of MEK/ERK signaling that was blocked by either PD15035 or PD98059. As a result, DNA binding activity of transcription factor AP-1 was enhanced during exposure to 1,2-NQ in the cells. These results suggest that the atmospheric electrophile phosphorylates EGFR, thereby activating the MEK/ERK/AP-1 signal transduction pathway in A549 cells.

[536]

**TÍTULO / TITLE:** - Clostridium difficile Infection in Lung Cancer Patients.

**RESUMEN / SUMMARY:** - Clostridium difficile infection (CDI) is a common nosocomial infection. Lung cancer patients have a high risk of developing CDI because of continuous antibiotic treatment or chemotherapy, prolonged hospitalization, and general weakness. This study aimed to analyze predisposing or associated risk factors for CDI in lung cancer patients receiving chemotherapy. This study was a retrospective review of 188 lung cancer patients who were admitted to the Wonkwang University Hospital between 2008 and 2009. Of the 188 patients, 44 were diagnosed with CDI. The albumin levels were significantly lower and the performance status (PS) score was significantly higher in lung cancer patients with CDI than in those without CDI (P < 0.05). In conclusion, clinicians should consider the possibility of CDI occurrence in lung cancer patients receiving chemotherapy, particularly in those with low albumin levels and high PS scores, because most lung cancer patients have a high risk of developing CDI.

[537]

**TÍTULO / TITLE:** - Targeted therapy for NSCLC with driver mutations.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Minuti G; D’Incecco A; Cappuzzo F

INSTITUCIÓN / INSTITUTION: - Medical Oncology Department, Civil Hospital of Livorno, Istituto Toscano Tumori, Viale Alfieri 36, 57100, Livorno, Italy +39 0586 223189 ; +39 0586 223457 ; f.cappuzzo@gmail.com.

RESUMEN / SUMMARY: - Introduction: Activating mutations of the epidermal growth factor receptor (EGFR) gene and rearrangement of anaplastic lymphoma kinase (ALK) gene best illustrate the therapeutic relevance of molecular characterization in non-small cell lung cancer (NSCLC) patients. Several genetic aberrations with a potential prognostic or predictive role have been identified, mainly in adenocarcinoma subtype, including ROS1, RET, MET, HER2, BRAF and KRAS. More recently oncogenic drivers, such as DDR2, FGFR1 and PI3KCA, have been characterized in squamous cell lung carcinoma (SCC) and target agents are currently under evaluation. The aim of this review is to summarize the growing scenario of new targetable oncogenes in NSCLC.

Areas covered: For this review article all published data on NSCLC genomic alterations, including the techniques employed for oncogenic drivers identification, the prevalence of each one in lung cancer subtypes, the preclinical data corroborating their role in tumorigenesis and the potential biological tailored agents tested and under evaluation were collected and analyzed using PubMed. Expert opinion: Oncogenic products represent reliable targets for drug therapy and the expanding knowledge of molecular pathways involved in lung tumorigenesis is resulting in a dramatic change of treatment strategies leading to an improvement in disease and symptom control, extending life duration and improving quality of life.

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TÍTULO / TITLE: - Erratum to: The role of SHP-1 promoter 2 hypermethylation detection of lymph node micrometastasis in resectable stage I non-small cell lung cancer as a prognostic marker of disease recurrence.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Vinayanuwattikun C; Chantranuwat P; Sriuranpong V; Mutirangura A

INSTITUCIÓN / INSTITUTION: - Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and The King Chulalongkorn Memorial Hospital, Bangkok, 10330, Thailand, Chanida.Vi@chula.ac.th.
TÍTULO / TITLE: - Treatment of malignant pleural mesothelioma by fibroblast activation protein-specific re-directed T cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Schuberth PC; Hagedorn C; Jensen SM; Gulati P; van den Broek M; Mischo A; Soltermann A; Jungel A; Marroquin Belaunzaran O; Stahel R; Renner C; Petrausch U

INSTITUCIÓN / INSTITUTION: - Department of Oncology, University Hospital Zurich, Ramistr. 100, 8091 Zurich, Switzerland.

RESUMEN / SUMMARY: - INTRODUCTION: Malignant pleural mesothelioma (MPM) is an incurable malignant disease, which results from chronic exposition to asbestos in at least 70% of the cases. Fibroblast activation protein (FAP) is predominantly expressed on the surface of reactive tumor-associated fibroblasts as well as on particular cancer types. Because of its expression on the cell surface, FAP is an attractive target for adoptive T cell therapy. T cells can be re-directed by retroviral transfer of chimeric antigen receptors (CAR) against tumor-associated antigens (TAA) and therefore represent a therapeutic strategy of adoptive immunotherapy. METHODS: To evaluate FAP expression immunohistochemistry was performed in tumor tissue from MPM patients. CD8+ human T cells were retrovirally transduced with an anti-FAP-F19-CD28/CD3zeta-CAR. T cell function was evaluated in vitro by cytokine release and cytotoxicity assays. In vivo function was tested with an intraperitoneal xenograft tumor model in immunodeficient mice. RESULTS: FAP was found to be expressed in all subtypes of MPM. Additionally, FAP expression was evaluated in healthy adult tissue samples and was only detected in specific areas in the pancreas, the placenta and very weakly for cervix and uterus. Expression of the anti-FAP-F19-CD28/CD3zeta-CAR in CD8+ T cells resulted in antigen-specific IFNgamma release. Additionally, FAP-specific re-directed T cells lysed FAP positive mesothelioma cells and inflammatory fibroblasts in an antigen-specific manner in vitro. Furthermore, FAP-specific re-directed T cells inhibited the growth of FAP positive human tumor cells in the peritoneal cavity of mice and significantly prolonged survival of mice. CONCLUSION: FAP re-directed CD8+ T cells showed antigen-specific functionality in vitro and in vivo. Furthermore, FAP expression was verified in all MPM histotypes. Therefore, our data support performing a phase I clinical trial in which MPM patients are treated with adoptively transferred FAP-specific re-directed T cells.
Metformin in lung cancer: rationale for a combination therapy.

Introduction: Metformin is a widely used antidiabetic drug, which also displays significant growth inhibitory and proapoptotic effects in several cancer models, including lung cancer, alone or in combination with chemotherapeutic drugs. Areas covered: The role of metformin as a chemopreventive drug in lung cancer is still an object of debate as epidemiological studies have shown contrasting results. More preclinical data support its role as an adjuvant drug in the treatment of lung cancer, in combination with chemotherapy or targeted molecular drugs, although the complete mechanism of action of metformin is still unclear, and potentially may exert unexpected effects with contradictory clinical implications. Expert opinion: Future perspective studies are required in nonsmall-cell lung cancer (NSCLC) patients to better investigate the effect of metformin action on the RAS/RAF/MAPK pathway and the best context in which to use metformin in combination with molecularly targeted agents.

Lung cancer and mesothelioma risk assessment for a population environmentally exposed to asbestos.

Asbestos-related cancer risk is usually a concern restricted to occupational settings. However, recent published data on asbestos environmental concentrations in Thetford Mines, a mining city in Quebec, Canada, provided an opportunity to undertake a prospective cancer risk assessment in the general population exposed to these concentrations. Using an updated Berman and Crump dose-response model for asbestos exposure, we selected population-specific potency factors for lung cancer and mesothelioma. These factors were evaluated on the basis of population-specific cancer data attributed to the studied area’s past environmental exposure.
levels of asbestos. We also used more recent population-specific mortality data along with the validated potency factors to generate corresponding inhalation unit risks. These unit risks were then combined with recent environmental measurements made in the mining town to calculate estimated lifetime risk of asbestos-induced lung cancer and mesothelioma. Depending on the chosen potency factors, the lifetime mortality risks varied between 0.7 and 2.6 per 100,000 for lung cancer and between 0.7 and 2.3 per 100,000 for mesothelioma. In conclusion, the estimated lifetime cancer risk for both cancers combined is close to Health Canada’s threshold for “negligible” lifetime cancer risks. However, the risks estimated are subject to several uncertainties and should be confirmed by future mortality rates attributed to present day asbestos exposure.

[542]

**TÍTULO / TITLE:** - Incorporation of quercetin in respirable lipid microparticles: Effect on stability and cellular uptake on A549 pulmonary alveolar epithelial cells.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUORES / AUTHORS:** - Scalia S; Trotta V; Traini D; Young PM; Sticozzi C; Cervellati F; Valacchi G

**INSTITUCIÓN / INSTITUTION:** - Department of Chemical and Pharmaceutical Sciences, University of Ferrara, 44121 Ferrara, Italy. Electronic address: sls@unife.it.

**RESUMEN / SUMMARY:** - The aim of the present study was to develop controlled release inhalable lipid microparticles (LMs) loaded with the antioxidant flavonoid, quercetin and to investigate the interaction of these microparticles with A549 pulmonary alveolar epithelial cells. The LMs were produced using different lipidic materials and surfactants, by melt emulsification followed by a sonication step. The most efficient modulation of the in vitro release of quercetin was achieved by the LMs prepared with tristearin and hydrogenated phosphatidylcholine, which were used for subsequent studies. These LMs exhibited a quercetin loading of 11.8+/−0.3%, and a volume median diameter, determined by laser diffraction, of 4.1+/−0.2µm. Moreover, their mass median aerodynamic diameter (4.82+/−0.15µm) and fine particle fraction (27.2+/−3.9%), as measured by multi-stage liquid impinger, were suitable for pulmonary delivery. Quercetin was found to be highly unstable (complete decomposition within 6-h incubation) in Ham’s F-12 medium used for A549 cell culture. Degradation was markedly reduced (16.4% of the initial quercetin content still present after 24-h incubation) after encapsulation in the lipid particle system. Viability studies performed by lactate dehydrogenase assay, demonstrated that quercetin LMs showed no significant cytotoxicity on the A549 cells, over the concentration 0.1-5µM. The
uptake of quercetin by the A549 lung alveolar cells was also investigated. After 4-h incubation, the accumulation of quercetin in the A549 cells was significantly higher (2.3-fold increase) for the microparticle entrapped flavonoid when compared to non-encapsulated quercetin. The enhanced intracellular delivery of quercetin achieved by the LMs is likely due to the flavonoid stabilization after encapsulation.

[543]
TÍTULO / TITLE - Peneciraistin C induces caspase-independent autophagic cell death through mitochondrial-derived reactive oxygen species production in lung cancer cells.
RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1111/cas.12253
AUTORES / AUTHORS - Pan X; Liu D; Wang J; Zhang X; Yan M; Zhang D; Zhang J; Liu W
INSTITUCIÓN / INSTITUTION - Department of Pharmaceutical Sciences, Binzhou Medical University, Yantai, China.
RESUMEN / SUMMARY - Peneciraistin C (Pe-C) is a novel spiroketal compound isolated from the saline soil derived fungus Penicillium raistrickii. Our previous study showed that Pe-C exerted a potent cytotoxic effect on many kinds of cancer cell lines, especially on human lung cancer A549 cells. Here, we report the anticancer mechanisms of Pe-C in a variety of lung cancer cells. The results showed that Pe-C induced caspase-independent autophagic cell death and elevated mitochondrial-derived reactive oxygen species levels. Interestingly, if autophagy was blocked by 3-methyladenine or Atg5 siRNA, Pe-C triggered a shift from autophagic cell death into caspase-dependent apoptotic cell death. In addition, cotreatment with the antioxidant N-acetyl-l-cysteine or Mito-TEMPO could effectively reverse the effect of the enhanced reactive oxygen species production, which in turn almost completely prevented the cell death induced by Pe-C. Thus, this study provided new insights into the mechanisms underlying Pe-C-mediated cell death, which indicated that Pe-C could be a potential drug candidate for therapy of lung cancers.

[544]
TÍTULO / TITLE - Anticancer effects of cinnamic Acid in lung adenocarcinoma cell line h1299-derived stem-like cells.
RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 3727/096504013X13685487925095
AUTORES / AUTHORS - Huang Y; Zeng F; Xu L; Zhou J; Liu X; Le H
INSTITUCIÓN / INSTITUTION: - Joint Laboratory of Immunogenomics, Zhoushan Hospital-BIG/CAS, Zhoushan, Zhejiang, People’s Republic of China.

RESUMEN / SUMMARY: - Lung cancer is a lethal solid tumor with poor prognosis because of its high metastasis and resistance to current therapies. Recently, cancer stem cells (CSCs) were suggested to be major contributors to tumorigenicity and cancer relapse. However, therapeutic targets for lung cancer-related CSCs remain undetermined. The objective of the current study was to investigate whether cinnamic acid (CINN) exerts an antitumor activity against sphere-derived lung CSCs. In this study, CSCs were isolated from the non-small cell lung cancer cell line H1299 as tumor spheres under CSC-selective conditions, and found to have increased tumorigenicity, chemoresistance, and higher expression of both embryonic stem cell-related and drug resistance-related genes compared with parental cells. These observations are consistent with the notion that CSCs are tumorigenic, display the ability to self-renew, and generate differentiated progeny that constitute the majority of cells in tumors. Treatment of sphere-derived stem cells with CINN could diminish their CSC-like abilities by decreasing their proliferation and invasive abilities and facilitating their differentiation into CD133-negative cells. Furthermore, CINN treatment increased the sensitivity of CSCs to chemotherapeutic drugs through apoptosis. Of note, xenotransplantation experiments revealed that CINN combined with cisplatin had a synergistic effect in inhibiting the tumorigenicity of CSCs. In summary, our study clearly revealed the presence of a population of sphere-forming cells with stem-like properties among H1299 cells and CINN can attenuate CSC properties of this stem-like cell population. The potential of CINN should be verified further in future studies of anti-CSC therapy.

[TÍTULO / TITLE]: - Induction of the Endoplasmic Reticulum Stress and Autophagy in Human Lung Carcinoma A549 Cells by Anacardic Acid.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Seong YA; Shin PG; Yoon JS; Yadunandam AK; Kim GD

INSTITUCIÓN / INSTITUTION: - Department of Microbiology, College of Natural Sciences, Pukyong National University, 45, Yongso-ro, Nam-Gu, Busan, 608-737, Korea.

RESUMEN / SUMMARY: - Anacardic acid (AA, 2-hydroxy-6-pentadecylbenzoic acid), a constituent of the cashew-nut shell, has a variety of beneficial effects on the treatment of cancer and tumors. However, the fact that AA induces ER stress and autophagy in cancer cell is not known. We investigated the effect of AA on ER-stress and autophagy-induced cell death in cancer cells. Because of our interest in lung cancer, we used the non-small cell lung adenocarcinoma A549 cells treated with 3.0 μg/ml of AA for this
research. In this research we found that AA induces intracellular Ca2+ mobilization and ER stress. AA induced the ER stress-inducing factors, especially IRE1alpha, and the hallmarks of UPR, Grp78/Bip and GADD153/CHOP. AA inhibited the expression of p-PERK and its downstream substrate, p-elf2alpha. We also demonstrated that AA induces autophagy. Up-regulation of autophagy-related genes and the appearance of autophagosome in transfected cells with green fluorescent protein (GFP)-LC3 and GFP-Beclin1 plasmids showed the induction of autophagy in AA-treated A549 cells. The morphological analysis of intracellular organelles by TEM also showed the evidence that AA induces ER stress and autophagy. For the first time, our research showed that AA induces ER stress and autophagy in cancer cells.

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[546]

**TÍTULO / TITLE:** - Capillary isoelectric-focusing immunoassays to study dynamic oncoprotein phosphorylation and drug response to targeted therapies in non-small cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Chen JQ; Lee JH; Herrmann MA; Park KS; Heldman MR; Goldsmith PK; Wang Y; Giaccone G

**INSTITUCIÓN / INSTITUTION:** - 1Collaborative Protein Technology Resource, National Cancer Institute.

**RESUMEN / SUMMARY:** - Developing proteomic biomarkers is valuable for evaluating therapeutic effects of drugs and generating better treatment strategies. However, conventional protein analysis is often challenging due to inadequate sample size of clinical specimens, lack of assay reproducibility, accuracy and sensitivity. A novel capillary isoelectric-focusing (IEF) immunoassay system (NanoPro) was used to study the dynamic phosphorylation status of signaling molecules in non-small cell lung cancer (NSCLC) cells treated with EGFR tyrosine kinase and MEK inhibitors. NanoPro showed the same dynamic ERK phosphorylation as western blotting with good assay reproducibility using 1,000 times less protein. The IEF separation in NanoPro system enables multiple protein phosphorylation isoforms to be resolved and detected simultaneously. With NanoPro, we identified a specific on-target MEK response pattern to MEK inhibitor PD325901, which was not detectable by western blotting. We also revealed a MEK2 signal that may be associated with NSCLC cell sensitivity to EGFR inhibitor erlotinib, and distinguish erlotinib-sensitive from -intrinsic as well as -acquired resistant cells. Moreover, NanoPro could differentiate human ERK1 isoforms from the mouse isoforms based on their pi differences and demonstrated that erlotinib effectively inhibited ERK phosphorylation in targeted human xenograft cancer
cells but not in surrounding mouse stromal cells. With 8 ug of tumor aspirates, we precisely quantified the response of 18 signaling molecules to erlotinib and MEK1 inhibitor treatments in a NSCLC patient. NanoPro’s higher sensitivity, better resolution of protein phosphorylation status and reduced tissue requirement warrant NanoPro’s investigation for future drug development and evaluation of drug effects of targeted therapies.

**RESUMEN / SUMMARY:** Non-small-cell lung cancer (NSCLC) remains the most common cause of cancer-related death worldwide. Traditional cytotoxic agents and their attendant toxicities have remained the mainstay of systemic therapy for this disease, until now. With the identification of novel molecular and immune cancer-specific aberrancies, molecular agents and immunotherapies have garnered increasing attention as attractive targets, with the potential for improved outcomes while mitigating systemic toxicities seen with traditional cytotoxic agents. Despite a longstanding interest in immunotherapy for the treatment of NSCLC, results of prior studies of therapeutic vaccines have failed to show durable or convincingly meaningful clinical responses. However, newer trials of therapeutic vaccines and checkpoint inhibitors have yielded more promising results. In particular, the checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death-1 (PD-1) pathway have shown meaningful clinical responses with manageable toxicities. Large phase III studies are underway, the results of which have the potential to revolutionize the way in which we care for patients with NSCLC. More studies also are needed to investigate the potentially synergistic effects of traditional and immune-based therapies. Given their unique antineoplastic effects, novel immune-specific clinical endpoints also are actively being investigated.
Most patients with lung cancer have non-small cell lung cancer (NSCLC) subtype and have advanced disease at the time of diagnosis. Improvements in both first-line and subsequent therapies are allowing longer survival and enhanced quality of life for these patients. The median overall survival observed in many second-line trials is approximately 9 months, and many patients receive further therapy after second-line therapy. The cytotoxic agents pemetrexed and docetaxel and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib are standard second-line therapies. For patients with EGFR mutation, a TKI is the favored second-line therapy if not already used in first-line therapy. For patients without the EGFR mutation, TKIs are an option, but many oncologists favor cytotoxic therapy. The inhibitor of the EML4/ALK fusion protein, crizotinib, has recently become a standard second-line treatment for patients with the gene rearrangement and has promise for patients with the ROS1 rearrangement.

PURPOSE: Epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer has an oncogene-addicted biology that confers sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Published data suggest that EGFR addiction persists after development of TKI acquired resistance, leading many clinicians to continue TKI with subsequent chemotherapy; however, this strategy has not been formally evaluated. METHODS: We retrospectively reviewed an institutional database to identify patients with advanced EGFR mutation with acquired resistance who...
subsequently received chemotherapy. Patients were classified as receiving chemotherapy with continued erlotinib or chemotherapy alone. We assessed differences in outcomes between the two strategies. RESULTS: Seventy-eight patients were included, 34 treated with chemotherapy and erlotinib and 44 treated with chemotherapy alone. Objective response rate was evaluable in 57 patients and was 41% for those treated with chemotherapy and erlotinib and 18% for those treated with chemotherapy alone. After adjusting for chemotherapy regimen and length of initial TKI course, the odds ratio for the response rate was 0.20 (95% confidence interval: 0.05-0.78; p = .02) favoring treatment with chemotherapy and erlotinib. The median progression-free survival was 4.4 months on chemotherapy and erlotinib and 4.2 months on chemotherapy alone (adjusted hazard ratio = 0.79; 95% confidence interval: 0.48-1.29; p = .34). There was no difference in overall survival. CONCLUSION: This is the first study, to our knowledge, to demonstrate that continuation of EGFR TKI with chemotherapy in patients with acquired resistance improves outcomes compared with chemotherapy alone. We observed an improved response rate but no difference in progression-free survival or overall survival. A larger prospective clinical trial is needed to evaluate this promising strategy further.

[550]

TÍTULO / TITLE: - Impact of baseline and nadir neutrophil index in non-small cell lung cancer and ovarian cancer patients: Assessment of chemotherapy for resolution of unfavourable neutophilia.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Carus A; Gurney H; Gebski V; Harnett P; Hui R; Kefford R; Wilcken N; Ladekarl M; von der Maase H; Donskov F

RESUMEN / SUMMARY: - BACKGROUND: Chronic inflammation has been recognized to foster tumour development. Whether chemotherapy can be used to neutralize chronic inflammation is unclear. METHODS: We evaluated baseline and nadir neutrophils in 111 patients (pts.) with non-small cell lung cancer (NSCLC) and 118 pts. with ovarian cancer (OC) treated with chemotherapy administered with dose-individualization to achieve nadir neutropenia of 1.5. We used predefined baseline neutrophil cut-offs 4.5x10^9/L (NSCLC) and 3.9x10^9/L (OC). RESULTS: Absence of chemotherapy-induced nadir neutropenia (CTCAE grade 0, neutrophils >= LLN) was seen in 23% of OC and 25% of NSCLC pts. Absence of nadir neutropenia was associated with decreased overall survival (OS) compared with presence (>grade 0) of neutropenia (9 vs. 14 months, P = 0.004 for NSCLC and 23 vs. 56 months; P = 0.01 for OC). Obtaining grade ¾ neutropenia did not improve survival compared with grade ½ neutropenia. In multivariate analyses, baseline neutrophils >=4.5x10^9/L HR: 2.0 (95%CI: 1.11-3.44;P = 0.02) and absence of
nadir neutropenia (HR: 1.6; 95%CI: 1.02-2.65;P = 0.04) for NSCLC and absence of nadir neutropenia (HR: 1.7; 95%CI: 1.04-2.93;P = 0.04) for OC were independently associated with short OS. Three prognostic neutrophil index (NI) groups were defined. Favourable NI: low baseline neutrophils and presence of nadir neutropenia (>grade 0), Intermediate NI: elevated baseline neutrophils and presence of nadir neutropenia (>grade 0), and Poor NI: elevated baseline neutrophils and absence of nadir neutropenia (grade 0). For NSCLC patients, the median OS was 18.0, 13.4, and 8.8 months for favourable, intermediate and poor NI, respectively (fav vs. poor P = 0.002; fav vs. intermed P = 0.04; and intermed vs. poor P = 0.03). For OC patients, median OS was 69, 52 and 23 months for favourable, intermediate and poor NI, respectively (fav vs. poor P = 0.03; fav vs. intermed P = 0.3; and intermed vs. poor P = 0.02).

Interestingly, survival rates in the intermediate NI groups indicated that individualised dose of chemotherapy to induce neutropenia may partly overcome the negative impact of elevated baseline neutrophils. CONCLUSIONS: A neutrophil index comprising elevated baseline neutrophils and absence of neutropenia identified a high risk group of NSCLC and ovarian cancer patients with only modest effect of chemotherapy. New treatment options for this subset of patients are required.

[551]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fusi A; Metcalf R; Krebs M; Dive C; Blackhall F
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Withington, Manchester, M20 4BX, UK.
OPINION STATEMENT: Recent years have witnessed increased interest in the detection of circulating tumour cells (CTCs) for diagnosis, monitoring, and treatment decision making in patients with cancer. Factors that have led to accelerated research in this field include advances in technologies for examination of intact CTCs, personalised medicine with treatment selection according to molecular characteristics, and continued lack of understanding of the biology of treatment resistance and metastasis. CTCs offer promise as a surrogate for tissue where there is insufficient tissue for molecular analysis and where there is a requirement to serially monitor molecular changes in cancer cells through treatment or on progression. In patients with either small cell or non-small cell lung cancer (NSCLC), there is evidence that CTC number is prognostic and that CTCs counted before and after treatment mirror treatment response. In patients with molecularly defined subtypes of NSCLC, CTCs demonstrate the same molecular changes as the cancer cells of the tumour.
However, CTCs are not quite ready for “primetime” in the lung cancer clinic. There are still more questions than answers with respect to the optimal technologies for their detection and analysis, their biological significance, and their clinical utility. Despite this the current pace of progress in CTC technology development seems set to make “liquid biopsies” a clinical reality within the next decade. For the everyday clinician and clinical trialist, it will be important to maintain knowledge of the strengths and weaknesses of the technologies and evolving evidence base for CTCs as a routinely used diagnostic tool.


RESUMEN / SUMMARY: AIMS: Total dose, dose per fraction, number of fractions and treatment time are important determinants of the biological effect of a radiation regimen. Several randomised clinical trials (RCTs) have tested a variety of dosing regimens in advanced unresected non-small cell lung cancer, but survival remains poor. This work used past RCT data to develop and validate a predictive model that could help in designing new radiation regimens for successful testing in RCTs.

MATERIALS AND METHODS: Eleven RCTs that compared radiation regimens alone were used to define the relationship between radiation regimens and 2-year survival. On the basis of this relationship, predictive models were developed. Predicted values were internally and externally validated against observed values from the same 11 RCTs and 21 other RCTs. Scatter plots and Pearson’s correlation coefficient for validation. Finally, regimens were explored that could improve survival. RESULTS: Increments in the total dose, dose per day and the number of treatment days were associated with improved survival; increments in dose-squared and treatment weeks were associated with reduced survival. The observed and predicted values were similar on internal (r = 0.96) and external validation (r = 0.76). Regimens that delivered a higher total dose over a shorter time had higher survival rates compared with the
standard (60 Gy, 30 fractions, 6 weeks); survival may be improved by delivering the standard treatment in 5 weeks rather than 6 weeks. CONCLUSION: The developed model can predict the effect of thoracic radiation on survival in advanced non-small cell lung cancer patients. It is a useful tool for designing new radiation regimens for clinical trials.

[553]
TÍTULO / TITLE: - High expression levels of class III beta-tubulin in resected non-small cell lung cancer patients are predictive of improved patient survival after vinorelbine-based adjuvant chemotherapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang Y; Yang H; Liu J; Deng Q; He P; Lin Y; Jiang J; Gu X; Mo M; Pan H; Xiong X; Qiu Y; He J
INSTITUCIÓN / INSTITUTION: - Southern Medical University, Guangzhou, Guandong 510515; ; Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, Guandong 510120;
RESUMEN / SUMMARY: - The aim of the present study was to determine the frequency and predictive value of the expression of tumor microtubule components in patients with resected non-small cell lung cancer (R-NSCLC) subsequently treated with vinorelbine-based adjuvant chemotherapy. The expression of the microtubule components was evaluated in 85 R-NSCLC tumor samples using immunohistochemistry. All patients received vinorelbine-based chemotherapy. The predictive value of microtubule protein expression for disease-free survival (DFS) and overall survival (OS) was assessed. The expression of the microtubule components was not associated with any baseline clinicopathological factors in the R-NSCLC patients. High tumor expression levels of class III beta-tubulin were correlated with an improved DFS (P=0.033) and a trend towards a longer OS (P=0.226). Class II and IV beta-tubulins were not correlated with patient outcome. Multivariate analysis of factors, including gender, age, histology, stage and class II, III and IV beta-tubulin expression demonstrated that high levels of class III beta-tubulin expression were correlated independently with DFS (P= 0.031). These findings suggest that high class III beta-tubulin expression levels in resected tumors are predictive of improved DFS in R-NSCLC patients receiving vinorelbine-based chemotherapy.

[554]
TÍTULO / TITLE: - Lower gefitinib dose led to earlier resistance acquisition before emergence of T790M mutation in EGFR mutated lung cancer model.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Non-small cell lung cancers (NSCLCs) with epidermal growth factor receptor (EGFR) mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs); however, unlike cytotoxic agents, it is generally accepted that minimal doses of drugs inhibiting target molecules are sufficient when molecular-targeted agents, including EGFR-TKIs, are administered. Thus, any utility of higher doses remains unclear. We compared low-dose (15 mg/kg) gefitinib therapy with high-dose (50 mg/kg) therapy using an EGFR-mutated lung cancer xenograft model. Both gefitinib doses induced tumor shrinkage, but tumors regrew in the low-dose group within 1 month, whereas tumors in the high-dose group did not. Neither the T790M mutation nor MET amplification was apparent in regrown tumors. We also compared outcomes after administration of two doses of gefitinib (5 and 25 mg/kg) in a transgenic EGFR-mutated lung cancer mouse model. In line with the results obtained using the xenograft model, both gefitinib doses completely inhibited tumor growth, but tumors treated with the lower dose of gefitinib developed earlier drug resistance. In conclusion, administration of a low gefitinib dose caused tumors to become drug-resistant prior to acquisition of the T790M mutation or MET amplification in EGFR-mutated models of lung cancer. This suggests that it is important to optimize the EGFR-TKI dose for treatment of EGFR mutation-associated lung cancer. Gefitinib may need to be administered at a dose greater than the minimum required for inhibition of target molecules. This article is protected by copyright. All rights reserved.

[SS5]

TÍTULO / TITLE: - BAP1 Protein is a Progression Factor in Malignant Pleural Mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Arzt L; Quehenberger F; Halbwedl I; Mairinger T; Popper HH

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Research Unit for Molecular Lung- and Pleura Pathology, Medical University of Graz, Auenbrugerplatz 25, 8036, Graz, Austria, lisa.arzt@medunigraz.at.

RESUMEN / SUMMARY: - Human malignant pleural mesothelioma (MPM) is an aggressive cancer due to former asbestos exposure with little knowledge about prognostic
factors of outcome and resistance to conventional therapy. BRCA1-associated protein 1 (BAP1) is a tumor suppressor gene that is frequently lost in MPM. Germline mutations of BAP1 predispose to several different tumors including malignant mesothelioma. Our study aimed to clarify if asbestos exposure has an influence on BAP1 expression and if BAP1 expression could be used as a prognostic factor of outcome. An immunohistochemical staining for BAP1 was performed on 123 MPM tissue samples and the expression levels have been correlated with asbestos exposure and overall survival time. BAP1 expression was not associated with asbestos exposure but we detected a significant effect of BAP1 expression on overall survival time - the higher the BAP1 expression (non-mutated BAP1), the shorter the overall survival. BAP1 mutation has been linked to non-asbestos induced familial mesotheliomas, which usually belong to the long survivor group and BAP1 is most probably functioning differently than in sporadic cases. Further investigations need to be performed to characterize the BAP1 mutations and to identify the BAP1 downstream targets in MPM.

[556]

**TÍTULO / TITLE:** Curcumin sensitizes lung adenocarcinoma cells to apoptosis via intracellular redox status mediated pathway.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Kaushik G; Kaushik T; Yadav SK; Sharma SK; Ranawat P; Khanduja KL; Pathak CM

**INSTITUCIÓN / INSTITUTION:** Department of Biophysics, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012, India.

**RESUMEN / SUMMARY:** The present study demonstrates that curcumin acts as pro-oxidant and sensitizes human lung adenocarcinoma epithelial cells (A549) to apoptosis via intracellular redox status mediated pathway. Results indicated that curcumin induced cell toxicity (light microscopy and MTT assay) and apoptosis (Annexin-V-FITC/PI labeling and caspase-3 activity) in these cells. These events seem to be mediated through generation of reactive oxygen species (ROS) and superoxide radicals (SOR) and enhanced levels of lipid peroxidation. These changes were accompanied by increase in oxidized glutathione (GSSG), reduced glutathione (GSH) and gamma-glutamylcysteine synthetase (gamma-GCS) activity, but decrease in GSH/GSSG ratio. The induction of apoptosis and decrease in GSH/GSSG ratio was also accompanied by sustained phosphorylation and activation of p38 mitogen activated protein kinase (MAPK). On the other hand, addition of N-acetyl cysteine (NAC), an antioxidant, blocked the curcumin-induced ROS production and rescued malignant cells from curcumin-induced apoptosis through caspase-3 deactivation. However, L-buthionine sulfoximine (BSO), a GSH synthesis blocking agent, further enhanced curcumin-induced ROS production.
and apoptosis in A549 cells. Decreased GSH/GSSG ratio seems to be a crucial factor for the activation of MAPK signaling cascade by curcumin. The study therefore, provides an insight into the molecular mechanism involved in sensitization of lung adenocarcinoma cells to apoptosis by curcumin.
**TÍTULO / TITLE:** The association of F-FDG PET/CT parameters with survival in malignant pleural mesothelioma.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Klabatsa A; Chicklore S; Barrington SF; Goh V; Lang-Lazdunski L; Cook GJ

**INSTITUCIÓN / INSTITUTION:** Department of Thoracic Oncology, Guys and St Thomas’ NHS Foundation Trust, London, UK.

**RESUMEN / SUMMARY:** PURPOSE: Malignant pleural mesothelioma (MPM) is a disease with poor prognosis despite multimodal therapy but there is variation in survival between patients. Prognostic information is therefore potentially valuable in managing
patients, particularly in the context of clinical trials where patients could be stratified according to risk. Therefore we have evaluated the prognostic ability of parameters derived from baseline 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT). METHODS: In order to determine the relationships between metabolic activity and prognosis we reviewed all 18F-FDG PET/CT scans used for pretreatment staging of MPM patients in our institution between January 2005 and December 2011 (n = 60) and measured standardised uptake values (SUV) including mean, maximum and peak values, metabolic tumour volume (MTV) and total lesion glycolysis (TLG). Overall survival (OS) or time to last censor was recorded, as well as histological subtypes. RESULTS: Median follow-up was 12.7 months (1.9-60.9) and median OS was 14.1 months (1.9-54.9). By univariable analysis histological subtype (p = 0.013), TLG (p = 0.024) and MTV (p = 0.038) were significantly associated with OS and SUVmax was borderline (p = 0.051). On multivariable analysis histological subtype and TLG were associated with OS but at borderline statistical significance (p = 0.060 and 0.058, respectively). No statistically significant differences in any PET parameters were found between the epithelioid and non-epithelioid histological subtypes. CONCLUSION: 18F-FDG PET/CT parameters that take into account functional volume (MTV, TLG) show significant associations with survival in patients with MPM before adjusting for histological subtype and are worthy of further evaluation to determine their ability to stratify patients in clinical trials.

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[560]

TÍTULO / TITLE: - Detection of novel paraja ring finger 2-fer tyrosine kinase mRNA chimeras is associated with poor postoperative prognosis in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kawakami M; Ishikawa R; Amano Y; Sunohara M; Watanabe K; Ohishi N; Yatomi Y; Nakajima J; Fukayama M; Nagase T; Takai D
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The University of Tokyo Hospital, Tokyo, Japan; Department of Clinical Laboratory, The University of Tokyo Hospital, Tokyo, Japan.
RESUMEN / SUMMARY: - Previously, we reported that the overexpression of fer tyrosine kinase (FER), a non-receptor tyrosine kinase, is correlated with poor postoperative prognosis and cancer-cell survival in non-small cell lung cancer (NSCLC). In the present study, we further analyzed FER-overexpressed NSCLC cases and identified various patterns of chimeric mRNAs, composed of paraja ring finger 2 (PJA2) and FER. We detected no genomic rearrangements between PJA2 and FER and attributed these chimeric mRNAs to alterations at the transcriptome level: i.e., trans-splicing. Several chimeric patterns were detected concurrently in each patient, and the pattern sets
varied among patients, although the pattern in which PJA2 exon 1 was fused to FER exon 3 (designated as Pe1-Fe3 mRNA) was detected constantly. Therefore, in a wide screening for PJA2-FER mRNAs in NSCLC, we focused on this chimeric pattern as a representative chimera. In analyses of 167 NSCLC samples, Pe1-Fe3 mRNA was identified in about 10% of the patients, and the presence of chimeric mRNA was significantly correlated with a high expression level of parental FER mRNA. Furthermore, we found that the detection of Pe1-Fe3 mRNA was correlated with poor postoperative survival periods in NSCLC, consistent with a previous finding in which FER overexpression was correlated with poor postoperative prognosis in NSCLC. This report is the first to suggest a correlation between chimeric mRNA and the expression level of parental mRNA. Furthermore, our findings may be clinically beneficial, suggesting that PJA2-FER mRNAs might serve as a novel prognostic biomarker in NSCLC.

[561]

**TÍTULO / TITLE:** - Enhanced interaction between natural killer cells and lung cancer cells: involvement in gefitinib-mediated immunoregulation.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** - J Transl Med. 2013 Aug 12;11(1):186.

**AUTORES / AUTHORS:** - He S; Yin T; Li D; Gao X; Wan Y; Ma X; Ye T; Guo F; Sun J; Lin Z; Wang Y

**RESUMEN / SUMMARY:** - BACKGROUND: Natural killer (NK) cells can kill tumor cells in a non-MHC-restricted manner. However, cancer cells frequently escape from the attack of NK cells by multiple ways. In this study, we investigated the effect of gefitinib on the interaction between NK cells and lung cancer cells. METHODS: 51Cr release assay, CD107a assay, and IFN-gamma secretion assay were performed to detect the sensitivity of lung cancer cell lines A549 and H1975 to NK cells cytotoxicity in the presence of gefitinib. Human NK cells were co-cultured with A549 and H1975 cell lines in the presence of gefitinib. NKG2D ligands, ULBP1, ULBP2, MICA, and MHC-I on tumor cells, and NKG2D, NKp44 and NKp46 on NK cells were evaluated with flow cytometry. 51Cr release assay was performed when NKG2D antibody were added into the co-culture system. Expressions of stat3 and LC3 I/II on tumor cells were determined with western blot after co-cultured with NK cells. After treated with gefitinib, mannose-6-phosphate receptor (MPR) on H1975 cells was evaluated by flow cytometry. 51Cr release assay were performed when MPR antagonist were used. RESULTS: Gefitinib increased cytotoxicity of NK cells to human lung cancer H1975 cells with EGFR L858R + T790M mutations, while not in A549 cells with wild type EGFR. Gefitinib could block the immune escape by up-regulating the expression of NKG2D ligands ULBP1, ULBP2 or MICA on tumor cells and NKG2D on NK cells in the co-culture system. Gefitinib and NK
cells up-regulated MHC-I expression in A549 while not in H1975 cells. NKG2D antibody blocked the enhanced NK cytotoxicity by gefitinib. The combination of NK cells and gefitinib could significantly down-regulate stat3 expression. Furthermore, NK cell-mediated tumor cell autophagy was observed in A549 cells while not in H1975 cells. Notably, gefitinib increased autophagy and MPR expression in H1975 cells, which improved the sensitivity to NK cell-based immunotherapy. CONCLUSIONS: Gefitinib greatly enhanced NK cell cytotoxicity to lung cancer cells with EGFR L858 + T790M resistance mutation. Combination of EGFR tyrosine inhibitors and NK cells adoptive immunotherapy may represent a potentially effective strategy for patients with non-small cell lung cancer.

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tumor-cell content and the degree of DNA degradation. Using sample multiplexing, focused MPS approached diagnostically acceptable cost rates.

[563]

Título / Title: Definition der stereotaktischen Strahlentherapie: Behandlung des nichtkleinzelligen Bronchialkarzinoms (NSCLC) Grad I.

Título / Title: Definition of stereotactic body radiotherapy: Principles and practice for the treatment of stage I non-small cell lung cancer.

Resumen / Summary: This report from the Stereotactic Radiotherapy Working Group of the German Society of Radiation Oncology (Deutschen Gesellschaft für Radioonkologie, DEGRO) provides a definition of stereotactic body radiotherapy (SBRT) that agrees with that of other international societies. SBRT is defined as a method of external beam radiotherapy (EBRT) that accurately delivers a high irradiation dose to an extracranial target in one or few treatment fractions. Detailed recommendations concerning the principles and practice of SBRT for early stage non-small cell lung cancer (NSCLC) are given. These cover the entire treatment process; from patient selection, staging, treatment planning and delivery to follow-up. SBRT was identified as the method of choice when compared to best supportive care (BSC), conventionally fractionated radiotherapy and radiofrequency ablation. Based on current evidence, SBRT appears to be on a par with sublobar resection and is an effective treatment option in operable patients who refuse lobectomy.

[564]

Título / Title: Vascular invasion features affect recurrence in lung adenocarcinoma. Immunohistochemical staining of tumor tissue with E-cadherin antibody in cases with intratumoral vascular invasion. See also Kaseda, K., et al.

Resumen / Summary: This report from the Stereotactic Radiotherapy Working Group of the German Society of Radiation Oncology (Deutschen Gesellschaft für Radioonkologie, DEGRO) provides a definition of stereotactic body radiotherapy (SBRT) that agrees with that of other international societies. SBRT is defined as a method of external beam radiotherapy (EBRT) that accurately delivers a high irradiation dose to an extracranial target in one or few treatment fractions. Detailed recommendations concerning the principles and practice of SBRT for early stage non-small cell lung cancer (NSCLC) are given. These cover the entire treatment process; from patient selection, staging, treatment planning and delivery to follow-up. SBRT was identified as the method of choice when compared to best supportive care (BSC), conventionally fractionated radiotherapy and radiofrequency ablation. Based on current evidence, SBRT appears to be on a par with sublobar resection and is an effective treatment option in operable patients who refuse lobectomy.
TÍTULO / TITLE: Subdiaphragmatic bronchogenic cyst at the gastroesophageal junction presenting with Dysphagia: a case report.

RESUMEN / SUMMARY: BACKGROUND: Bronchogenic cysts are benign lesions derived from the primitive foregut. They frequently occur in the mediastinum, most commonly at the subcarinal level. Subdiaphragmatic location for bronchogenic cysts is extremely rare. METHODS: A 40-year-old woman presented with worsening dysphagia and was diagnosed as a bronchogenic cyst arising from infradiaphragmatic esophagus by computed tomographic scan and endoscopic ultrasound-guided aspiration. Total laparoscopic enucleation of the cystic mass was performed. RESULTS: The postoperative esophagogram revealed no leak or reflux and the patient was discharged on day 2. The histopathologic examination revealed a bronchogenic cyst. No recurrence of the cyst or symptoms was noted at 6 months. CONCLUSIONS: Infradiaphragmatic bronchogenic cysts are uncommon and may become symptomatic secondary to compression of surrounding structures. A complete resection by laparoscopy is feasible and represents a safe and minimally invasive alternative to traditional resection through laparotomy or thoracotomy.

TÍTULO / TITLE: In Search of the Ideal Immunopanel to Distinguish Metastatic Mammary Carcinoma From Primary Lung Carcinoma: A Tissue Microarray Study of 207 Cases.

RESUMEN / SUMMARY: BACKGROUND: Bronchogenic cysts are benign lesions derived from the primitive foregut. They frequently occur in the mediastinum, most commonly at the subcarinal level. Subdiaphragmatic location for bronchogenic cysts is extremely rare. METHODS: A 40-year-old woman presented with worsening dysphagia and was diagnosed as a bronchogenic cyst arising from infradiaphragmatic esophagus by computed tomographic scan and endoscopic ultrasound-guided aspiration. Total laparoscopic enucleation of the cystic mass was performed. RESULTS: The postoperative esophagogram revealed no leak or reflux and the patient was discharged on day 2. The histopathologic examination revealed a bronchogenic cyst. No recurrence of the cyst or symptoms was noted at 6 months. CONCLUSIONS: Infradiaphragmatic bronchogenic cysts are uncommon and may become symptomatic secondary to compression of surrounding structures. A complete resection by laparoscopy is feasible and represents a safe and minimally invasive alternative to traditional resection through laparotomy or thoracotomy.

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Background: Distinguishing metastatic carcinoma of breast origin (MCBO) to lung from primary lung carcinomas (PLC) is a diagnostic quandary with clinical ramifications. Immunostains CK7, CK20, ER, PR, and Mammaglobin as well as pertinent negative stains are utilized but prove insufficient. We set out to identify stains either alone or as a group that would better discern between these 2 entities.

Design: Tissue microarrays of 109 MCBO to lung and 102 PLC were stained with CK7, CK20, ER, PR, AR, Mammaglobin, Napsin A, GATA-3, and TTF-1. An H-score was calculated for each case and stain.

Results: The highest area under the receiver-operating characteristic curves for each stain was seen with GATA-3 (0.817), Napsin A (0.817), and TTF-1 (0.854). When all possible combinations were analyzed, GATA-3 and TTF-1 proved to correctly classify with the highest accuracy (0.934). Combinations of GATA-3 and Napsin A (0.920) and GATA-3, Napsin A, and TTF-1 (0.933) were not significantly different from GATA-3 and TTF-1. The odds ratios for each stain and combination of stains showed that those for GATA-3 and TTF-1 were divergent, signifying that cases with higher H-scores for GATA-3 and TTF-1 were more likely to be classified as MCBO and PLC, respectively.

Conclusions: GATA-3 and TTF-1 can correctly classify a case as either MCBO or PLC in 93.4% of cases. Although highly specific and sensitive for PLC, Napsin A in lieu of TTF-1 or as an additional stain did not improve classification accuracy.

Title: Dosimetric and clinical predictors of acute esophagitis in lung cancer patients in Turkey treated with radiotherapy.

Background: The purpose of this study was to determine the clinical and dosimetric factors associated with acute esophagitis (AE) in lung cancer patients treated with conformal radiotherapy (RT) in Turkey. Materials and Methods: In this retrospective review 104 lung cancer patients were examined. Esophagitis grades were verified weekly during treatment, and at 1 week, and 1 and 2 months afterwards. The clinical parameters included patient age, gender, tumor pathology, number of chemotherapy treatments before RT, concurrent chemotherapy, radiation dose, tumor response to RT, tumor localization, interruption of RT, weight loss, tumor and nodal stage and tumor volume. The following dosimetric parameters were analyzed for correlation of AE: The maximum (Dmax) and mean (Dmean) doses delivered to the esophagus, the percentage of esophagus volume receiving ≥10 Gy (V10), ≥20 Gy (V20), ≥30 Gy (V30), ≥35 Gy (V35), ≥40 Gy (V40), ≥45 Gy (V45),
Results: Fifty-five patients (52.9%) developed AE. Maximum grades of AE were recorded: Grade 1 in 51 patients (49%), and Grade 2 in 4 patients (3.8%). Clinical factors had no statistically significant influence on the incidence of AE. In terms of dosimetric findings, correlation analyses demonstrated a significant association between AE and Dmax (>5117 cGy), Dmean (>1487 cGy) and V10-60 (percentage of volume receiving >10 to 60 Gy). The most significant relationship between RT and esophagitis were in Dmax (>5117 cGy) (p=0.002) and percentage of esophageal volume receiving >30 Gy (V30>31%) (p=0.008) in the logistic regression analysis. Conclusions: The maximum dose esophagus greater than 5117 cGy and approximately one third (31%) of the esophageal volume receiving >30 Gy was the most statistically significant predictive factor associated with esophagitis due to RT.

[568] TÍTULO / TITLE: - Bevacizumab in Advanced NSCLC: Chemotherapy Partners and Duration of Use.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gentzler RD; Yentz SE; Patel JD
INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 676 North St. Clair, Suite 850, Chicago, IL, 60611, USA.
RESUMEN / SUMMARY: - OPINION STATEMENT: Bevacizumab is an effective targeted therapy with demonstrated survival benefits for many patients with advanced nonsquamous non-small cell lung cancer (NSCLC). Some patient populations are at higher risk for bleeding complications and bevacizumab should be avoided, but advanced age should not be used as the sole exclusion criterion for use. Bevacizumab is generally a well-tolerated therapy that can be safely given in combination with multiple chemotherapy agents in the induction and maintenance phases of therapy. The optimal maintenance strategy is yet to be determined and is the focus of ongoing trials, such as ECOG 5508. Early use of bevacizumab in the adjuvant setting and continued use in the second-line setting are being investigated in current clinical trials.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
The knowledge that the organism’s metabolome is a potentially informative mirror of the impact of disease and its dynamics has led to promising developments in cancer research, strongly geared toward the discovery of new biomarkers of disease onset and progression. The present text reviews the advances made in the last 10 years in lung cancer research making use of the metabolomics strategies, particularly concerning metabolite profiling of human biofluids (blood serum and plasma, urine and others), expected to reflect the deviant metabolic behavior of lung tumors. The main goal of this article is to provide the reader with an up-to-date summary of the main metabolic variations taking place in biofluids, in relation to lung cancer, as well as of the analytical strategies employed to unveil them. Furthermore, particular needs and challenges are identified and possible developments envisaged.
stage-specific costs were estimated from medical records of patients diagnosed and treated at Hadassah Medical Center in the period 2003 to 2004. The analysis considered possible biases—lead time, overdiagnosis, and self-selection. Cost per quality-adjusted-life-year (QALY) gained by screening was estimated. RESULTS: Base-case incremental cost per QALY gained was $1464 (2011 prices). Extensive sensitivity analysis affirmed the low cost per QALY gained. The cost per QALY gained is lower than $10,000 with probability 0.937 and is lower than $20,000 with probability 0.978. CONCLUSIONS: Our analysis suggests that baseline LDCT lung cancer screening in Israel presents a good value for the money and should be considered for inclusion in the National List of Health Services financed publicly.

[571]

TÍTULO / TITLE: - Epidermal growth factor receptor exon 20 mutation increased in post-chemotherapy patients with non-small cell lung cancer detected with patients’ blood samples.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Wang Y; Bao W; Shi H; Jiang C; Zhang Y

INSTITUCIÓN / INSTITUTION: - Department of Basic Medical Science, Zhejiang Chinese Medical University. Hangzhou, China.

RESUMEN / SUMMARY: - PURPOSE: Patients with non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR)-mutations have excellent response to EGFR tyrosine kinase inhibitors (TKIs), and exon 20 mutation accounts for most of TKI drug resistance. Nested polymerase chain reaction (PCR) was used to detect EGFR exon 20 mutations of patients with NSCLC after chemotherapy. The same is being analyzed with patients’ characteristics. METHODS: Peripheral blood samples were collected from 273 patients with NSCLC, including 143 with adenocarcinoma (ADC) and 130 with squamous cell carcinoma (SCC), after chemotherapy. DNA was extracted from whole blood for nested PCR amplification and purification. Sequencing was carried out in an automated 3730 sequencer, followed by analysis of EGFR exon 20 mutations from nested PCR products. RESULTS: The mutations of EGFR exon 20 were mainly point mutations in rs1050171 (c.2361A>G) and rs56183713 (c.2457G>A). The point mutation was 28.21%, 28.46%, and 27.97% in patients with NSCLC, ADC and SCC, respectively. Men had an equivalent mutation (27.18%) to women (30.77%). The mutation in smokers and nonsmokers was 27.68% and 29.17%, respectively. In unselected patients, there was no correlation between EGFR exon 20 mutations and patients’ characteristics of age, gender, smoking history, histologic type, or tumor-node-metastasis (TNM) staging system. In subgroup analyses, the EGFR mutation of patients with SCC was correlated with TNM stage [P = .013; odds ratio = 1.758; 95% confidence interval (CI) = 1.125-2.747]. CONCLUSIONS: The data indicate that the chemotherapy...
may induce EGFR-TKI-resistant mutation in NSCLC cells and EGFR-TKI should be used in the early stage of NSCLC but not after chemotherapy.
Non-small cell lung cancer is possibly the solid tumor with more potential drugable molecular targets, but the smallest tumor specimens. An optimization of tumor tissue handling is then mandatory. In this landscape, the precise definition of non-small cell lung cancer histologic type had a renewal role in selecting different therapeutic strategies, also leading to a large use of immunohistochemistry even in malignancies showing an overt morphologic differentiation. We suggest here 4 different clinicopathologic scenarios with some helpful rules aimed at preventing unnecessary and expensive immunostains, then underlining the ageless value of morphology and preserving tumor tissues for molecular investigations.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Takagi-Kimura M; Yamano T; Tamamoto A; Okamura N; Okamura H; Hashimoto-Tamaoki T; Tagawa M; Kasahara N; Kubo S

INSTITUCIÓN / INSTITUTION: - Department of Genetics, Hyogo College of Medicine, Nishinomiya, Japan.

RESUMEN / SUMMARY: - Oncolytic virotherapy using adenoviruses has potential for therapeutic benefits in malignant mesothelioma. However, the downregulation of coxackie virus/adenovirus receptor (CAR) expression is frequently a critical rate-limiting factor that impedes the effectiveness of adenovirus serotype 5 (Ad5)-based vectors in many cancer types. We evaluated CAR (Ad5 receptor) and CD46 (adenovirus serotype 35 [Ad35] receptor) expression in six human malignant mesothelioma cell lines. Very low CAR expression was observed in MSTO-211H and NCI-H2052 cells, whereas the other cell lines showed strong expression. In contrast, CD46 was highly expressed in all mesothelioma cell lines. On this basis, we replaced the CAR binding sequence of Ad5 with the CD46 binding sequence of Ad35 in the replication-defective adenoviruses and the tumor-specific midkine promoter-regulated oncolytic adenoviruses. By this fiber modification, the infectivity, virus progeny production, and in vitro cytocidal effects of the adenoviruses were significantly enhanced in low CAR-expressing MSTO-211H and NCI-H2052 cells, also resulting in similar or even higher levels in high CAR-expressing mesothelioma cell lines. In MSTO-211H xenograft models, the fiber-modified oncolytic adenovirus significantly enhanced antitumor effect compared to its equivalent Ad5-based vector. Our data demonstrate that Ad35
fiber modification of binding tropism in a midkine promoter-regulated oncolytic Ad5 vector confers transductional targeting to oncolytic adenoviruses, thereby facilitating more effective treatment of malignant mesothelioma.

[575]
**TÍTULO / TITLE:** Sequential Chemoradiotherapy with Accelerated Hypofractionated Radiotherapy Compared to Concurrent Chemoradiotherapy with Standard Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer.

**RESUMEN / SUMMARY:** To compare the outcomes and treatment-related toxicities of two chemoradiotherapy schedules given to the patients with unresectable locally advanced non-small cell lung cancer (NSCLC): sequential chemotherapy with accelerated hypofractionated radiotherapy (SCRT), and concurrent chemotherapy with standard radiotherapy (CCRT), 68 patients from two prospective clinical trials were included. Thirty-four patients were treated with SCRT using an accelerated hypofractionated radiation schedule, 34 patients received CCRT with standard radiation. Between the two treatment groups there were no significant differences in terms of overall survival, progression-free survival (PFS), locoregional-PFS or distant metastasis-PFS. For the SCRT group, the median survival time and 2- and 4-year overall survival rates were 19 months, 38.2%, and 23.5%, respectively, and for the CCRT group these were 19 months, 44.1%, and 19.6%. Esophageal and constitutional toxicities were more pronounced in the CCRT group, while there was no significant difference in pulmonary toxicities. The results suggest that for unresectable stage III NSCLC, the outcomes of SCRT with accelerated hypofractionated radiotherapy and CCRT with standard radiotherapy are similar, but the toxicities associated with treatment are less in the SCRT group.

[576]
**TÍTULO / TITLE:** Screening for lung cancer with low-dose computed tomography.

**RESUMEN / SUMMARY:** To compare the outcomes and treatment-related toxicities of two chemoradiotherapy schedules given to the patients with unresectable locally advanced non-small cell lung cancer (NSCLC): sequential chemotherapy with accelerated hypofractionated radiotherapy (SCRT), and concurrent chemotherapy with standard radiotherapy (CCRT), 68 patients from two prospective clinical trials were included. Thirty-four patients were treated with SCRT using an accelerated hypofractionated radiation schedule, 34 patients received CCRT with standard radiation. Between the two treatment groups there were no significant differences in terms of overall survival, progression-free survival (PFS), locoregional-PFS or distant metastasis-PFS. For the SCRT group, the median survival time and 2- and 4-year overall survival rates were 19 months, 38.2%, and 23.5%, respectively, and for the CCRT group these were 19 months, 44.1%, and 19.6%. Esophageal and constitutional toxicities were more pronounced in the CCRT group, while there was no significant difference in pulmonary toxicities. The results suggest that for unresectable stage III NSCLC, the outcomes of SCRT with accelerated hypofractionated radiotherapy and CCRT with standard radiotherapy are similar, but the toxicities associated with treatment are less in the SCRT group.
A Study of the Anatomic Changes and Dosimetric Consequences in Adaptive CRT of Non-small-cell Lung Cancer Using Deformable CT and CBCT Image Registration.

The aim of this study is to evaluate anatomic lung tumor changes and dosimetric consequences utilizing the deformable daily kilovolt (KV) cone-beam computer tomography (CBCT) image registration. Five patients diagnosed with NSCLC were treated with three-dimensional conformal radiotherapy (3D CRT) and 10 daily KV CBCT image sets were acquired for each patient. Each CBCT image and plan CT were imported into the deformable image registration (DIR) system. The plan CT image was deformed by the DIR system and a new contour on CBCT was obtained by using the auto-contouring function of the DIR. These contours were individually marked as CBCT f1, CBCT f2, ..., and CBCT f10, and imported into a treatment planning system (TPS). The daily CBCT plan was individually generated with the same planning criteria based on new contours. These plans were individually marked as CBCTp1, CBCTp2, ..., and CBCTp10, followed by generating a dose accumulation plan (DA plan) in original pCT image contour sets by adding all CBCT plans using Varian Eclipse TPS. The maximum, minimum and mean doses to the plan target volume (PTV) in the 5 DA plans were the same with the CT plans. However, the volume of radiation 5, 10, 20, 30, and 50 Gy of the total lungs in DA plans were less than those of the CT plans. The maximum dose of the spinal cord in the DA plans were average 27.96% less than the CT plans. The mean dose for the left, right, and total lungs in the DA plans were reduced by 13.80%, 23.65%, and 12.96%, respectively. The adaptive 3D CRT based on the deformable registration can reduce the dose to the lung and the spinal cord with the same PTV dose coverage. Moreover, it provides a method for further adaptive radiotherapy exploration.
TÍTULO / TITLE: Individual nodule tracking in micro-CT images of a longitudinal lung cancer mouse model.

RESUMEN / SUMMARY: We present and evaluate an automatic and quantitative method for the complex task of characterizing individual nodule volumetric progression in a longitudinal mouse model of lung cancer. Fourteen A/J mice received an intraperitoneal injection of urethane. Respiratory-gated micro-CT images of the lungs were acquired at 8, 22, and 37 weeks after injection. A radiologist identified a total of 196, 585 and 636 nodules, respectively. The three micro-CT image volumes from every animal were then registered and the nodules automatically matched with an average accuracy of 99.5%. All nodules detected at week 8 were tracked all the way to week 37, and volumetrically segmented to measure their growth and doubling rates. 92.5% of all nodules were correctly segmented, ranging from the earliest stage to advanced stage, where nodule segmentation becomes more challenging due to complex anatomy and nodule overlap. Volume segmentation was validated using a foam lung phantom with embedded polyethylene microspheres. We also correlated growth rates with nodule phenotypes based on histology, to conclude that the growth rate of malignant tumors is significantly higher than that of benign lesions. In conclusion, we present a turnkey solution that combines longitudinal imaging with nodule matching and volumetric nodule segmentation resulting in a powerful tool for preclinical research.

AUTORES / AUTHORS: Rudyanto RD; Bastarrika G; de Biurrun G; Agorreta J; Montuenga LM; Ortiz-de-Solorzano C; Munoz-Barrutia A

INSTITUCIÓN / INSTITUTION: Cancer Imaging Laboratory, Oncology Division, Center for Applied Medical Research, University of Navarra, 55 Pio XII, 31008 Pamplona, España. Electronic address: rrudyanto@alumni.unav.es.

RESUMEN / SUMMARY: - In this geostatistical analysis we present the results of interrelation between unemployment rate and lung cancer incidence ratios in the Province of Opole, Poland. In the study, unemployment statistics and population data were analyzed together with the registered (histopathologically confirmed) lung cancer cases (C34, ICD10) in sex-stratified working age population (18-65 years). The data were collected in the years 2006-2008 in the Statistical Office in Opole and Opole Cancer Registry, Poland. The statistically significant positive correlation/interrelation between unemployment rate and lung cancer incidence ratios in male population was established; in females, this effect was statistically insignificant. The obtained results are consistent with the most up-to-date reports supporting the thesis that a higher burden of disease is observed in more deprived areas. The statistics may have practical relevance in terms of improving health status of the local population following economic reforms.

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TÍTULO / TITLE: - Levothyroxine and lung cancer in females: the importance of oxidative stress.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1186/1477-7827-11-75
AUTORES / AUTHORS: - Cornelli U; Belcaro G; Recchia M; Finco A
INSTITUCIÓN / INSTITUTION: - Cor Con International-Ox Res Dept, Parma(PR), Italy. finco.annarosa@libero.it.
RESUMEN / SUMMARY: - BACKGROUND: Levothyroxine (LT4) treatment can lead to iatrogenic hyperthyroidism and oxidative stress that can cause patient discomfort. Oxidative stress is also recognized as one of the causes of chronic diseases and cancer. METHODS: The prevalence of breast, colorectal, gastric and lung cancer in 18 Italian Regions during 2010 was correlated with the sales of LT4 in 2009. The cancer prevalence was analyzed in women aged 30-84. This age range corresponds to more than 80% of the consumers of the drug and to about 99% of all malignant cancers. The correlation between sales of LT4 and cancers was determined with the technique of Density Ellipses. The age and smoking contribution for lung cancer was determined with the Sequential test. RESULTS: No significant correlation was seen between LT4 sales and breast, colorectal and gastric cancers. A significant correlation was instead found for lung cancer (p < 0.05) corrected for smoking and age. CONCLUSIONS: LT4 consumption in Italy is about 0.7 boxes/women/year. There is a correlation between lung cancer and LT4 treatment and oxidative stress caused by LT4 supplementation can be one of the causes. Although we cannot exclude that dysthyroidism needing LT4...
supplementation might be the ground for lung cancer itself and measuring oxidative stress could be helpful in avoiding excessive use of the drug.

[581]
TÍTULO / TITLE: - Role of PAX-8, CD5, and CD117 in Distinguishing Thymic Carcinoma from Poorly Differentiated Lung Carcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Asirvatham JR; Esposito MJ; Bhuiya TA
INSTITUCIÓN / INSTITUTION: - Department of Pathology, North Shore-Long Island Jewish Health System, NY.
RESUMEN / SUMMARY: - AIM:: To determine if PAX-8, CD5, and CD117 can differentiate thymic carcinoma from poorly differentiated lung carcinoma. DESIGN:: Archived cases of thymic (n=13) and poorly differentiated lung (n=15) carcinoma were analyzed for intensity and proportion of expression of PAX-8, CD117, and CD5. RESULTS:: PAX-8 was positive in 69.2% of thymic and 5.8% of lung carcinomas. CD117 was positive in 84% of thymic and 26.6% of lung carcinomas. A total of 53% of thymic and none of the lung carcinomas were positive for CD5. Forty-six percent, 53%, and 69% of thymic carcinomas were dual positive for combinations of CD5/PAX-8, CD117/CD5, and CD117/PAX-8, respectively. None of the lung carcinomas were dual positive. Positivity for any 2 of the 3 markers was seen in 84% of thymic and none of the lung carcinomas. Triple positivity was seen in 53% of thymic carcinomas. CONCLUSION:: Adding PAX-8 to CD117 and CD5 increases the diagnostic yield for thymic carcinoma.

[582]
TÍTULO / TITLE: - The evaluation of mdct and quantitative first-pass perfusion in lung cancers.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yildirim IO; Baysal T; Celik MR
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Kecioren Training and Research Hospital, Ankara, Turkey. joyildirim@gmail.com
RESUMEN / SUMMARY: - OBJECTIVES: The aim of this study was the in vivo evaluation of tumor angiogenesis in lung cancers grouped according to their histopathological diagnosis, localization and necrosis characteristics determined using CT first-pass parameters. MATERIALS AND METHODS: The study was performed between January and April 2012 on 44 patients consisting of 38 males and 6 females who were diagnosed with lung cancer as a result of cytological and/or histopathological
evaluations. Patients who had not received radiotherapy and/or chemotherapy previously were included in the study. Images were obtained for each patient by using the 64-detector MDCT scanner. Colored perfusion maps were created from the obtained images. Perfusion parameter measurements were performed by placing ROI at 3 different locations in the solid sections, avoiding the necrotic cystic areas of the masses. Obtained BV, BF, TTP, and MTT perfusion parameters were recorded.

RESULTS: The BF values of central and peripherally located lung cancers that showed normal distribution were found to be statistically significantly different. No statistically significant difference was found between TTP values. The BV values of central and peripherally located lung cancers that did not show normal distribution showed a statistically significant difference. There was a statistically significant difference between the BV and BF values of lung cancer with and without necrosis that did not show a normal distribution and the BV and BF values of lung cancers with and without necrosis.

CONCLUSIONS: Non-invasive evaluation of tumor perfusion of first-pass perfusion CT in lung cancers provides valuable information about tumor angiogenesis. However, we believe that peripheral and solid lung cancers will benefit more from treatments such as anti-angiogenetic drugs, radiotherapy and chemotherapy more than the centrally located and necrotic lung cancers and that perfusion CT will play a greater role in the evaluation of the efficiency of these treatments in the future.

[583]

TÍTULO / TITLE: Neferine, an alkaloid from lotus seed embryo, inhibits human lung cancer cell growth by MAPK activation and cell cycle arrest.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Poornima P; Weng CF; Padma VV

INSTITUCIÓN / INSTITUTION: Animal Tissue Culture and Molecular Genetics Laboratory, Department of Biotechnology, School of Biotechnology and Genetic Engineering, Bharathiar University, Coimbatore, Tamil Nadu, India.

RESUMEN / SUMMARY: Neferine is the major bisbenzylisoquinoline alkaloid isolated from the seed embryo of a traditional medicinal plant Nelumbo nucifera (Lotus). Epidemiological studies have revealed the therapeutic potential of lotus seed embryo. Although several mechanisms have been proposed, a clear anticancer action mechanism of neferine on lung cancer cells is still not known. Lung cancer is the most common cause of cancer death in the world, and the patients with advanced stage of nonsmall lung cancer require adjunct chemotherapy after surgical resection for the eradication of cancer cells. In this study, the effects of neferine were evaluated and characterized in A549 cells. Neferine induced apoptosis in a dose-dependent manner with the hypergeneration of reactive oxygen species, activation of MAPKs, lipid
peroxidation, depletion of cellular antioxidant pool, loss of mitochondrial membrane potential, and intracellular calcium accumulation. Furthermore, neferine treatment leads to the inhibition of nuclear factor kappaB and Bcl2, upregulation of Bax and Bad, release of cytochrome C, activation of caspase cascade, and DNA fragmentation. In addition, neferine could induce p53 and its effector protein p21 and downregulation of cell cycle regulatory protein cyclin D1 thereby inducing G1 cell cycle arrest. These results suggest a novel function of neferine as an apoptosis inducer in lung cancer cells. © 2013 BioFactors, 2013.

[584]

TÍTULO / TITLE: Variability of Total Lesion Glycolysis by 18F-FDG-Positive Tissue Thresholding in Lung Cancer.

RESUMEN / SUMMARY: The aim of this work was to assess the variability of total lesion glycolysis (TLG) measurements in lung cancer patients, obtained with fixed percentages of the maximum standardized uptake value (SUVmax) thresholds.

METHODS: Thirteen lesions (10 patients) were analyzed in 10 successive 2.5-min frames of an (18)F-FDG PET dynamic acquisition obtained between 60 and 110 min after injection. (18)F-FDG-positive lesion volume, associated average SUV (SUVmean), and TLG (volume x SUVmean) were assessed in each frame using thresholds of 40%, 50%, 60%, 70%, and 80%. For each threshold, the average relative SD of TLG, leading to relative measurement error and repeatability, was calculated over the lesion series. The dependence of TLG variability on volume and SUVmean variability was also assessed. RESULTS: The average relative SD of TLG correlated strongly with threshold: 1.0866 x exp(0.0472 x threshold) (r = 0.999; P < 0.01). For the 40% threshold, average TLG over the series was 225.9 g (range, 41.7-1,086.3), relative measurement error and repeatability were 14.5%-20.4% (95% confidence interval), and no significant difference was found between TLG and volume variability. For the other thresholds, TLG variability was significantly lower or greater than volume or SUVmean variability, respectively. CONCLUSION: In current clinical practice, a formula allows quick estimation of TLG variability for any percentage of the SUVmax threshold: the higher the threshold the greater the TLG variability.
MicroRNAs in Body Fluids as Biomarkers for Non-small Cell Lung Cancer: A Systematic Review.

Non-small cell lung cancer (NSCLC) is one of the most common life-threatening malignant tumors. A test for early diagnosis of NSCLC needs to be not too invasive and not too heavy a burden for weakened patients. A series of studies reported various microRNAs (miRNAs) could be novel serum biomarkers for NSCLC. However, the diagnostic ability of different miRNA biomarkers varies among the reports. The goal of this study was to perform a systematic review to examine the effect of miRNAs on NSCLC-related outcomes. We systematically searched The Cochrane Central Register of Controlled Trials, MEDLINE, Pub Med, EMBASE, the Chinese Biomedical Literature Database, the China Academic Journals Full-text Database, and the Chinese Scientific Journals Database for potential studies. Studies were included if they were related to miRNAs, NSCLC, and reported diagnostic outcomes. Diagnostic values analysis was used to summarize the overall test performance of miRNAs. 13 studies were included in this systematic review. The ranges of sensitivity (SEN) and specificity (SPE) of diagnosis model with miRNAs as identifying NSCLC were 0.69 1.00 and 0.66 1.00, respectively. The overall area under the curve (AUC) value of summary receiver operating characteristic (SROC) curve was 0.9151. The ranges of positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 2.33 24.75 and 0.01 0.40, respectively. The range of diagnostic odds ratio (DOR) was 6.52 983.38. The current evidence indicates that miRNAs in body fluids show high accuracy in identifying NSCLC, and could be a useful screening tool for diagnosing NSCLC patients.


Non-small cell lung cancer (NSCLC) is one of the most common life-threatening malignant tumors. A test for early diagnosis of NSCLC needs to be not too invasive and not too heavy a burden for weakened patients. A series of studies reported various microRNAs (miRNAs) could be novel serum biomarkers for NSCLC. However, the diagnostic ability of different miRNA biomarkers varies among the reports. The goal of this study was to perform a systematic review to examine the effect of miRNAs on NSCLC-related outcomes. We systematically searched The Cochrane Central Register of Controlled Trials, MEDLINE, Pub Med, EMBASE, the Chinese Biomedical Literature Database, the China Academic Journals Full-text Database, and the Chinese Scientific Journals Database for potential studies. Studies were included if they were related to miRNAs, NSCLC, and reported diagnostic outcomes. Diagnostic values analysis was used to summarize the overall test performance of miRNAs. 13 studies were included in this systematic review. The ranges of sensitivity (SEN) and specificity (SPE) of diagnosis model with miRNAs as identifying NSCLC were 0.69 1.00 and 0.66 1.00, respectively. The overall area under the curve (AUC) value of summary receiver operating characteristic (SROC) curve was 0.9151. The ranges of positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 2.33 24.75 and 0.01 0.40, respectively. The range of diagnostic odds ratio (DOR) was 6.52 983.38. The current evidence indicates that miRNAs in body fluids show high accuracy in identifying NSCLC, and could be a useful screening tool for diagnosing NSCLC patients.
INSTITUCIÓN / INSTITUTION: - Department of Pathology, M.D. Anderson Cancer Center, Houston, TX 77030, USA. aweissferdt@doctors.org.uk

RESUMEN / SUMMARY: - Over the last decade, considerable changes have been made to the classification of pulmonary adenocarcinoma, mainly with respect to the classification of small solitary tumors. The main goal seems to have been the identification of tumors that not only follow an indolent clinical course but that can also be treated more conservatively. Thus, the most important change to the classification of lung adenocarcinoma was proposed for a tumor no greater than 3.0 cm in size with a pure lepidic growth pattern and lacking stromal, vascular, or pleural invasion, which should now be categorized as in situ adenocarcinoma. At the same time, a category of minimally invasive adenocarcinoma was proposed for tumors with a predominantly lepidic growth pattern, <3 cm in size, and with <5 mm invasion in greatest dimension in any 1 focus. What is interesting about all these developments is the fact that all the publications on this issue have been presented under the terms of small adenocarcinomas or bronchioloalveolar carcinoma. Unfortunately, the literature reviews that have proposed the change in nomenclature to in situ adenocarcinoma have not offered a more in-depth assessment of these neoplasms. More recently, a publication of a large series of cases of small adenocarcinomas has offered a different view and underscored some of the important issues that need to be taken into account before a serious change in the nomenclature can be considered.

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TÍTULO / TITLE: - CXCL12 induces lung cancer cell migration by polarized mtDNA redistribution.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Ma J; Zheng J; Li Y; Zhang S; Bai D; Zou H; Han C

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Shengjing Hospital of China Medical University, Shenyang, 110022, China, ma_jt@126.com.

RESUMEN / SUMMARY: - Instability of mitochondrial DNA (mtDNA) has been associated with the initiation and development of cancer, but the specific role of mtDNA in the invasiveness and migration of cancer cells remains unclear. In this study, we investigated whether the chemokine CXCL12 causes intact mitochondria to redistribute in cancer cells and, in this way, to increase cell invasiveness and migration. A549 lung cancer cells with intact mtDNA (mtDNA+) and rho0A549 cells depleted of mtDNA (mtDNA-) by long-term ethidium bromide incubation were examined for their responses to CXCL12 in a transwell migration assay and for mitochondrial distribution by fluorescence microscopy. Intact A549 cells showed significantly increased migration and increased polar distribution of mitochondria (asymmetry) in response to CXCL12.
However, rho0A549 cells showed no changes in mitochondrial distribution in response to CXCL12, and only a few rho0A549 cells migrated across the transwell membrane after CXCL12 treatment. These results demonstrate that, in A549 lung cancer cells, intact mitochondrial DNA is necessary for mitochondrial redistribution and a chemotactic response to CXCL12.

[588]

TÍTULO / TITLE: - Cutaneous metastasis of primitive neuroectodermal lung tumor.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Garcia Romero D; Hilara Sanchez Y; Perez Alvarez J; Ramirez Garcia JR; De Pable Martin MP
INSTITUCIÓN / INSTITUTION: - Hospital del Tajo, Aranjuez, Madrid, España.
RESUMEN / SUMMARY: - Primary sarcomas of the chest are rare. Although primitive neuroectodermal tumor (PNET) usually develops in the chest wall, it has been described as a primary pulmonary tumor. We present an unusual case of PNET arising in the lung of an 89-year-old man.

[589]

TÍTULO / TITLE: - Association of small foci of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) with adenocarcinoma of the lung.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mireskandari M; Abdirad A; Dietel M; Petersen I
INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Jena University Hospital, Friedrich Schiller University, Jena, Germany.
RESUMEN / SUMMARY: - DIPNECH is regarded as a precursor lesion of neuroendocrine lung tumors, specifically carcinoids. A relationship with lung adenocarcinomas has not been clearly established so far. We present a series of four cases with a concomitant presence of adenocarcinoma and DIPNECH in the lung. The cases were retrieved from the archives of the Institutes of Pathology of the Jena University Hospital and the Charite, Berlin. The clinical data were collected from the hospital information system. The microscopic findings of adenocarcinoma and DIPNECH were reviewed. A panel of neuroendocrine and epithelial markers was analyzed immunohistochemically. In addition, the H&E slides of a series of 82 lung carcinomas were reevaluated for the presence of DIPNECH foci and the parameters of the IASLC/ATS/ERS classification for lung adenocarcinoma. DIPNECH foci were composed of small intramucosal nests of
proliferating pulmonary neuroendocrine cells alongside or at the periphery of terminal airways. All detected foci measured less than 5mm in maximal diameter and showed a consistent reactivity against Synaptophysin. They did not express epithelial markers of squamous cell carcinoma and adenocarcinoma. In three cases, the DIPNECH foci were clearly associated with the adenocarcinoma, while in one case, they were observed in the non-neoplastic lung tissue. The adenocarcinoma with DIPNECH inside mainly showed low grade histology, while the fourth case was intermediate to high grade. The histologic evaluation of the HE slides of the other 82 lung cancer cases showed no suspected or definite DIPNECH foci. Within this series, we could confirm the prognostic significance of the IASLC/ATS/ERS classification of lung adenocarcinoma. Our series suggest that a subset of lung adenocarcinoma is characterized by the concomitant presence of DIPNECH within the tumor, suggesting a causal relationship. These adenocarcinomas seem to be low grade ones, and may have a particular tumorigenesis and clinical behavior. These observations need to be confirmed in larger tumor collectives. We could confirm the prognostic relevance of the new adenocarcinoma classification.

[590]

TÍTULO / TITLE: - Alteration in the Balance of Prosurvival and Proapoptotic Signalling Pathways Leads to Sequence-Dependent Synergism Between Docetaxel and Sorafenib in Human Non-small Cell Lung Cancer Cell Lines.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - He X; Zhang T
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Taizhou Second People’s Hospital, Jiangyan, 225599, China.
RESUMEN / SUMMARY: - To examine the antiproliferative effect of the combination of docetaxel and sorafenib, applied to the representative non-small cell lung cancer cell line A549 cells either wild type or with acquired resistance to docetaxel (A549/D). The aim of this study is to evaluate the synergistic effect of combination treatment on cell growth inhibition and to elucidate the involved molecular mechanisms. A549 cells with acquired resistance to docetaxel were established by continuous exposure to docetaxel. We examined the effect of different combinatorial treatment on cell proliferation and cell cycle distribution. In addition, the effect of combinatorial treatments on proliferative and apoptotic signalling pathway were studied. Our results showed that the synergistic effect presented when A549 cells were treated with docetaxel followed by sorafenib or when A549/D cells were treated in reverse sequence. Furthermore, we suggested that synergistic effect in A549/D cells was caused by inhibiting P-gp function and altering in the balance of growth and apoptotic
signalling pathways. Our data suggested a potential role of sorafenib in chemosensitizing docetaxel-resistant cancer cells. This study also provides molecular evidence for applying different therapeutic strategies for patients with different genetic and proteomic profile.

[591]
**TÍTULO / TITLE:** - Global analysis of serum microRNAs as potential biomarkers for lung adenocarcinoma.
**RESUMEN / SUMMARY:** - Global analysis of serum microRNAs as potential biomarkers for lung adenocarcinoma.
**REVISTA / JOURNAL:** - Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** - Rani S; Gately K; Crown J; O’Byrne K; O’Driscoll L
**INSTITUCIÓN / INSTITUTION:** - School of Pharmacy & Pharmaceutical Sciences and Trinity Biomedical Sciences Institute; Trinity College Dublin; Dublin, Ireland.
**RESUMEN / SUMMARY:** - Early diagnosis and the ability to predict the most relevant treatment option for individuals is essential to improve clinical outcomes for non-small cell lung cancer (NSCLC) patients. Adenocarcinoma (ADC), a subtype of NSCLC, is the single biggest cancer killer and therefore an urgent need to identify minimally invasive biomarkers to enable early diagnosis. Recent studies, by ourselves and others, indicate that circulating miRNAs have potential as biomarkers. Here we applied global profiling approaches in serum from patients with ADC of the lung to explore if miRNAs have potential as diagnostic biomarkers. This study involved RNA isolation from 80 sera specimens including those from ADC patients (equal numbers of Stages 1, 2, 3, and 4) and age- and gender-matched controls (n = 40 each). 667 miRNAs were co-analyzed in these specimens using TaqMan low density arrays and qPCR validation using individual miRNAs. Overall, approximately 390 and 370 miRNAs were detected in ADC and control sera, respectively. A group of 6 miRNAs, miR-30c-1* (AUC = 0.74; p<0.002), miR-616* (AUC = 0.71; p = 0.001), miR-146b-3p (AUC = 0.82; p<0.0001), miR-566 (AUC = 0.80; p<0.0001), miR-550 (AUC = 0.72; p = 0.0006), and miR-939 (AUC = 0.82; p<0.0001) was found to be present at substantially higher levels in ADC compared with control sera. Conversely, miR-339-5p and miR-656 were detected at substantially lower levels in ADC sera (co-analysis resulting in AUC = 0.6; p = 0.02). Differences in miRNA profile identified support circulating miRNAs having potential as diagnostic biomarkers for ADC. More extensive studies of ADC and control serum specimens are warranted to independently validate the potential clinical relevance of these miRNAs as minimally invasive biomarkers for ADC.

[592]
**TÍTULO / TITLE:** - Non small cell lung cancer revealed by a solitary splenic metastasis of lung cancer.

INTRODUCTION: This prospective observational study evaluated the effect of race on disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) in patients with NSCLC treated with second-line pemetrexed. Noninferiority was evaluated using logistic regression analysis of DCR, controlling for predefined covariates. Noninferiority was considered if the upper 95% confidence bound on the adjusted odds ratio (OR) for Caucasian vs. African-American individuals was less than 1.78, corresponding to a difference in proportion of 14% assuming Caucasian individuals to have a DCR of approximately 50%. The bound was chosen to be half of the anticipated difference between treatment and no second-line treatment. PFS and OS were estimated using the Kaplan-Meier method. Tools were used to measure functional status and symptom burden. RESULTS: The unadjusted DCR was 43.7% (117/268) for Caucasian and 45.0% (27/60) for African-American individuals (unadjusted OR, 0.95; 95% confidence interval [CI], 0.54-1.66). The adjusted OR in the final logistic regression model was 0.82 (95% CI, 0.43-1.58). This upper 95% confidence bound was within the prespecified acceptable bound of 1.78. Median PFS times (months) were 2.7 (95% CI, 2.4-3.4) for Caucasian and 3.0 (95% CI, 2.3-4.7) for African-American individuals (P = .91). Median OS times (months) were 6.7 (95% CI, 5.7-7.9) for Caucasian and 6.9 (95% CI, 4.5-8.9) for African-American individuals (P = .92). Baseline and functional status after baseline assessment and mean symptom burden did not differ substantially among races. CONCLUSION: African-American race
was not considered to be a significant predictor of disease control after second-line treatment with pemetrexed.
TÍTULO / TITLE: Clinical characteristics of patients with bronchioloalveolar carcinoma: a retrospective study of 44 cases.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Dirican N; Baysak A; Cok G; Goksel T; Aysan T

INSTITUCIÓN / INSTITUTION: Dr Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey E-mail: nigardirican@yahoo.com.

RESUMEN / SUMMARY: Background: Bronchioloalveolar carcinoma (BAC) is considered a subtype of adenocarcinoma of the lung. Recently BAC has been variously termed adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant invasive adenocarcinoma, and invasive mucinous adenocarcinoma. The aim of the study was to analyze and detect prognostic factors of patients with BAC over a 7-year period. Materials and Methods: This retrospective single-center study included 44 patients with BAC. The impact on survival of fifteen variables (gender, age, smoking status, cough, dyspnea, hemoptysis, fever, chest pain, sputum, metastasis number, Karnofsky performance status, pT, pN, TNM stage, cytotoxic chemotherapy) were assessed. Results: Median age was 55 years (38-83). Most patients were male (63.6%) and stage IV (59.1%). Twenty-one patients (47.7%) received cytotoxic chemotherapy (platinum-based regimens) for metastatic disease. Objective response rate was 33.3% (4 partial, 3 complete responses). Stable disease was observed in nine in patients (42.8%). Disease progression was noted in 5 (23.8%). The median OS for all patients was 12 months (95%CI, 2.08-22.9 months). Independent predictors for overall survival were: Karnofsky performance status (HR:3.30, p 0.009), pN (HR:3.81, p 0.018), TNM stage (HR:6.49, p 0.012) and hemoptysis (HR:2.31, p 0.046). Conclusions: Karnofsky performance status, pN, TNM stage and hemoptysis appear to have significant impact on predicting patient survival in cases of BAC.

TÍTULO / TITLE: Therapeutic Strategies for Well-differentiated Papillary Mesothelioma of the Peritoneum.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Lee YK; Jun HJ; Nahm JH; Lim TS; Park JS; Ahn JB; Rha SY; Chung HC; Oh HE; Song JS; Yang WI; Kim HS

INSTITUCIÓN / INSTITUTION: *Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea. hyosong77@yuhs.ac.

RESUMEN / SUMMARY: OBJECTIVE: Well-differentiated papillary mesothelioma is an uncommon subtype of mesothelioma with a frequently indolent course, although it occasionally manifests in a more aggressive form. To establish a treatment strategy for
this rare disease, we report the clinical characteristics and outcomes of 15 patients with well-differentiated papillary mesothelioma. METHODS: All pathologically diagnosed well-differentiated papillary mesothelioma cases were reviewed between 1998 and 2012. RESULTS: Of the 15 cases, 8 and 7 presented with single and multiple lesions, respectively. All cases with single lesions were asymptomatic, while 4 out of the 7 cases with multiple lesions were symptomatic. After tumor excision, none of the eight single-lesion cases experienced tumor recurrence. Among the other seven cases with multiple lesions, only one patient with disseminated lesions died due to disease burden. Five patients with multiple lesions received cisplatin-based intravenous or intraperitoneal chemotherapy, with a mix of complete (n=2) and partial (n=2) responses observed. Of particular note, one patient receiving cisplatin and pemetrexed combination chemotherapy experienced complete tumor resolution without any serious toxicity. CONCLUSIONS: We recommend different treatment strategies based on the disease status. If the tumor is completely resectable, an excisional biopsy seems to be sufficient. If complete resection is unavailable for the asymptomatic patient with a localized tumor extent, close follow-up is an appropriate option. When the tumor is extensive or accompanied by symptoms, chemotherapy should be strongly considered.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Chang GC; Tsai CM; Hsia TC; Yang CH; Abdulnabi R; Blair JM; Linn C

INSTITUCIÓN / INSTITUTION: - Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND/PURPOSE: Although global and Asian studies on second-line pemetrexed for the treatment of advanced nonsmall cell lung cancer have confirmed its efficacy and safety, a pivotal postcommitment study to consolidate the evidence regarding the Taiwanese population was warranted. This open-label single-arm study assessed the objective response rate to a tailored dose of single-agent pemetrexed in Taiwanese patients with advanced nonsmall cell lung cancer who had received prior chemotherapy. METHODS: Patients with stage IIIB/IV disease were treated with pemetrexed on day 1 of each 21-day cycle. A 500 mg/m(2) dose was administered in cycle 1. For cycle 2, the dose was increased to 1000 mg/m(2) (if there was no toxicity above predefined levels) or decreased to 375 mg/m(2). All patients
received standard supplemental therapy. Patient follow-up continued until 18 months after the last patient was enrolled in this study or death. All patients were included in all analyses. RESULTS: Of the 33 patients who were enrolled, 25 (75.8%) received the 1000 mg/m2 dose during cycle 2; 18 patients were dropped from the study, including 17 (51.5%) who had died by the time of analysis. The objective response and disease control rates were 18.2% (95% confidence limits [CI]: 7.0-35.5) and 54.5% (95% CI: 36.4-71.9), respectively. No patients exhibited a complete response. There were two serious drug-related adverse events (neutropenia and leukopenia) and two drug-related adverse events that resulted in removal from the study. Decreased neutrophil/granulocyte counts were the most frequently observed drug-related grade ¾ events (9 patients, 24 treatment cycles). CONCLUSION: The objective response rate, disease control rate, and safety and tolerability profile in this population of Taiwanese patients were consistent with the published findings that were conducted using Asian and Western populations. These findings support the use of single-agent, second-line pemetrexed for the treatment of advanced nonsmall cell lung cancer in Taiwanese patients.

[598]


RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Oskan F; Kornhuber C; Krause G; Vordermark D

RESUMEN / SUMMARY: The co-incidence of synchronous intraepithelial neoplasia and early stage invasive lung cancer is not a rare phenomenon. The need for curative treatment and the invasive potential of squamous cell pulmonary carcinoma in situ have been a topic of controversy. Surgical resection still remains the treatment of choice. Varieties of endoscopic techniques such as brachytherapy were developed as an alternative to surgery in selected patients. External beam radiation therapy has been used traditionally in combination with endobronchial brachytherapy in the treatment of roentgenographically occult lung cancer, and can be offered for all patients, but is handicapped, because these tumors are radiographically invisible. We report the first case of a pulmonary carcinoma in situ that was successfully treated with stereotactic body radiation therapy.
**TÍTULO / TITLE:** - Morphological characteristics of potentially malignant pulmonary nodules in high-risk male smokers detected in lung cancer screening trial in Cracow, Poland.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Kiszka K; Rudnicka-Sosin L; Tomaszewska R; Urbanczyk-Zawadzka M; Krupinski M; Pikul P; Podsiadlo K; Pasowicz M; Vliegenthart R; Oudkerk M; Miszalski-Jamka T

**INSTITUCIÓN / INSTITUTION:** - Kinga Kiszka, Department of Radiology, John Paul II Hospital, Pradnicka 80, 31-202 Krakow, Poland, tel. +48 126142526, fax +48 126142500, e-mail: k.kiszka@szpitaljp2.krakow.pl, kinga_kiszka@wp.pl.

**RESUMEN / SUMMARY:** - The purpose of this paper was to present morphological characteristics of potentially malignant nodules revealed in a group of male smokers aged 50-74 with a very high risk for developing lung cancer estimated in the study for lung cancer screening in Cracow (Poland). Nine hundred male smokers aged 50 to 74 years were invited to the study and were asked in questionnaires about e.g. smoking exposure history. Exclusion criteria included e.g. positive cancer history and chest computed tomography (CT) examination in the previous year. Based on CT results and characteristics of pulmonary nodules subjects were classified to group A (low risk), group B (indeterminate) and group C (high-risk individuals - required work-up). Final diagnosis was based on pathological results of postoperative material. Thirty-nine males of mean age 63.4 (standard deviation (SD): 6.69 years) revealed 41 potentially malignant pulmonary nodules in baseline screening. In 14 subjects 16 type C pulmonary nodules were histologically proved. Nine nodules were found to be benign lesions, while 7 nodules revealed malignant lung cancer: 5 cases of adenocarcinoma and 2 cases of adenosquamous carcinoma. We determined morphological characteristics of potentially malignant pulmonary nodules in 39 high-risk male smokers and proved lung cancer in 7 subjects.

[600]

**TÍTULO / TITLE:** - Thoracoscopic minimally invasive surgery for non-small cell lung cancer in patients with chronic obstructive pulmonary disease.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Cui F; Liu J; Shao W; He J

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Guangzhou Institute of
OBJECTIVE: To determine the incidence of peri-operative complications in non-small cell lung cancer (NSCLC) patients with co-existent chronic obstructive pulmonary disease (COPD) who undergo lung resection via traditional and minimally invasive techniques. METHODS: A retrospective analysis was conducted of 152 NSCLC patients with COPD who underwent thoracoscopic minimally invasive surgery. Particular attention is given to the relationship between disease severity or surgical approach and the incidence of complications. RESULTS: THE PREVALENCE OF RESPIRATORY AND CARDIAC COMPLICATIONS WAS SIGNIFICANTLY HIGHER IN PATIENTS WITH SEVERE/EXTREMELY SEVERE COPD THAN THOSE WITH MILD TO MODERATE COPD (RESPIRATORY COMPlications: 37.3% vs. 20.4%, P=0.022; cardiac complications: 16.9% vs. 6.5%, P=0.040). Patients who underwent complete-video assisted thoracoscopic surgery (c-VATS) had a significantly lower overall morbidity of adverse reactions than those who had undergone VATS major resection (26.3% vs. 42.1%, P=0.044). Among patients with severe/extremely severe COPD, there was no significant difference in the incidence of any complication between the lobectomy group and wedge resection group (38.8% vs. 70.0%, P=0.072). Overall, the occurrence of adverse reactions was significantly lower in patients who underwent c-VATS than in those who had undergone VATS major resection surgery (34.2% vs. 61.9%, P=0.038). CONCLUSIONS: VATS techniques are suitable for COPD patients and are demonstrated here to lower the incidence of post-operative complications when compared with more invasive approaches.

[601]

- Immunomodulatory effects of BCG in patients with recurrent respiratory papillomatosis.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Vetskova EK; Muhtarova MN; Avramov TI; Stefanova TR; Chalakov IJ; Nikolova MH

INSTITUCIÓN / INSTITUTION: - BB-NCIPD Ltd, Sofia, Bulgaria.

RESUMEN / SUMMARY: - BACKGROUND: Recurrent respiratory papillomatosis (RRP) is a rare manifestation of human papilloma virus (HPV) infection with extremely high relapse frequency, poorly understood immunopathogenesis, and lack of efficient treatment. Immunotherapy with Calgevax (BCG) in combination with CO2 surgery significantly improves the outcome of RRP. The present study investigates cellular immunity parameters in RRP patients, and the effects of 20-month Calgevax immunomodulation. MATERIALS AND METHODS: RRP patients (n = 15) subjected to combined therapy were tested before, 6, 12 and 20 months after the start of immunomodulation. Absolute counts and percentage of T, B and NK cells, effector T1
(CD8 + IFNgamma+), Th1 (CD4+IFNgamma+), Th17 (CD4+IL-17+) and regulatory (CD4+FoxP3+) T lymphocytes, as well as the in vitro stimulated secretion of IL-2, IL-4, IL-5, IL-10, IFNgamma and TNFalpha were determined by flow cytometry (FACSCanto II, BD). RESULTS: While no significant changes were detected in the circulating T, B and NK subsets, RRP patients presented increased proportions of Tc1, Th1 and Th17 cells, and significantly reduced IFNgamma/IL-4 and IFNgamma/IL-10 ratios as compared to healthy controls (15% vs. 8%), (58 vs. 139 and 15 vs. 26, respectively), p < 0.05 for all comparisons. Increased Treg (9% vs. 4%), and decreased Th17 effectors share (0.7% vs. 0.4%) were observed at 12 months, while IFNgamma/IL-4 and IFNgamma/IL-10 ratios were restored after 20 months of Calgevax application. CONCLUSIONS: Antiviral response closely depends on cytokine background. Calgevax potentiates Treg differentiation at the expense of proinflammatory Th17, limits hyperactivation and virus-specific T cell clones depletion, and restores a Th1 cytokine background.

[602]

TÍTULO / TITLE: - Serum CEA Level Change and Its Significance Before and after Gefitinib Therapy on Patients with Advanced Non-small Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Qin HF; Qu LL; Liu H; Wang SS; Gao HJ
INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Neoplasms Internal Medicine, The Affiliated Hospital of Academy of Military Medical Science, Beijing, China E-mail: gaohj6708@hotmail.com.
RESUMEN / SUMMARY: - Objective: The aim of this study was to explore change and significance of serum carcinoid-embryonic antigen (CEA) before and after gefitinib therapy in patients with advanced non-small-cell lung cancer (NSCLC). Methods: Forty patients with advanced NSCLCs in III“IV stages were selected as study objects given gefitinib therapy combined with routine local radiotherapy until tumor progression or intolerable toxicity. After treatment, all patients were divided into control and non-control groups according to the results of evaluation based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors in 2009). Peripheral fasting blood from all patients was collected in the early morning and serum CEA was assessed by electro-chemiluminescence immunoassay (ECLIA) before and after treatment. Before treatment, patients were divided into high CEA group (CEA level > 50 ng/mL) and low CEA group (CEA level </= 50 ng/mL). Adverse reactions were noted and progression-free survival (PFS) in both groups was recorded after long-term follow-up that ended in December, 2012. Results: There was no difference between control and non-control groups in CEA level before treatment (P>0.05), whereas serum CEA decreased more markedly lower in the control group after treatment (P<0.01). All patients were divided into high CEA group (26) and low CEA group (14) according to serum CEA level. There
was no statistically significant difference between two groups in adverse reactions (P>0.05) but the rate in former group was lower. Additionally, survival rates at 9 and 12 months in high CEA group were clearly higher than in the low CEA group (P<0.01).

Conclusions: Serum CEA level can serve as a biochemical index to evaluate the prognosis with gefitinib treatment for NSCLC.
grade 3 radiation oesophagitis, one case of grade 3 radiation pneumonitis, and one case of grade 4 neutropenia. All of these cases of DLT occurred in the 72 Gy group. Therefore, 72 Gy was designated as the DLT dose level, and the lower dose of 69 Gy was regarded as the MTD. CONCLUSIONS: For unresectable stage III NSCLC 69 Gy (at 3 Gy/fraction) was the MTD of accelerated hypofractionated 3-DCRT administered in combination with concurrent NVB and CBP chemotherapy. The toxicity of this chemoradiotherapy regimen could be tolerated. A phase II trial is recommended to further evaluate the efficacy and safety of this regimen.

TÍTULO / TITLE: Local and systemic neutrophilic inflammation in patients with lung cancer and chronic obstructive pulmonary disease.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1186/1471-2172-14-36
AUTORES / AUTHORS: Vaguliene N; Zemaitis M; Lavinskiene S; Miliauskas S; Sakalauskas R
INSTITUCIÓN / INSTITUTION: Department of Pulmonology and Immunology, Medical Academy, Hospital of Lithuanian University of Health Sciences, Eiveniu 2, Kaunas LT-50028, Lithuania. neringa.vaguliene@gmail.com
RESUMEN / SUMMARY: BACKGROUND: Recent investigations suggest that neutrophils play an important role in the immune response to lung cancer as well as chronic obstructive pulmonary disease (COPD). The aim of this study was to evaluate the amount of neutrophils and markers of their activity in lung cancer and COPD and in coexistence of these two diseases. METHODS: In total, 267 persons were included in the study: 139 patients with lung cancer, 55 patients with lung cancer and COPD, 40 patients with COPD, and 33 healthy subjects. Peripheral blood and BAL fluid samples were obtained for cell count analysis and determination of NE, MPO levels and ROS production. NE and MPO levels in the serum and BAL fluid were determined by ELISA. ROS production was analyzed by flow cytometer. RESULTS: The percentage, cell count of neutrophils and neutrophil to lymphocyte ratio in the peripheral blood were significantly higher in lung cancer patients with or without COPD compared to COPD patients or healthy individuals (P < 0.05). The percentage and cell count of neutrophils in BAL fluid were significantly lower in patients with lung cancer with or without COPD than in patients with COPD (P < 0.05). However, BAL fluid and serum levels of both NE and MPO were significantly higher in patients with lung cancer than COPD patients or healthy individuals (P < 0.05). Neutrophils produced higher amounts of ROS in patients with lung cancer with or without COPD compared with COPD patients or healthy individuals (P < 0.05). CONCLUSIONS: The results from this study demonstrate higher degree of local and systemic neutrophilic inflammation in patients with lung cancer (with or without COPD) than in patients with COPD.
**TÍTULO / TITLE:** Evaluation of changes in the attitudes and behaviors of relatives of lung cancer patients toward cancer prevention and screening.

**RESUMEN / SUMMARY:** Background: Cancer diagnosis affects all the relatives living with the patient; however, whether the behavior of family members changes or not is unknown. To end this we evaluated the relatives of lung cancer patients. Materials and Methods: Forty-one questions were used to collect data from the relatives of lung cancer patients who had been living with them for at least one year, to evaluate changes in their attitudes and behaviors related to cancer prevention. Results: The study included 246 lung cancer patients’ relatives, of them 172 (69.9%) were women and 74 (30.1%) were men. The median age was 46 years (range: 20-83 years). Patients and their relatives had been living together for an average of 28 years (range: 1-68 years), and 88 (35.7%) of the patients’ relatives were their children. We found changes in the attitudes and behaviors toward prevention and screening for cancer in 92 (37.4%) of the relatives. Fifty-two (21.1%) of them changed their smoking habits, 34 (13.8%) altered their eating habits, 25 (10.2%) changed their exercise habits, 13 (5.3%) visited a doctor due to a suspicion of having cancer, 12 (4.9%) changed their lifestyles, seven (2.8%) underwent cancer screening tests, three (1.2%) started using alternative medicines, and three (1.2%) started using vitamins for cancer prevention. Conclusions: Important changes occur in the attitudes and behaviors of patients’ relatives toward cancer prevention and screening after the patients are diagnosed with lung cancer. Being aware of how patients’ relatives react to a family member’s cancer diagnosis may provide healthcare professionals with more incentive to address the relatives’ special needs.

**AUTORES / AUTHORS:** Koca D; Oztop I; Yilmaz U

**INSTITUCIÓN / INSTITUTION:** Department of Internal Diseases, Dokuz Eylul University, Medical Faculty, Division of Medical Oncology, Inciralti, 35340, Izmir, Turkey.


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**TÍTULO / TITLE:** Video-assisted thoracoscopic lobectomy for non-small cell lung cancer in patients with severe chronic obstructive pulmonary disease.

**RESUMEN / SUMMARY:** Background: Cancer diagnosis affects all the relatives living with the patient; however, whether the behavior of family members changes or not is unknown. To end this we evaluated the relatives of lung cancer patients. Materials and Methods: Forty-one questions were used to collect data from the relatives of lung cancer patients who had been living with them for at least one year, to evaluate changes in their attitudes and behaviors related to cancer prevention. Results: The study included 246 lung cancer patients’ relatives, of them 172 (69.9%) were women and 74 (30.1%) were men. The median age was 46 years (range: 20-83 years). Patients and their relatives had been living together for an average of 28 years (range: 1-68 years), and 88 (35.7%) of the patients’ relatives were their children. We found changes in the attitudes and behaviors toward prevention and screening for cancer in 92 (37.4%) of the relatives. Fifty-two (21.1%) of them changed their smoking habits, 34 (13.8%) altered their eating habits, 25 (10.2%) changed their exercise habits, 13 (5.3%) visited a doctor due to a suspicion of having cancer, 12 (4.9%) changed their lifestyles, seven (2.8%) underwent cancer screening tests, three (1.2%) started using alternative medicines, and three (1.2%) started using vitamins for cancer prevention. Conclusions: Important changes occur in the attitudes and behaviors of patients’ relatives toward cancer prevention and screening after the patients are diagnosed with lung cancer. Being aware of how patients’ relatives react to a family member’s cancer diagnosis may provide healthcare professionals with more incentive to address the relatives’ special needs.

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The epidermal growth factor receptor-tyrosine kinase inhibitor era has changed the causes of death of patients with advanced non-small-cell lung cancer.

**RESUMEN / SUMMARY:**

**BACKGROUND:** Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective against tumor EGFR-mutated non-small cell lung cancer (NSCLC). Patients with the tumor EGFR-activating mutation (EGFRmu) had superior survival, compared to patients with EGFR wild-type tumors (EGFRwt). Many patients with the EGFRmu have had disease progression with EGFR-TKI treatment because of central nervous system (CNS) metastases. The objective of this retrospective study was to compare the causes of death in patients with a known tumor EGFR mutation status who had been treated with EGFR-TKIs. **METHODS:** We retrospectively reviewed the chart records of our patients with advanced NSCLC who had received diagnosis, treatment, and supportive and hospice care in our hospital between July 2005 and June 2010. The tumor EGFR mutation status was analyzed by using a DNA sequence method. All enrolled patients had a documented cause of death. **RESULTS:** Ninety-four patients had documented tumor EGFR data, had received EGFR-TKI treatment (either erlotinib or gefitinib), and were with or without previous or salvage systemic chemotherapy. Of the 94 patients, 36 patients had EGFRwt and 58 patients had EGFRmu. The overall patient survival after starting EGFR-TKI treatment was significantly longer in the EGFRmu patients (median 17.2 months) than in the EGFRwt patients (median 11.6 months; \( p = 0.0058 \)). Twenty-nine patients died of CNS metastases and 65 died of organ failure (other than the CNS). Patients who died of CNS metastases had undergone EGFR-TKI treatment significantly longer than patients who died of other organ failure (median, 8 months vs. 1.9 months; \( p = 0.0003 \)) with a hazard ratio of 2.308 [95% confidence interval (C.I.), 1.452-3.668; \( p = 0.0004 \)]. A
significantly higher proportion of EGFRmu patients (26 of 58 patients; 44.8%) than EGFRwt patients (3 of 36 patients; 8.3%) \((p < 0.001)\) died of CNS metastases.

**CONCLUSION:** The EGFRmu NSCLC patients survived longer and had a significantly higher probability of mortality due to CNS metastases, compared to the EGFRwt patients. This change in the causes of death was noted after the era of EGFR-TKI treatment, and will have an important impact on the strategies and management of supportive and hospice care for patients.

[608]  
**TÍTULO / TITLE:** - Epidermal growth factor receptor mutation subtypes and geographical distribution among Indian non-small cell lung cancer patients.  
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary  

**AUTORES / AUTHORS:** - Choughule A; Noronha V; Joshi A; Desai S; Jambhekar N; Utture S; Thavamanni A; Prabhash K; Dutt A  

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Tata Memorial Hospital, Navi Mumbai, Maharashtra, India.  

**RESUMEN / SUMMARY:** - Background: The Medical Oncology Department at Tata Memorial Hospital, the single largest tertiary cancer care center in Asia, receives in-house registered and referral patient samples from all parts of the country. Our recent studies establish 23% EGFR mutation frequency among Indian population. Here, we extend our study and report further analysis of distribution of different types of EGFR mutations in 1018 non small cell lung cancer patient, and its co-relation with clinical parameters and geographical variations across the country. Material and Methods: This study is a retrospective analysis on all the patients who were referred for EFGR testing as a routine service over a 1.5 year period. This was part of standard care. EGFR kinase domain mutations in exon 18-21 were probed by TaqMan probe-based assays in 1018 NSCLC patients. Results and Discussion: While EGFR exon 19 mutations, the most frequent EGFR mutation, were found be higher among non smokers females, we find surprisingly higher incidence of exon 21 mutations among EGFR mutation positive male smokers of Indian ethnicity. Furthermore, as Indian population is known to be composed of a gradient admixture of Ancestral North Indian (with genetic influence from Middle Easterners, Central Asians, and Europeans harboring variant EGFR mutation frequency) and Ancestral South Indians, as a paradox our study indicates comparable EGFR mutation frequency across different geographical locations within India. Conclusion: Geographically there is uniform distribution in the EGFR mutation frequency within India. Further more, while exon 19 mutations are predominant
among non smokers, higher incidence of exon 21 mutations exists among EGFR mutation positive male smokers of Indian ethnicity.
RESUMEN / SUMMARY: - The roles of many genes in the pathophysiology of lung cancer have been investigated in different studies. Cyclin D1 (CCND1) gene plays a significant role in the transition from G1 to S phase of the cell cycle and in the phosphorylation of retinoblastoma tumor suppressor protein. In this study, we aimed to identify the relationship between CCND1 A870G gene polymorphism with lung cancer. CCND1 A870G genotypes were determined in 75 patients with lung cancer and in 65 control subjects. DNA was isolated from blood samples and then CCND1 A870G gene polymorphism was identified using PCR and RFLP assay. The distribution of CCND1 A870G polymorphism did not show any significant differences in all lung cancer patients and controls. There was no correlation between CCND1 A870G polymorphism and histopathological findings. However, the AA + AG genotype was significantly higher in metastatic patients, when compared with non-metastatic patients. Thus, the results show that CCND1 gene polymorphism may be a predictor for detecting patients with poor survival who having metastatic disease.

TÍTULO / TITLE: - Distinct features of distant metastasis and lymph node stage in lung adenocarcinoma patients with epidermal growth factor receptor gene mutations.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Enomoto Y; Takada K; Hagiwara E; Kojima E

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RESUMEN / SUMMARY: - BACKGROUND: The influence of epidermal growth factor receptor (EGFR) mutation status on distant and lymph node metastasis is not fully understood. METHODS: Ninety-five consecutive patients with stage IV lung adenocarcinoma, who had been examined for the EGFR mutation status, were retrospectively analyzed with regard to numbers of distant metastasis and clinical stage of lymph node metastasis at the time of diagnosis. RESULTS: While EGFR mutation status did not influence the presence or absence of distant metastasis in the lung, brain, or liver, patients with EGFR mutations demonstrated a significantly greater number of metastatic lesions in the lung (median: 85 vs. 4, P=0.01) and the brain (11 vs. 3.5, P=0.04). On the other hand, patients with EGFR mutations showed a significantly lower lymph node staging (P<0.01). CONCLUSION: The presence of EGFR
mutations in patients with lung adenocarcinoma correlates with lower lymph node stage and a greater number of metastatic lesions in the lung and brain.

[612]
TÍTULO / TITLE: - Predictive Value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPOMicron-IIA, TOPOIIB and C-MYC Genes in Patients with Small Cell Lung Cancer (SCLC) Who Received First Line Therapy with Cisplatin and Etoposide.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Karachaliou N; Papadaki C; Lagoudaki E; Trypaki M; Sfakianaki M; Koutsooulos A; Mavroudis D; Stathopoulos E; Georgoulas V; Souglakos J
INSTITUCIÓN / INSTITUTION: - Laboratory of Tumour Cell Biology, School of Medicine, University of Crete, Heraklion, Crete, Greece; Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece.
RESUMEN / SUMMARY: - BACKGROUND: The aim of the study was to evaluate the predictive value of genes involved in the action of cisplatin-etoposide in Small Cell Lung Cancer (SCLC). METHODS: 184 SCLC patients’ primary tumour samples were analyzed for ERCCI, BRCA1, ATP7B, PKM2 TOPOI, TOPOIIA, TOPOIIB and C-MYC mRNA expression. All patients were treated with cisplatin-etoposide. RESULTS: The patients’ median age was 63 years and 120 (65%) had extended stage, 75 (41%) had increased LDH serum levels and 131 (71%) an ECOG performance status was 0-1. Patients with limited stage, whose tumours expressed high ERCC1 (p=0.028), PKM2 (p=0.046), TOPOI (p=0.008), TOPOIIA (p=0.002) and TOPOIIB (p<0.001) mRNA had a shorter Progression Free Survival (PFS). In limited stage patients, high expression of ERCC1 (p=0.014), PKM2 (p=0.026), TOPOIIA (p=0.021) and TOPOIIB (p=0.019) was correlated with decreased median overall survival (mOS) while in patients with extended stage, only high TOPOIIB expression had a negative impact on Os (p=0.035). The favorable expression signature (low expression of ERCC1, PKM2, TOPOIIA and TOPOIIB) was correlated with significantly better PFS and Os in both LS-SCLC (p<0.001 and p=0.007, respectively) and ES-SCLC (p=0.007 and p=0.011, respectively) group. The unfavorable expression signature was an independent predictor for poor PFS (HR: 3.18; p=0.002 and HR: 3.14; p=0.021) and Os (HR: 4.35; p=0.001 and HR: 3.32; p=0.019) in both limited and extended stage, respectively. CONCLUSIONS: Single gene’s expression analysis as well as the integrated analysis of ERCC1, PKM2, TOPOIIA and TOPOIIB may predict treatment outcome in patients with SCLC. These findings should be further validated in a prospective study.

[613]
TÍTULO / TITLE: - Contribution of MRI in lung cancer staging.
RESUMEN / SUMMARY: Major advances in the WB-MRI in the initial evaluation and follow-up of patients with lung cancer have been performed in recent years. Multicentric studies using different magnet systems are necessary to confirm these promising results.

AUTORES / AUTHORS: Khalil A; Bouhela T; Carette MF

INSTITUCIÓN / INSTITUTION: Radiology Department, Tenon Hospital, Paris.

RESUMEN / SUMMARY: Insulin-like growth factor binding protein-2 level is increased in blood of lung cancer patients and associated with poor survival.

AUTORES / AUTHORS: Guo C; Lu H; Gao W; Wang L; Lu K; Wu S; Pataer A; Huang M; El-Zein R; Lin T; Roth JA; Mehran R; Hofstetter W; Swisher SG; Wu X; Fang B

INSTITUCIÓN / INSTITUTION: Department of Thoracic and Cardiovascular Surgery, the University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America; Department of Neurosurgery/Neuro-Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China.

RESUMEN / SUMMARY: BACKGROUND: We recently showed that IGFBP2 is overexpressed in primary lung cancer tissues. This study aims to determine whether IGFBP2 is elevated in blood samples of lung cancer patients and whether its level is associated with clinical outcomes. METHODOLOGY/PRINCIPAL FINDINGS: Plasma IGFBP2 levels were determined blindly by enzyme-linked immunosorbent assay in 80 lung cancer patients and 80 case-matched healthy controls for comparison. We analyzed blood samples for IGFBP2 levels from an additional 84 patients with lung cancer and then tested for associations between blood IGFBP2 levels and clinical parameters in all 164 lung cancer patients. All statistical tests were two-sided and differences with p<0.05 were considered significant. The mean plasma concentration of IGFBP2 in lung cancer patients was significantly higher than that in healthy controls (388.12+/-261.00 ng/ml vs 219.30+/-172.84 ng/ml, p<0.001). IGFBP2 was increased in all types of lung cancer, including adenocarcinoma, squamous cell cancer, and small-cell cancer, regardless of patients’ age, sex, or smoking status. IGFBP2 levels were mildly but significantly associated with tumor size and were significantly higher in stage IV than stage I or III disease. A multivariate analysis showed that lung cancer patients whose blood IGFBP2 was higher than 160.9 ng/ml had a poor survival outcome, with a hazard ratio of 8.76 (95% CI 1.12-68.34, p=0.038 after adjustment for
The median survival time for patients with blood IGFBP2 >160.9 ng/ml is 15.1 months; whereas median survival time was 128.2 months for the patients whose blood IGFBP2 was ≤160.9 ng/ml (p =0.0002).

CONCLUSIONS/SIGNIFICANCE: Blood IGFBP2 is significantly increased in lung cancer patients. A high circulating level of IGFBP2 is significantly associated with poor survival, suggesting that blood IGFBP2 levels could be a prognostic biomarker for lung cancer.

TÍTULO / TITLE: Epidemiology of malignant pleural mesothelioma in the province of Sassari (Sardinia, Italy) A population-based report.

RESUMEN / SUMMARY: The aim of this population-based study was to analyze and describe the epidemiological characteristics and trends of malignant pleural mesothelioma in the province of Sassari (Sardinia, Italy), in the period 1992-2010. Data were obtained from the local tumor registry which makes part of a wider registry web, coordinated today by the Italian Association for Tumor Registries. The overall number of malignant pleural mesothelioma cases registered was 70. The male-to-female ratio was 4:1 and the mean age 65.1 years for males and 63.4 years for females. The standardized incidence rates were 1.2/100,000 and 0.3/100,000 and the standardized mortality rates 0.6/100,000 and 0.2/100,000 for males and females respectively. A trend to increase in incidence in recent years was evidenced. This trend seems to follow the general national tendency and it depends on a large diffusion of asbestos usage in the past, delayed legislative interventions and probably a cleaning strategy of residual contamination fonts to intensify. The relative 5 years survival was low, suggesting the necessity to further intensify research and cure methods for the treatment of this extremely aggressive disease. KEY WORDS: Asbestos exposure, Mesothelioma, Pleura, Sassari.

TÍTULO / TITLE: Downregulation of KPNA2 in non-small-cell lung cancer is associated with Oct4 expression.

RESUMEN / SUMMARY: BACKGROUND: Oct4 is a major transcription factor related to stem cell self-renewal and differentiation. To fulfill its functions, it must be able to
enter the nucleus and remain there to affect transcription. KPNA2, a member of the karyopherin family, plays a central role in nucleocytoplasmic transport. The objective of the current study was to examine the association between Oct4 and KPNA2 expression levels with regard to both the clinicopathological characteristics and prognoses of patients with non-small-cell lung cancer (NSCLC). METHODS: Immunohistochemistry was used to detect the expression profile of Oct4 and KPNA2 in NSCLC tissues and adjacent noncancerous lung tissues. Real-time polymerase chain reaction and western blotting were used to detect the mRNA and protein expression profiles of Oct4 and KPNA2 in lung cancer cell lines. Small interfering RNAs were used to deplete Oct4 and KPNA2 expressions. Double immunofluorescence was used to detect Oct4 expression in KPNA2 knockdown cells. Co-immunoprecipitation was used to detect the interaction of Oct4 and KPNA2. RESULTS: Oct4 was overexpressed in 29 of 102 (28.4%) human lung cancer samples and correlated with differentiation (P = 0.002) and TNM stage (P = 0.003). KPNA2 was overexpressed in 56 of 102 (54.9%) human lung cancer samples and correlated with histology (P = 0.001) and differentiation (P = 0.045). Importantly, Oct4 and KPNA2 expression levels correlated significantly (P < 0.01). Expression of Oct4 and KPNA2 was associated with short overall survival. In addition, depleting Oct4 and KPNA2 expression using small interfering RNAs inhibited proliferation in lung cancer cell lines. Real-time polymerase chain reaction and western blotting analysis indicated that reduction of KPNA2 expression significantly reduced mRNA and nucleoprotein levels of Oct4. Double immunofluorescence analysis revealed that nuclear Oct4 signals were reduced significantly in KPNA2 knockdown cells. Co-immunoprecipitation experiments revealed that KPNA2 interacts with Oct4 in lung cancer cell lines. CONCLUSION: Oct4 and KPNA2 play an important role in NSCLC progression. Oct4 nuclear localization may be mediated by its interaction with KPNA2.

[617]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Domen H; Hida Y; Okamoto S; Hatanaka KC; Hatanaka Y; Kaga K; Tamaki N; Hirano S; Matsuno Y
INSTITUCIÓN / INSTITUTION: - *Department of Surgical Pathology, Hokkaido University Hospital, North 14, West 5, Kita-ku, Sapporo 060-8648, Japan.
ymatsuno@med.hokudai.ac.jp.
RESUMEN / SUMMARY: - BACKGROUND: Fluorine-18-fluorodeoxyglucose uptake on positron emission tomography is reported to have prognostic significance in patients after resection of lung adenocarcinoma. However, its relationship with histopathologic features remains unknown. METHODS: We conducted a retrospective analysis of 205 patients who had undergone surgical resection of primary lung adenocarcinoma (>1.0 cm) after preoperative fluorine-18-fluorodeoxyglucose-positron emission tomography between January 1999 and December 2008 at Hokkaido University Hospital. Fluorine-18-fluorodeoxyglucose uptake was measured by the maximum standardized uptake value. A histopathologic review was performed according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification, and various histopathologic factors were evaluated semi-quantitatively. Correlations between these clinicopathologic factors and the maximum standardized uptake value (high >/=2.0 vs low <2.0) were analyzed. RESULTS: Univariate analysis of clinicopathologic factors demonstrated that the following were significantly correlated with a high maximum standardized uptake value: an elevated carcinoembryonic antigen level, larger tumor size, upgraded pT, pN, pStage, non-lepidic histology, abundant fibroblastic/hyalinized stroma, necrosis, presence of pleural involvement, lymphatic and vascular invasion and more intra- and extracellular mucin. Multivariate analysis demonstrated that a tumor size of >2.0 cm, non-lepidic histology and abundant fibroblastic/hyalinized stroma were significantly correlated with the high maximum standardized uptake value. CONCLUSION: More histopathologic factors are known to correlate with poor prognosis in lung adenocarcinomas showing high maximum standardized uptake values than in those showing low maximum standardized uptake values. Therefore, prognostication of patients with a resectable lung adenocarcinoma on the basis of preoperative fluorine-18-fluorodeoxyglucose uptake is histopathologically valid. Such observations may also help us to clarify the pathobiological mechanism responsible for the increased fluorine-18-fluorodeoxyglucose uptake in lung adenocarcinomas with a poor prognosis.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Takamochi K; Takeuchi K; Hayashi T; Oh S; Suzuki K
**RESUMEN / SUMMARY:** - BACKGROUND: EML4-ALK fusion gene is found in only a small subset (2-6%) of non-small cell lung cancer. There is an urgent need to establish a rational diagnostic algorithm to identify this rare but important fusion in lung cancer. METHODS: We performed a comprehensive analysis of EGFR/KRAS mutation and ALK rearrangement in a total of 360 surgically resected lung cancers. ALK rearrangement was examined by 3 analyses: multiplex reverse transcription-PCR, fluorescent in situ hybridization (FISH), and immunohistochemistry (IHC) with the intercalated antibody-enhanced polymer method. A scoring system was used for IHC (iScore). A test set (202 patients with unselected lung cancer) was used for proposing a diagnostic algorithm. This diagnostic algorithm was validated in 158 patients with EGFR and KRAS mutation-negative adenocarcinoma. RESULTS: ALK rearrangement was identified in 2 patients (1.0%) from the test set and both adenocarcinomas were negative for EGFR and KRAS mutations. The results of FISH and RT-PCR were completely matched. The highest iScore 3 was found only in the 2 positive cases. A diagnostic algorithm was proposed: IHC screening for ALK rearrangement followed by confirmatory FISH. In the validation set, 8 cases (5.1%) had iScore 3 and were positive for FISH, while the other cases had iScore 0 and were negative for FISH. CONCLUSIONS: Screening for ALK rearrangement by IHC followed by confirmatory FISH is a rational diagnostic algorithm. If needed, patients may be selected for screening ALK rearrangement by their EGFR and KRAS mutation status.

[619]

**TÍTULO / TITLE:** - Clinical Benefit From Pemetrexed Before and After Crizotinib Exposure and From Crizotinib Before and After Pemetrexed Exposure in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Berge EM; Lu X; Maxson D; Baron AE; Gadgeel SM; Solomon BJ; Doebele RC; Varella-Garcia M; Camidge DR

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, University of Colorado, Aurora, CO. Electronic address: Eamon.Berge@ucdenver.edu.

**RESUMEN / SUMMARY:** - BACKGROUND: Crizotinib produces high response rates and prolonged PFS in ALK+ NSCLC. Retrospective analyses suggest enhanced sensitivity to pemetrexed in crizotinib naive ALK+ NSCLC. Cross-resistance between crizotinib and pemetrexed has not been previously investigated. PATIENTS AND METHODS: Patients with stage IV ALK+ NSCLC treated with PEM-CRIZ, or CRIZ-PEM were identified. Overall PFS and PFS excluding central nervous system events (eCNS) were compared. RESULTS:
Objective response rates in evaluable patients were 66% (PEM-CRIZ) and 75% (CRIZ-PEM) for pemetrexed and 84% (CRIZ-PEM) and 66% (PEM-CRIZ) for crizotinib. For PEM-CRIZ (n = 29), median PFS and eCNS PFS were both 6 months with pemetrexed, and 10 and 14.5 months, respectively, with crizotinib. For CRIZ-PEM (n = 9), median PFS and eCNS PFS were 4.5 and 3 months, respectively, with pemetrexed, and 8.5 and 7.5 months, respectively, with crizotinib. There was a statistically significant increase in the risk of an overall PFS event with pemetrexed when administered after crizotinib (P = .0277; hazard ratio [HR], 2.5898; 95% confidence interval [CI], 1.1100-6.0424), but differences in the risk of an eCNS PFS event were not significant (P = 0.4913; HR, 1.3521; 95% CI, 0.5727-3.1920). Neither overall nor eCNS PFS for patients while taking crizotinib was associated with a sequence effect relative to pemetrexed. CONCLUSION: Crizotinib and pemetrexed are active drugs in ALK+ NSCLC. PFS benefit appeared higher with crizotinib than with pemetrexed. PFS benefit from pemetrexed was less after crizotinib compared with before crizotinib, however, this difference was only statistically significant for overall and not eCNS PFS. Pemetrexed exposure did not seem to affect crizotinib outcomes.

[620]
TÍTULO / TITLE: - Examining the association between statins and lung cancer incidence in patients with type 2 diabetes mellitus.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dong YH; Lin JW; Wu LC; Chen CY; Chang CH; Chen KY; Lai MS
INSTITUCIÓN / INSTITUTION: - Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.
RESUMEN / SUMMARY: - BACKGROUND/PURPOSE: The relationship between statin use and lung cancer remains unclear. Patients with diabetes mellitus, who are at higher risks for both cancer and atherosclerosis, are usually indicated for statin use. The objective was to explore the relationship between statins, lung squamous cell carcinoma (SCC), and lung adenocarcinoma incidence in diabetic patients. MATERIALS AND METHODS: A cohort of 596,812 type 2 diabetic patients was identified from the Taiwan National Health Insurance claims database in the year 2000, and followed until the earliest of lung cancer diagnosis, death, or December 31, 2007. A Cox regression model with time-varying statin use was applied to estimate the hazard ratio (HR) of lung cancer incidence comparing use and nonuse of statins. A sensitivity analysis was applied to examine the association after adjustment for smoking effect. RESULTS: In the original diabetic cohort, 60,969 statin users and 535,843 statin nonusers were identified. In a median follow-up time of 7.9 years, a total of 1182 incident SCC cases and 2345 adenocarcinoma cases developed. Initial analysis showed a decreased risk of
SCC if statins were ever used (HR, 0.69; 95% confidence interval, 0.60-0.81). However, the relative risk would be 0.92 for males and 0.90 for females for statins after adjusting for smoking effect. There was no association between statin use and adenocarcinoma (HR, 0.97; 95% confidence interval, 0.88-1.07), with similar findings after controlling for smoking effect. CONCLUSION: There is no statistically significant association between statin use with lung cancer incidence in diabetic patients after adjustment for the confounding effect attributed to cigarette smoking.
INSTITUCIÓN / INSTITUTION: - University of Groningen, University Medical Center Groningen, Center for Medical Imaging—North East Netherlands, Department of Radiology, Groningen, the Netherlands.

RESUMEN / SUMMARY: - The NELSON trial is the first randomised lung cancer screening trial in which pulmonary nodule management is based on volumetry. This led to considerably less false-positive referrals compared to other lung cancer screening trials, with very high negative predictive values found in the first and second screening rounds. Mortality results are still pending, but the knowledge already gained in the NELSON trial and its side-studies provide valuable information in the field of screening for lung cancer.

[623]

TÍTULO / TITLE: - Isolation and mutational analysis of circulating tumor cells from lung cancer patients with magnetic sifters and biochips.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Earhart CM; Hughes CE; Gaster RS; Ooi CC; Wilson RJ; Zhou LY; Humke EW; Xu L; Wong DJ; Willingham SB; Schwartz EJ; Weissman IL; Jeffrey SS; Neal JW; Rohatgi R; Wakelee HA; Wang SX

INSTITUCIÓN / INSTITUTION: - Department of Materials Science and Engineering, Stanford University, Stanford, CA 94305, USA.

RESUMEN / SUMMARY: - Detection and characterization of circulating tumor cells (CTCs) may reveal insights into the diagnosis and treatment of malignant disease. Technologies for isolating CTCs developed thus far suffer from one or more limitations, such as low throughput, inability to release captured cells, and reliance on expensive instrumentation for enrichment or subsequent characterization. We report a continuing development of a magnetic separation device, the magnetic sifter, which is a miniature microfluidic chip with a dense array of magnetic pores. It offers high efficiency capture of tumor cells, labeled with magnetic nanoparticles, from whole blood with high throughput and efficient release of captured cells. For subsequent characterization of CTCs, an assay, using a protein chip with giant magneto-resistive nanosensors, has been implemented for mutational analysis of CTCs enriched with the magnetic sifter. The use of these magnetic technologies, which are separate devices, may lead the way to routine preparation and characterization of “liquid biopsies” from cancer patients.

[624]

TÍTULO / TITLE: - Assessment of lung tumor response by perfusion CT.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Coche E
INSTITUCIÓN / INSTITUTION: - Department of Medical Imaging, Cliniques Universitaires St-Luc, Brussels, Belgium. Emmanuel.coche@uclouvain.be
RESUMEN / SUMMARY: - Perfusion CT permits evaluation of lung cancer angiogenesis and response to therapy by demonstrating alterations in lung tumor vascularity. It is advocated that perfusion CT performed shortly after initiating therapy may provide a better evaluation of physiological changes rather than the conventional size assessment obtained with RECIST. The radiation dose, the volume of contrast medium delivered to the patient and the reproducibility of blood flow parameters remain an issue for this type of investigation.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Rao CV; Patlolla JM; Qian L; Zhang Y; Brewer M; Mohammed A; Desai D; Amin S; Lightfoot S; Kopelovich L
INSTITUCIÓN / INSTITUTION: - Center for Cancer Prevention and Drug Development, Hematology-Oncology Section, Department of Medicine, Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK.
RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer deaths worldwide. Expression of the p53 tumor suppressor protein is frequently altered in tobacco-associated lung cancers. We studied chemopreventive effects of p53-modulating agents, namely, CP-31398 and Prima-1, on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung adenoma and adenocarcinoma formation in female A/J mice. Seven-week-old mice were treated with a single dose of NNK (10 micromol/mouse) by intraperitoneal injection and, 3 weeks later, were randomized to mice fed a control diet or experimental diets containing 50 or 100 ppm CP-31398 or 150 or 300 ppm Prima-1 for either 17 weeks (10 mice/group) or 34 weeks (15 mice/group) to assess the efficacy against lung adenoma and adenocarcinoma. Dietary feeding of 50 or 100 ppm CP-31398 significantly suppressed (P < .0001) lung adenocarcinoma by 64% and 73%, respectively, after 17 weeks and by 47% and 56%, respectively, after 34 weeks. Similarly, 150 or 300 ppm Prima-1 significantly suppressed (P < .0001) lung adenocarcinoma formation by 56% and 62%, respectively, after 17 weeks and 39% and 56%, respectively, after 34 weeks. Importantly, these results suggest that both p53 modulators cause a delay in the progression of adenoma to adenocarcinoma. Immunohistochemical analysis of lung tumors from mice exposed
to p53-modulating agents showed a significantly reduced tumor cell proliferation and increased accumulation of wild-type p53 in the nucleus. An increase in p21- and apoptotic-positive cells was also observed in lung tumors of mice exposed to p53-modulating agents. These results support a chemopreventive role of p53-modulating agents in tobacco carcinogen-induced lung adenocarcinoma formation.

[626]

TÍTULO / TITLE: - The association of race with timeliness of care and survival among Veterans Affairs health care system patients with late-stage non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zullig LL; Carpenter WR; Provenzale DT; Weinberger M; Reeve BB; Williams CD; Jackson GL

INSTITUCIÓN / INSTITUTION: - Center of Excellence for Health Services Research in Primary Care, Durham Veterans Affairs Medical Center, Durham, NC, USA ; Department of Health Policy and Management, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

RESUMEN / SUMMARY: - BACKGROUND: Non-small cell lung cancer is the leading cause of cancer-related mortality in the United States. Patients with late-stage disease (stage IV) have five-year survival rates of 2%-15%. Care quality may be measured as time to receiving recommended care and, ultimately, survival. This study examined the association between race and receipt of timely non-small cell lung cancer care and survival among Veterans Affairs health care system patients. METHODS: Data were from the External Peer Review Program, a nationwide Veterans Affairs quality-monitoring program. We included Caucasian or African American patients with pathologically confirmed late-stage non-small cell lung cancer in 2006 and 2007. We examined three quality measures: time from diagnosis to (1) treatment initiation, (2) palliative care or hospice referral, and (3) death. Unadjusted analyses used log-rank and Wilcoxon tests. Adjusted analyses used Cox proportional hazard models. RESULTS: After controlling for patient and disease characteristics using Cox regression, there were no racial differences in time to initiation of treatment (72 days for African American versus 65 days for Caucasian patients, hazard ratio 1.04, P = 0.80) or palliative care or hospice referral (129 days versus 116 days, hazard ratio 1.10, P = 0.34). However, the adjusted model found longer survival for African American patients than for Caucasian patients (133 days versus 117 days, hazard ratio 0.31, P < 0.01). CONCLUSION: For process measures of care quality (eg, time to initiation of treatment and referral to supportive care) the Veterans Affairs health care system provides racially equitable care. The small racial difference in survival time of
approximately 2 weeks is not clinically meaningful. Future work should validate this possible trend prospectively, with longer periods of follow-up, in other veteran groups.

[627]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Weynand B; Cohen J; Delos M; Fervaille C; Michoud M; Nollevaux MC; Reymond E; Ferretti GR

INSTITUCIÓN / INSTITUTION: - Department of Pathology, CHU Mont-Godinne, UCL, Belgium.

RESUMEN / SUMMARY: - The present manuscript is a summary of two lectures which were given respectively by B. Weynand and G.R. Ferretti. The new classification of lung adenocarcinomas has changed the view of the radiologists and the pathologists especially regarding the former bronchiolo-alveolar carcinoma (BAC). The aim of this paper is to correlate radiological and histopathological images according to the 2011 classification for lung adenocarcinoma proposed by the International Association for the Study of Lung cancer, the American Thoracic Society and the European Respiratory Society and to draw attention to the way these lesions can be approached preoperatively.

[628]

TÍTULO / TITLE: - Health effects of air pollution on length of respiratory cancer survival.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Xu X; Ha S; Kan H; Hu H; Curbow BA; Lissaker CT

RESUMEN / SUMMARY: - BACKGROUND: Air pollution has been extensively and consistently linked with mortality. However, no study has investigated the health effects of air pollution on length of survival among diagnosed respiratory cancer patients. METHODS: In this study, we conducted a population-based study to investigate if air pollution exposure has adverse effects on survival time of respiratory cancer cases in Los Angeles (LA), CA and Honolulu, HI. We selected all White respiratory cancer patients in the two study areas from the 1992--2008 Surveillance Epidemiology and End Results cancer data. Death from respiratory cancer and length of survival were the main outcomes. RESULTS: Kaplan-Meier survival analysis shows that all respiratory cancer cases exposed to high air pollution referring to the individuals from LA had a significantly shorter survival time than the low pollution
exposure group referring to those from Honolulu without adjusting for other covariates (p < 0.0001). Moreover, the results from the Cox Proportional-Hazards models suggest that exposure to particles less than 10 micrometers in diameter (PM10) was associated with an increased risk of cancer death (HR = 1.48, 95%CI: 1.44-1.52 per 10 mug/m3 increase in PM10) after adjusting for demographic factors and cancer characteristics. Similar results were observed for particles less than 2.5 micrometers in diameter and ozone. CONCLUSION: Our study indicates that air pollution may have deleterious effects on the length of survival among White respiratory cancer patients. This study calls for attention to preventive effort from air pollution for this susceptible population in standard cancer patient care. The findings from this study warrant further investigation.

[629]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dong YQ; Liang JS; Zhu SB; Zhang XM; Ji T; Xu JH; Yin GL
INSTITUCIÓN / INSTITUTION: - Department of Cardio-Thoracic Surgery, Wuhan General Hospital of Guangzhou Military Command, Wuhan, China E-mail: yin52@yahoo.cn, yin52@aliyun.com.
RESUMEN / SUMMARY: - Objective: The present study employed 5-aza-2’-deoxycytidine (5-Aza-CdR) to treat non-small cell lung cancer (NSCLC) cell line A549 to investigate the effects on proliferation and expression of the TFPI-2 gene. Methods: Proliferation was assessed by MTT assay after A549 cells were treated with 0, 1, 5, 10 mumol/L 5-Aza-CdR, a specific demethylating agent, for 24, 48 and 72h. At the last time point cells were also analyzed by flow cytometry (FCM) to identify any change in their cell cycle profiles. Methylation-specific polymerase chain reaction (MSPCR), real time polymerase chain reaction(real-time PCR) and western blotting were carried out to determine TFPI-2 gene methylation status, mRNA expression and protein expression. Results: MTT assay showed that the growth of A549 cells which were treated with 5-Aza-CdR was significantly suppressed as compared with the control group (0 mumol/L 5-Aza-CdR). After treatment with 0, 1, 5, 10 mumol/L 5-Aza-CdR for 72h, FCM showed their proportion in G0/G1 was 69.7+/−0.99%, 76.1+/−0.83%, 83.8+/−0.35%, 95.5+/−0.55% respectively (P<0.05), and the proportion in S was 29.8+/−0.43%, 23.7+/−0.96%, 15.7+/−0.75%, 1.73+/−0.45%, respectively (P<0.05), suggesting 5-Aza-CdR treatment induced G0/G1 phase arrest. MSPCR showed that hypermethylation in the promoter region of TFPI-2 gene was detected in control group (0 mumol/L 5-Aza-CdR), and demethylation appeared after treatment with 1, 5, 10 mumol/L 5-Aza-CdR for 72h. Real-time PCR showed that the expression levels of TFPI-2 gene mRNA were 1+/−0,
1.49+/−0.14, 1.86+/−0.09 and 5.80+/−0.15 (P<0.05) respectively. Western blotting analysis showed the relative expression levels of TFPI-2 protein were 0.12+/−0.01, 0.23+/−0.02, 0.31+/−0.02, 0.62+/−0.03 (P<0.05). TFPI-2 protein expression in A549 cells was gradually increased significantly with increase in the 5-Aza-CdR concentration. Conclusions: TFPI-2 gene promoter methylation results in the loss of TFPI-2 mRNA and protein expression in the non-small cell lung cancer cell line A549, and 5-Aza-CdR treatment could induce the demethylation of TFPI-2 gene promoter and restore TFPI-2 gene expression. These findings provide theoretic evidence for clinical treatment of advanced non-small cell lung cancer with the demethylation agent 5-Aza-CdR. TFPI-2 may be one molecular marker for effective treatment of advanced non-small cell lung cancer with 5-Aza-CdR.

[630]
TÍTULO / TITLE: - A case of pulmonary tumor thrombotic microangiopathy diagnosed by transbronchial lung biopsy and treated with chemotherapy and long-term oxygen and anticoagulation therapies.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kitamura A; Nishimura N; Jinta T; Suda R; Ishikawa G; Tomishima Y; Hamaoka T; Suzuki K; Chohnabayashi N
INSTITUCIÓN / INSTITUTION: - Division of Pulmonary Medicine, St. Luke’s International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan.
RESUMEN / SUMMARY: - A 41-year-old woman, who underwent breast resection for cancer of the right breast and adjuvant chemotherapy 2 years ago, was admitted to our hospital due to shortness of breath upon exertion. High-resolution computed tomography of the chest showed small nodular opacities in the peribronchiolar area in both lungs, as well as mediastinal and hilar lymphadenopathy. A transbronchial lung biopsy revealed breast cancer metastasis and pulmonary tumor thrombotic microangiopathy (PTTM). Treatment of PTTM is rarely reported due to the difficulty of antemortem diagnosis; however, the patient was effectively treated with chemotherapy and oxygen and anticoagulation therapies for 3 months.

[631]
TÍTULO / TITLE: - Small cell carcinoma of the uterine cervix metastasising to the cerebellum.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 3109/01443615.2013.798631

AUTORES / AUTHORS: - Scutiero G; Loizzi V; Macarini L; Landriscina M; Greco P
INSTITUCIÓN / INSTITUTION: - Institute of Obstetrics and Gynaecology, Department of Surgical Sciences, University of Foggia, Foggia, Italy. g.scutiero@hotmail.com

TÍTULO / TITLE: - Update in non small-cell lung cancer staging.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Salgado RA; Snoeckx A; Spinhoven M; Op de Beeck B; Corthouts B; Parizel PM
INSTITUCIÓN / INSTITUTION: - Dept. of Radiology, Antwerp University Hospital, Edegem, Belgium.
RESUMEN / SUMMARY: - Significant progress has been made with the introduction of the TNM-7 staging system for non-small cell lung cancer (NSCLC). Constituting the first major revision in 12 years, the seventh edition of NSCLC TNM (TNM-7) is based on the recommendations from the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project of 2007. This new TNM iteration includes a subset analysis on SCLC and carcinoid tumors. A thorough understanding of its principles by the radiologist is helpful to increase efficiency and to improve communication with the referring clinicians.

Enlace al texto completo (gratuito o de pago) 3109/01443615.2013.798631

AUTORES / AUTHORS: - Hanin FX
INSTITUCIÓN / INSTITUTION: - Nuclear Medicine Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
RESUMEN / SUMMARY: - FDG PET has been used for years in the diagnosis and recurrence of non small cell lung cancer (NSCLC). It has an important impact on patient management, and its coupling with CT for immediate fusion allows immediate localization and characterization of uptake. This article reviews the role of FDG PET-CT in the staging of NSCLC for the detection of metastatic disease.

Enlace al texto completo (gratuito o de pago) 3109/01443615.2013.798631

TÍTULO / TITLE: - Whole body PET-CT: M staging in non small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hanin FX
INSTITUCIÓN / INSTITUTION: - Nuclear Medicine Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
RESUMEN / SUMMARY: - FDG PET has been used for years in the diagnosis and recurrence of non small cell lung cancer (NSCLC). It has an important impact on patient management, and its coupling with CT for immediate fusion allows immediate localization and characterization of uptake. This article reviews the role of FDG PET-CT in the staging of NSCLC for the detection of metastatic disease.
**TÍTULO / TITLE:** - The impact of polymorphic variations in the 5p15, 6p12, 6p21 and 15q25 Loci on the risk and prognosis of portuguese patients with non-small cell lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - de Mello RA; Ferreira M; Soares-Pires F; Costa S; Cunha J; Oliveira P; Hespanhol V; Reis RM

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Faculty of Medicine, University of Porto (FMUP), Porto, Portugal ; Department of Medical Oncology, Instituto Portugues de Oncologia Francisco Gentil (IPO PORTO), Porto, Portugal.

**RESUMEN / SUMMARY:** - INTRODUCTION: Polymorphic variants in the 5p15, 6p12, 6p21, and 15q25 loci were demonstrated to potentially contribute to lung cancer carcinogenesis. Therefore, this study was performed to assess the role of those variants in non-small cell lung cancer (NSCLC) risk and prognosis in a Portuguese population. MATERIALS AND METHODS: Blood from patients with NSCLC was prospectively collected. To perform an association study, DNA from these patients and healthy controls were genotyped for a panel of 19 SNPs using a Sequenom MassARRAY platform. Kaplan-Meier curves were used to assess the overall survival (OS) and progression-free survival (PFS). RESULTS: One hundred and forty-four patients with NSCLC were successfully consecutively genotyped for the 19 SNPs. One SNP was associated with NSCLC risk: rs9295740 G/A. Two SNPs were associated with non-squamous histology: rs3024994 (VEGF intron 2) T/C and rs401681 C/T. Three SNPs were associated with response rate: rs3025035 (VEGF intron 7) C/T, rs833061 (VEGF -460) C/T and rs9295740 G/A. One SNP demonstrated an influence on PFS: rs401681 C/T at 5p15, \( p = 0.021 \). Four SNPs demonstrated an influence on OS: rs2010963 (VEGF +405 G/C), \( p = 0.042; \) rs3025010 (VEGF intron 5 C/T), \( p = 0.047; \) rs401681 C/T at 5p15, \( p = 0.046; \) and rs31489 C/A at 5p15, \( p = 0.029. \) CONCLUSIONS: Our study suggests that SNPs in the 6p12, 6p21, and 5p15 loci may serve as risk, predictive and prognostic NSCLC biomarkers. In the future, SNPs identified in the genomes of patients may improve NSCLC screening strategies and therapeutic management as well.

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[635]


**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - de Mello RA; Ferreira M; Soares-Pires F; Costa S; Cunha J; Oliveira P; Hespanhol V; Reis RM

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine, Faculty of Medicine, University of Porto (FMUP), Porto, Portugal ; Department of Medical Oncology, Instituto Portugues de Oncologia Francisco Gentil (IPO PORTO), Porto, Portugal.

**RESUMEN / SUMMARY:** - INTRODUCTION: Polymorphic variants in the 5p15, 6p12, 6p21, and 15q25 loci were demonstrated to potentially contribute to lung cancer carcinogenesis. Therefore, this study was performed to assess the role of those variants in non-small cell lung cancer (NSCLC) risk and prognosis in a Portuguese population. MATERIALS AND METHODS: Blood from patients with NSCLC was prospectively collected. To perform an association study, DNA from these patients and healthy controls were genotyped for a panel of 19 SNPs using a Sequenom MassARRAY platform. Kaplan-Meier curves were used to assess the overall survival (OS) and progression-free survival (PFS). RESULTS: One hundred and forty-four patients with NSCLC were successfully consecutively genotyped for the 19 SNPs. One SNP was associated with NSCLC risk: rs9295740 G/A. Two SNPs were associated with non-squamous histology: rs3024994 (VEGF intron 2) T/C and rs401681 C/T. Three SNPs were associated with response rate: rs3025035 (VEGF intron 7) C/T, rs833061 (VEGF -460) C/T and rs9295740 G/A. One SNP demonstrated an influence on PFS: rs401681 C/T at 5p15, \( p = 0.021 \). Four SNPs demonstrated an influence on OS: rs2010963 (VEGF +405 G/C), \( p = 0.042; \) rs3025010 (VEGF intron 5 C/T), \( p = 0.047; \) rs401681 C/T at 5p15, \( p = 0.046; \) and rs31489 C/A at 5p15, \( p = 0.029. \) CONCLUSIONS: Our study suggests that SNPs in the 6p12, 6p21, and 5p15 loci may serve as risk, predictive and prognostic NSCLC biomarkers. In the future, SNPs identified in the genomes of patients may improve NSCLC screening strategies and therapeutic management as well.

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[635]
RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor (EGFR)-targeted therapy has shown a favorable efficacy in patients with non-small-cell lung cancer (NSCLC). Conversely, K-RAS mutations were reported to have an adverse effect on the survival of patients with NSCLC. These studies suggest that the tumor biology of patients with EGFR or K-RAS mutations is different from that of patients with wild-type mutations. Therefore, we hypothesized that the response to cytotoxic chemotherapy may differ among patients with and without EGFR or K-RAS mutations. METHODS: A total of 229 patients with advanced NSCLC who received platinum doublet chemotherapy were included in this retrospective study, and their clinical outcomes were analyzed according to EGFR and K-RAS mutation status. RESULTS: EGFR and K-RAS mutations were found in 52.4% and 27.9% of patients, respectively. Progression-free survival (PFS) was significantly higher in patients with EGFR mutations than in patients with wild-type EGFR (P = .008), and multivariate analysis showed that EGFR mutation was an independent factor to chemotherapy (P = .01). Among the patients with EGFR mutations, the disease control rate for docetaxel was higher than for gemcitabine-based therapy (P = .031). In addition, docetaxel or vinorelbine showed a longer PFS than gemcitabine-based chemotherapy in patients with EGFR mutations (P = .033 and P = .028). However, no similar differences were found according to the K-RAS mutations. CONCLUSIONS: EGFR, but not K-RAS mutation, is associated with improved survival time to platinum-based chemotherapy. In patients with EGFR mutations, PFS for docetaxel and gemcitabine was higher than for vinorelbine-based chemotherapies. The predictive meaning of EGFR mutation for chemotherapy should be further investigated.

[636]

TÍTULO / TITLE: - A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Petereit C; Zaba O; Teber I; Luders H; Grohe C

RESUMEN / SUMMARY: - BACKGROUND: Hyponatremia based on syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) is observed in up to 15% of patients with small cell lung cancer (SCLC). The electrolyte imbalance is associated with a high morbidity and mortality and often delays appropriate treatment. Management of hyponatremia proved to be challenging until new vasopressin-2 receptor antagonists such as tolvaptan became available. This is the first report which presents a prospective case series with an efficient management of hyponatremia.
including tolvaptan in ten patients with SCLC and severe SIADH (plasma sodium < 125 mmol/l). METHODS: Ten patients with SCLC and severe SIADH were followed after the onset of clinical symptoms of SIADH. Patients were chosen on the basis of histological proven diagnosis of SCLC and the clinical picture of a neurocognitive deficit caused by SIADH-related hyponatremia. All patient data were monitored for clinical improvement based on ECOG status, commencement of chemotherapy and correction of sodium levels. RESULTS: The treatment followed a diagnostic and treatment algorithm and lead to a rapid and efficient correction of both clinical symptoms and plasma sodium level. CONCLUSIONS: Based on this algorithm all patients started chemotherapy in time. Subsequently, the treatment with tolvaptan lead to an improvement of the ECOG-performance status. In addition, all patients benefit from the effective management of SIADH which omitted prolonged hospital stays and non-elective hospitalizations due to an unstable clinical condition due to severe hyponatremia. These observations add new insight to management of SIADH in thoracic oncology and are of interest for specialists in oncology, endocrinology and pulmonary medicine.

[637]

TÍTULO / TITLE: - Ctl4-4 expression and polymorphisms in lung tissue of patients with diagnosed non-small-cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Antczak A; Pastuszak-Lewandoska D; Gorski P; Domanska D; Migdalska-Sek M; Czarnecka K; Nawrot E; Kordiak J; Brzezianska E

INSTITUCIÓN / INSTITUTION: - Department of General and Oncological Pulmonology, 1st Chair of Internal Diseases, Medical University of Lodz, Kopcinskiego 22, 90-153 Lodz, Poland.

RESUMEN / SUMMARY: - Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is a potent immunoregulatory molecule that downregulates T-cell activation and thus influences the antitumor immune response. CTLA-4 polymorphisms are associated with various cancers, and CTLA-4 mRNA/protein increased expression is found in several tumor types. However, most of the studies are based on peripheral blood mononuclear cells, and much less is known about the relationship between CTLA-4 expression, especially gene expression, and its polymorphic variants in cancer tissue. In our study we assessed the distribution of CTLA-4 two polymorphisms (+49°C/G and -318C/T), using TaqMan probes (rs231775 and rs5742909, resp.), and CTLA-4 gene expression in real-time PCR assay in non-small-cell lung cancer (NSCLC) tissue samples. The increased CTLA-4 expression was observed in the majority of NSCLC patients, and it was significantly correlated with TT genotype (-318C/T) and with tumor size (T2 versus T3 + T4). The presence of G allele and GG genotype in cancer tissue (+49°C/G)
was significantly associated with the increased NSCLC risk. Additionally, we compared genotype distributions in the corresponding tumor and blood samples and found statistically significant differences. The shift from one genotype in the blood to another in the tumor may confirm the complexity of gene functionality in cancer tissue.

[638]
TÍTULO / TITLE: - Erlotinib and Concurrent Chemoradiation in Pretreated NSCLC Patients: Radiobiological Basis and Clinical Results.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Ramella S; Alberti AM; Cammilluzzi E; Fiore M; Ippolito E; Greco C; De Quarto AL; Ramponi S; Apolone G; Trodella L; Cesario A; D'Angelillo RM
INSTITUCIÓN / INSTITUTION: - Radiation Oncology, Campus Bio-Medico University, Via Alvaro del Portillo 21, 00128 Roma, Italy.

RESUMEN / SUMMARY: - Aims. To establish feasibility of the combination of Erlotinib and concurrent chemoradiation in pre-treated patients with locally advanced or metastatic NSCLC. Materials and Methods. Data regarding 60 consecutive patients with NSCLC previously treated with chemotherapy alone were prospectively collected. All patients started Erlotinib concurrently with chemotherapy and radiation delivered to primary tumor. These data were retrospectively analyzed (observational study). Feasibility and toxicity were the primary endpoints, with response rate and progression being the secondary ones, while survival data are reported just as exploratory analysis. The EGFR mutational status was recorded in 32% of cases and it was always wild type. Results. Compliance to the combination protocol was good. Grade 3-4 esophagitis and acute lung toxicity occurred in 2% and 8% of patients, respectively. No progressive disease was recorded in the majority of cases (65%). Median OS and PFS were 23.3 and 4.7 months, respectively. Patients not responding to chemotherapy administered prior to chemoradiation achieved an objective response rate of 53.3% and complete response in 13.3% of cases. Conclusions. The addition of Erlotinib to chemoradiation in inoperable NSCLCs is feasible with interesting efficacy profile. These preliminary results warrant further investigation in patients with locally advanced nonmetastatic NSCLC with EGFR mutations.

[639]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
BACKGROUND: Although a number of studies in patients with a variety of malignant tumors have shown that metabolic activity on fluorine-18 deoxyglucose positron emission tomography computed tomography (18F-FDG-PET/CT) is correlated with survival, there are few studies about the impact of 18F-FDG-PET/CT for survival in small cell lung cancer (SCLC) patients. There is still some ambiguity as to whether FDG PET in patients with SCLC will ensure prognostic knowledge for survival.

We performed a retrospective analysis of prognostic implication of 18F-FDG-PET/CT in patients with SCLC. METHODS: We retrospectively reviewed 54 patients with histologically or cytologically proven SCLC who had undergone pre-treatment 18F-FDG-PET/CT scanning between September 2007 and November 2011 in the Dicle University, School of Medicine, Department of Medical Oncology. SUVmax and other potential prognostic variables were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival.

RESULT: Among the eleven variables of univariate analysis, three variables were identified as having prognostic significance: Performance status (p<0.001), stage (p=0.02) and diabetes mellitus (p=0.05). Multivariate analysis showed that performance status and stage were considered independent prognostic factors for survival (p<0.001 and p=0.002 respectively).

CONCLUSION: In conclusion, performance status and stage were identified as important prognostic factors, while 18F-FDG-PET/CT uptake of the primary lesions was not associated with prognostic importance for survival in patients with SCLC.
January 2012, 138 consecutively diagnosed NSCLC patients were included in this study. The patient, tumor and treatment related factors were analyzed. Median overall survival (OS), Kaplan-Meier survival plots, t-test, Cox proportional hazards models were generated by multivariate analysis (MVA) and analyzed on SPSS software (version 19.0; SPSS, Inc., Chicago, IL). RESULTS: Median OS of stage III patients was 9.26 +/- 1.85 months and 2-year survival rate of 13% while stage IV patients had median OS of 5 +/- 1.5 months with a 2-year survival rate of 8%. Cox regression modeling for MVA demonstrated higher biologically equivalent dose (BED) (P = 0.01) in stage III while in stage IV non-squamous histology (P = 0.01), administration of chemotherapy (P = 0.02), partial responders to chemotherapy (P = 0.001), higher BED (P = 0.02), and those with skeletal metastasis alone (P = 0.17) showed a better OS.

CONCLUSION: Our data showed that a higher BED is associated with favorable outcomes, indicating a role of dose escalated radiation therapy to the primary lesion in both stage III and essentially in stage IV NSCLC. Additionally, optimal use of chemotherapy relates to better survival. The developing, resource restrained nations need to follow an economically feasible multimodality approach.

[641]

- Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases.
metastases at diagnosis (9.8 months vs. 4.8 months). Among patients who received chemotherapy, the survival of patients with brain metastases at diagnosis was still poor (6.2 months). CONCLUSIONS: Our data show limited survival in patients with brain metastases from nsclc. Careful patient selection for more aggressive treatment approaches is necessary.

[642]

TÍTULO / TITLE: - Up-regulation of miR-9 expression as a poor prognostic biomarker in patients with non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Xu T; Liu X; Han L; Shen H; Liu L; Shu Y

INSTITUCIÓN / INSTITUTION: - Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing, 210029, People’s Republic of China.

RESUMEN / SUMMARY: - PURPOSE: Emerging evidences indicate that dysregulated microRNAs are implicated in cancer tumorigenesis and progression. MicroRNA-9 (miR-9) has various expression patterns in diverse human cancers. However, its clinical significance in human non-small cell lung cancer has not yet been elucidated. In the present study, we detected the expression of miR-9 in non-small cell lung cancer and adjacent noncancerous tissues and explored its relationships with clinicopathological characteristics and prognosis. METHODS: Expression levels of miR-9 in 116 pairs of non-small cell lung cancer and adjacent normal tissues were detected by real-time quantitative RT-PCR assay. To determine its prognostic value, overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method. Univariate and multivariate analysis were performed using the Cox proportional hazard analysis. RESULTS: MiR-9 expression in non-small cell lung cancer tissues was significantly higher than that in adjacent normal tissues (p = 0.001), and its up-regulation was significantly correlated to advanced tumor-node-metastasis (TNM) stage (p < 0.001), tumor size (p = 0.013), and lymph node metastasis (p = 0.001). Furthermore, Kaplan-Meier analysis demonstrated that high miR-9 expression clearly predicted poorer PFS (p < 0.001) and OS (p < 0.001). In the multivariate analysis, increased miR-9 expression was an independent prognostic factor for both PFS (p = 0.002) and OS (p = 0.013). CONCLUSIONS: MiR-9 was up-regulated in non-small cell lung cancer tissues and correlated with adverse clinical features and unfavorable survival, indicating that miR-9 might be involved in non-small lung cancer progression and could serve as a promising biomarker for further risk stratification in the treatment of this cancer.

[643]
TÍTULO / TITLE: - Prognostic Value of EGFR Mutation and ERCC1 in Patients with Non-Small Cell Lung Cancer Undergoing Platinum-Based Chemotherapy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Yamashita F; Azuma K; Yoshida T; Yamada K; Kawahara A; Hattori S; Takeoka H; Zaizen Y; Kawayama T; Kage M; Hoshino T

INSTITUCIÓN / INSTITUTION: - Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan.

RESUMEN / SUMMARY: - BACKGROUND: In order to improve the outcome of patients with non-small cell lung cancer (NSCLC), a biomarker that can predict the efficacy of chemotherapy is needed. The aim of this study was to assess the role of EGFR mutations and ERCC1 in predicting the efficacy of platinum-based chemotherapy and the outcome of patients with NSCLC. METHODS: We conducted a retrospective study to analyze the relationships between EGFR mutations or ERCC1 expression and progression-free survival (PFS) in patients with NSCLC who received platinum-based chemotherapy. EGFR mutation status was determined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, and immunohistochemistry was used to examine the expression of ERCC1 in tumor samples obtained from the patients. RESULTS: Among the NSCLC patients who received platinum-based chemotherapy, the median PFS was significantly better in those who had never smoked and those with exon 19 deletion, and the median overall survival (OS) was significantly better in those who had never smoked, those with exon 19 deletion, and women. Cox regression analysis revealed that exon 19 deletion and having never smoked were significantly associated with both PFS and OS. Subset analysis revealed a significant correlation between ERCC1 expression and EGFR mutation, and ERCC1-negative patients with exon 19 deletion had a longer PFS than the other patients; ERCC1-positive patients without exon 19 deletion had a shorter PFS than the other patients. CONCLUSIONS: Our results indicate that among NSCLC patients receiving platinum-based chemotherapy, those with exon 19 deletion have a longer PFS and OS. Our findings suggest that platinum-based chemotherapy is more effective against ERCC1-negative and exon 19-positive NSCLC.

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TÍTULO / TITLE: - Predicting 7-day survival using heart rate variability in hospice patients with non-lung cancers.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

BACKGROUND: A simple and accurate survival prediction tool can facilitate decision making processes for hospice patients with advanced cancers. The objectives of this study were to explore the association of cardiac autonomic functions and survival in patients with advanced cancer and to evaluate the prognostic value of heart rate variability (HRV) in 7-day survival prediction.

METHODS: A prospective study was conducted on 138 patients with advanced cancer recruited from the hospice ward of a regional hospital in southern Taiwan. Information on functional status and symptom burden of the patients was recorded. Frequency-domain HRV was obtained for the evaluation of cardiac autonomic functions at admission. The end point of the study was defined as the survival status at day 7 after admission to the hospice ward. Multivariate logistic regression analyses were performed to evaluate the independent associations between HRV indices and survival of 7 days or less.

RESULTS: The median survival time of the patients was 20 days (95% CI, 17-28 days). Results from the multivariate logistic regression analysis indicated that the natural logarithm-transformed high-frequency power (lnHFP) of a value less than 2 (OR = 3.8, p = 0.008) and ECOG performance status of 3 or 4 (OR = 3.4, p = 0.023) were significantly associated with a higher risk of survival of 7 days or less. Receiver operating characteristic (ROC) curve analysis revealed that the area under the curve was 0.71 (95% CI, 0.61-0.81).

CONCLUSIONS: In hospice patients with non-lung cancers, an lnHPF value below 2 at hospice admission was significantly associated with survival of 7 days or less. HRV might be used as a non-invasive and objective tool to facilitate medical decision making by improving the accuracy in survival prediction.
was to determine the prognostic value of preoperative CRP in patients with SCCE.

METHODS: From January 2001 to December 2010, a retrospective analysis of 43 consecutive patients with SCCE was conducted. Univariate and multivariate analyses were performed to evaluate the prognostic parameters. RESULTS: In our study, elevated CRP levels (>10 mg/L) were found in 16 patients (37.2%). CRP levels were significantly higher in patients with deeply invasive tumors (P = 0.018) and those associated with nodal metastasis (P = 0.018). Patients with CRP </=10 mg/L had a significantly better overall survival than patients with CRP >10 mg/L (25.9% vs 6.3%, P = 0.004). Multivariate analyses showed that CRP was a significant predictor for overall survival. CRP >10 mg/L had a hazard ratio of 2.756 (95% confidence interval: 1.115-6.813, P = 0.028) for overall survival. CONCLUSION: Preoperative CRP is an independent predictive factor for long-term survival in patients with SCCE.

[646]

TÍTULO / TITLE: - Role of gender in the survival of surgical patients with nonsmall cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


PROFESIONAL / PROFESSIONAL: - Scaglia NC; Chatkin JM; Pinto JA; Tsukazan MT; Wagner MB; Saldanha AF

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, Hospital Sao Lucas da Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, Brazil.

RESUMEN / SUMMARY: - PURPOSE: There are reports of greater survival rates in nonsmall cell lung cancer (NSCLC) patients of female gender. The objective of this study was to evaluate the role of gender in survival of NSCLC patients treated surgically with curative intent (stage I/II). METHODS: In a retrospective cohort design, we screened 498 NSCLC patients submitted to thoracotomies at the hospital Sgammao Lucas, in Porto Alegre, Brazil from 1990 to 2009. After exclusion of patients that did not fit to all the inclusion criteria, we analyzed survival rates of 385 subjects. Survival was analyzed using the Kaplan-Meier method. The Cox regression model was used to evaluate potential confounding factors. RESULTS: Survival rates at 5 and 10 years were 65.3% and 49.5% for women and 46.5% and 33.2% for men, respectively (P = 0.006). Considering only stage I patients, the survival rates at 5 and 10 years were 76.2% and 55.1% for women and 50.7% and 35.4% for men, respectively (P = 0.011). No significant differences in survival rates were found among stage II patients.

CONCLUSIONS: Our results show female gender as a possible protective factor for better survival of stage I NSCLC patients, but not among stage II patients. This study adds data to the knowledge that combined both genders survival rates for NSCLC is not an adequate prognosis.
The role of CD133 expression in the carcinogenesis and prognosis of patients with lung cancer.

Cancer stem cells (CSCs) are a small population of undifferentiated cancer cells within tumors, which contribute to tumorigenicity and relapse. In the current study, CD133 (also termed prominin1), a CSC marker, was investigated to determine its involvement in predicting carcinogenesis and prognosis in patients with nonsmall cell lung carcinoma (NSCLC). CD133positive lung cancer cells were isolated to analyze selfrenewal, differentiation and tumorigenic abilities in vitro and in vivo. Quantitative polymerase chain reaction was used to detect the expression of CD133 and three other CSCassociated markers, octamerbinding transcription factor 4 (OCT4A), Nanog homeobox (NANOG) and multidrug resistance protein 1 (MDR1), in primary NSCLC and adjacent noncancer tissues. A series of statistical methods were used to analyze the correlation between mRNA expression levels, clinicopathological features and patient survival. The results showed that CD133positive NSCLC cells demonstrated clonogenic, tumorigenic and drugresistance properties compared with their CD133negative counterparts or parental cells. In addition, compared with the adjacent normal lung tissue, the levels of CSCassociated biomarkers CD133, OCT4A, NANOG and MDR1 were significantly increased in NSCLC tissue. Elevated expression of CD133 was associated with stage, tumor size and differentiation of NSCLC; however, the cox hazard regression analysis showed no significant association between CD133 expression and overall patient survival. The present study supports the hypothesis that the stem cell population can be enriched in cells expressing the CD133 cell surface marker and that highly expressed CD133 is involved in the occurrence of NSCLC. However, CD133 may not be considered as an independent factor in predicting the prognosis of patients with NSCLC. Further studies are required to investigate the association between CD133 expression and overall patient survival.
RESUMEN / SUMMARY: - Background: Previous studies have shown that the outcome of lung cancer patients who were admitted to the Intensive Care Unit (ICU), especially those requiring mechanical ventilation, is extremely poor. The present study was conducted in order to assess the outcome of a recent cohort of lung cancer patients admitted to the ICU with acute respiratory failure. Methods: A retrospective analysis of the medical records of 105 lung cancer patients who were admitted to the ICU between January 2008 and January 2011 was performed. Severity of illness on the first day of ICU admission was assessed using the acute physiology and chronic health evaluation (APACHE) II and the sequential organ failure assessment (SOFA) scoring systems. Associated organ failure was determined according to the Knaus criteria. Results: Eighty four (80%) patients were diagnosed with non-small cell lung cancer, 14 (13.3%) with small cell lung cancer, one patient with mesothelioma, and in the remaining 6 patients, the type of lung cancer could not be determined. Significant factors on admission were APACHE II and SOFA scores, poor performance status and severe comorbidity. During ICU stay, the main risk factors for poor outcome were the long term mechanical ventilation duration, use of vasopressors, more than two organ system failures and septic condition. The overall ICU, hospital and 6-month mortality rates were 44.7% (47/105), 56.1% (59/105) and 77.1% (81/105) respectively. Conclusions: The present data show that the medical intensive care unit outcome of lung cancer patients is improving. Further studies of patients selected to ICU admission are needed to assess long-term mortality, quality of life, ability to continue chemotherapy and economic cost.

[649]

TÍTULO / TITLE: - High plasma fibrinogen concentration and platelet count unfavorably impact survival in non-small cell lung cancer patients with brain metastases.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhu JF; Cai L; Zhang XW; Wen YS; Su XD; Rong TH; Zhang LJ

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China; Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China. zhanglj@sysucc.org.cn.

RESUMEN / SUMMARY: - High expression of fibrinogen and platelets are often observed in non-small cell lung cancer (NSCLC) patients with local regional or distant metastasis. However, the role of these factors remains unclear. The aims of this study were to evaluate the prognostic significance of plasma fibrinogen concentration and platelet
count, as well as to determine the overall survival of NSCLC patients with brain metastases. A total of 275 NSCLC patients with brain metastasis were enrolled into this study. Univariate analysis showed that high plasma fibrinogen concentration was associated with age \( \geq 65 \) years (\( P = 0.011 \)), smoking status (\( P = 0.009 \)), intracranial symptoms (\( P = 0.022 \)), clinical T category (\( P = 0.010 \)), clinical N category (\( P = 0.003 \)), increased partial thromboplastin time (\( P < 0.001 \)), and platelet count (\( P < 0.001 \)). Patients with low plasma fibrinogen concentration demonstrated higher overall survival compared with those with high plasma fibrinogen concentration (median, 17.3 months versus 11.1 months; \( P \leq 0.001 \)). A similar result was observed for platelet counts (median, 16.3 months versus 11.4 months; \( P = 0.004 \)). Multivariate analysis showed that both plasma fibrinogen concentration and platelet count were independent prognostic factors for NSCLC with brain metastases (RR = 1.698, \( P < 0.001 \) and RR = 1.699, \( P < 0.001 \), respectively). Our results suggest that high plasma fibrinogen concentration and platelet count indicate poor prognosis for NSCLC patients with brain metastases. Thus, these two biomarkers might be independent prognostic predictors for this subgroup of NSCLC patients.

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**TÍTULO / TITLE:** - Pleurectomy/decortication, chemotherapy, and intensity modulated radiation therapy for malignant pleural mesothelioma: rationale for multimodality therapy incorporating lung-sparing surgery.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2225-319X.2012.10.08

**AUTORES / AUTHORS:** - Zauderer MG; Krug LM

**INSTITUCIÓN / INSTITUTION:** - Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY 10065, USA.

[651]

**TÍTULO / TITLE:** - Clinicopathologic features of non-small cell lung cancer in India and correlation with epidermal growth factor receptor mutational status.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 4103/0019-509X.117016

**AUTORES / AUTHORS:** - Bhatt AD; Pai R; Rebekah G; Nehru GA; Dhananjayan S; Samuel A; Singh A; Joel A; Korula A; Chacko RT
Introduction: We performed retrospective analysis of 106 patients with lung cancer for which formalin-fixed paraffin-embedded tissues was available. Their epidermal growth factor receptor (EGFR) mutation status and treatment outcomes are described. Materials and Methods: All patients with confirmed non-small cell lung cancer (NSCLC) during Jan 2008 to Dec 2010 were included. EGFR sequencing was performed with ABI PRISM 310 genetic analyzer. Results: Forty-two (39.6%) patients had mutation in one of the four exons characterized. Patients whose EGFR mutational status was not available at presentation before the start of treatment were started on chemotherapy, n = 46 (43.39%). If EGFR mutational analysis was available and mutations were present, the patients were started on either upfront tyrosine kinase inhibitor (TKI), n = 15 (14.15%) or if on chemotherapy arm were allowed to finish six cycles and then start with maintenance TKIs, n = 26 (24.52%). The median progression free survival for patients with and without mutations was 11 months (95% CI, 7-14) and 9 months (95% CI, 7-10) respectively. A median PFS of 14 months (95% CI, 12-16) was seen in the mutation-positive group that received both chemotherapy followed by switch maintenance with TKIs versus 8 months (95% CI, 7-8 months) in the group that received only TKI. Conclusion: The prevalence of EGFR mutations in this population of NSCLC patients was 39.6% with exon 19 mutation being the most common. The observed benefit of addition of chemotherapy over TKI in EGFR mutation-positive group raises the question, can we offer the therapy of chemotherapy-TKI combination to EGFR mutation-positive lung cancer patients as shown in the present study.

CHANGE OF CMTM7 EXPRESSION, A POTENTIAL TUMOR SUPPRESSOR, IS ASSOCIATED WITH POOR CLINICAL OUTCOME IN HUMAN NON-SMALL CELL LUNG CANCER.

BACKGROUND: CKLF-like MARVEL transmembrane domain-containing 7 (CMTM7) located at 3p22.3, is a frequent deletion site and a tumor suppressor gene (TSG) locus in many cancer, which suggests CMTM7 may be a potential TSG. The aim of this study was to investigate the correlations of CMTM7 expression and survival rate in patients with non-small cell lung cancer (NSCLC).

METHODS: Surgical specimens of 180 cases with pathologically confirmed NSCLC were grouped into 18 tissue microarray slides. CMTM7 expression in these specimens were
detected by immunohistochemistry staining and representative cases were confirmed by Western blotting. Univariate and multivariate analyses were performed to identify the association of CMTM7 expression with pathological features and survival of patients with NSCLC. RESULTS: A total of 78.9% of the 180 patients had variations of CMTM7 protein expression, either up-regulated or down-regulated. Univariate analysis showed that the patients’ survival rate after surgery was highly correlated with CMTM7 expression (P = 0.0091). In addition, prognostic factors were examined by multivariate Cox regression analysis, and results suggested that CMTM7 expression was a unique prognostic factor in NSCLC survival. CONCLUSIONS: The CMTM7 expression may be related to survival of patients with NSCLC and a unique prognostic factor. CMTM7 may play an important role in NSCLC development.

[653]

TÍTULO / TITLE: Silica-induced chronic inflammation promotes lung carcinogenesis in the context of an immunosuppressive microenvironment.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Freire J; Ajona D; de Biurrun G; Agorreta J; Segura V; Guruceaga E; Bleau AM; Pio R; Blanco D; Montuenga LM

INSTITUCIÓN / INSTITUTION: Center for Applied Medical Research (CIMA), Pamplona, España.

RESUMEN / SUMMARY: The association between inflammation and lung tumor development has been clearly demonstrated. However, little is known concerning the molecular events preceding the development of lung cancer. In this study, we characterize a chemically induced lung cancer mouse model in which lung cancer developed in the presence of silicotic chronic inflammation. Silica-induced lung inflammation increased the incidence and multiplicity of lung cancer in mice treated with N-nitrosodimethylamine, a carcinogen found in tobacco smoke. Histologic and molecular analysis revealed that concomitant chronic inflammation contributed to lung tumorigenesis through induction of preneoplastic changes in lung epithelial cells. In addition, silica-mediated inflammation generated an immunosuppressive microenvironment in which we observed increased expression of programmed cell death protein 1 (PD-1), transforming growth factor-beta1, monocyte chemotactic protein 1 (MCP-1), lymphocyte-activation gene 3 (LAG3), and forkhead box P3 (FOXP3), as well as the presence of regulatory T cells. Finally, the K-RAS mutational profile of the tumors changed from Q61R to G12D mutations in the inflammatory milieu. In summary, we describe some of the early molecular changes associated to lung carcinogenesis in a chronic inflammatory microenvironment and provide novel information concerning the mechanisms underlying the formation and the fate of preneoplastic lesions in the silicotic lung.
**TÍTULO / TITLE:** Somatostatin receptor type 2-based reporter expression after plasmid-based in vivo gene delivery to non-small cell lung cancer.

**RESUMEN / SUMMARY:** ABSTRACT Plasmids tend to have much lower expression than viruses. Gene expression after systemic administration of plasmid vectors has not been assessed using somatostatin receptor type 2 (SSTR2)-based reporters. The purpose of this work was to identify gene expression in non-small cell lung cancer (NSCLC) after systemic liposomal nanoparticle delivery of plasmid containing SSTR2-based reporter gene. In vitro, Western blotting was performed after transient transfection with the plasmid cytomegalovirus (CMV)-SSTR2, CMV-TUSC2-IRES-SSTR2, or CMV-TUSC2. SSTR2 is the reporter gene, and TUSC2 is a therapeutic gene. Mice with A549 NSCLC lung tumors were injected intravenously with CMV-SSTR2, CMV-TUSC2-IRES-SSTR2, or CMV-TUSC2 plasmids in DOTAP:cholesterol-liposomal nanoparticles. Two days later, mice were injected intravenously with 111In-octreotide. The next day, biodistribution was performed. The experiment was repeated including single-photon emission computed tomography/computed tomography (SPECT/CT). Immunohistochemistry was performed. In vitro, SSTR2 expression was similar in cells transfected with CMV-SSTR2 or CMV-TUSC2-IRES-SSTR2. TUSC2 expression was similar in cells transfected with CMV-TUSC2 or CMV-TUSC2-SSTR2. Biodistribution demonstrated significantly greater 111In-octreotide uptake in tumors from mice injected with CMV-TUSC2-IRES-SSTR2 or CMV-SSTR2 than the control plasmid, CMV-TUSC2 (p < .05). Gamma-camera and SPECT/CT imaging illustrated SSTR2 expression in tumors in mice injected with CMV-TUSC2-IRES-SSTR2 or CMV-SSTR2 versus background with control plasmid. Immunohistochemistry corresponded with imaging. SSTR2-based reporter imaging can visualize gene expression in lung tumors after systemic liposomal nanoparticle delivery of plasmid containing SSTR2-based reporter gene or SSTR2 linked to a second therapeutic gene, such as TUSC2.

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**TÍTULO / TITLE:** Feasibility and long-term efficacy of video-assisted thoracic surgery for unexpected pathologic N2 disease in non-small cell lung cancer.

**RESUMEN / SUMMARY:** ABSTRACT Feasibility and long-term efficacy of video-assisted thoracic surgery for unexpected pathologic N2 disease in non-small cell lung cancer.


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4103/1817-1737.114291
autores / authors: - Wang S; Zhou W; Zhang H; Zhao M; Chen X
institución / institution: - Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University; Shanghai First People’s Hospital, Shanghai Jiaotong University, Shanghai, China; Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China.
resumen / summary: - objetivos: This study compares early and late outcomes for treatment by video-assisted thoracic surgery (VATS) versus treatment by thoracotomy for clinical N0, but post-operatively unexpected, pathologic N2 disease (cN0-pN2).

metodos: Clinical records of patients with unexpected N2 non-small cell lung cancer (NSCLC) who underwent VATS were retrospectively reviewed, and their early and late outcomes were compared to those of patients undergoing conventional thoracotomy during the same period. resultados: VATS lobectomy took a longer time than thoracotomy (P < 0.001), but removal of thoracic drainage and patient discharge were earlier for patients in the VATS group (P < 0.001). There was no difference in lymph node dissection, mortality and morbidity between the two groups (P > 0.05). The median follow-up time for 287 patients (89.7%) was 37.0 months (range: 7.0-69.0). The VATS group had a longer survival time than the thoracotomy group (median 49.0 months vs. 31.7 months, P < 0.001). The increased survival time of the VATS group was due to patients with a single station of N2 metastasis (P = 0.001), rather than to patients with multiple stations of N2 metastasis (P = 0.225). conclusiones: It is both feasible and safe to perform VATS lobectomy on patients with unexpected N2 NSCLC. VATS provides better survival rates for those patients with just one station of metastatic mediastinal lymph nodes.

[656]
título / title: - Dexamethasone enhances invasiveness of Aspergillus fumigatus conidia and fibronectin expression in A549 cells.
resumen / summary: - Enlace al resumen / Link to its Summary
autores / authors: - Li T; Li JC; Li Y
institución / institution: - Department of Respiratory Medicine, Qilu Hospital of Shandong University, Jinan, Shandong 250012, China.
resumen / summary: - background: The efficacies of current treatments for invasive aspergillus (IA) are unsatisfactory and new therapeutic targets or regimens to treat IA are urgently needed. Previous studies have indicated that the ability of conidia to invade host cells is critical in IA development and fibronectin has a hand in the conidia adherence process. In the clinical setting, many patients who receive glucocorticoid for extended periods are susceptible to Aspergillus fumigatus (A. fumigatus) infection, for this reason we investigated the effect of glucocorticoid on conidia invasiveness by comparing the invasiveness of A. fumigatus conidia in the type II human alveolar cell line (A549) cultured with different concentrations of dexamethasone. We also
explored the relationships between dexamethasone and fibronectin expression. METHODS: Following culture with anti-fibronectin antibodies and/or dexamethasone, type II human alveolar A549 cells were infected with conidia of A. fumigatus. After 4 hours, the extracellular free conidia were washed away and the remaining immobilized conidia were released using Triton-X 100 and quantified by counting the colony-forming units. The invasiveness of conidia was measured by calculating the invasion rate (%). The transcription of the fibronectin gene in cells cultured with different concentrations of dexamethasone for 24 hours was tested by fluorogenic quantitative RT-PCR while the expression of fibronectin in cells cultured for 48 hours was tested by Western blotting and immunocytochemistry. RESULTS: A significant reduction in the invasiveness of conidia was seen in the cells cultured with anti-fibronectin antibody ((14.42+/−1.68)% vs. (19.17+/−2.53)% , P < 0.05), but no significant difference was observed in cells cultured with a combination of anti-fibronectin antibody and dexamethasone (6.37+/−10(−5) mol/L). There was no correlation between the dexamethasone concentration and the invasiveness of conidia after dexamethasone pretreatment of cells for 4 hours. In contrast, after pretreated for 24 hours, the invasiveness of conidia in the presence of 6.37x10(-5) mol/L dexamethasone ((24.66+/−2.41)% ) was higher than for the control ((19.17+/−2.53)% ) and the 0.25x10(-5) mol/L group ((19.93+/−3.06)% ), and the invasiveness in the 1.27x10(-5) mol/L group ((22.47+/−2.46)% ) was also higher than in the control, P < 0.05. The relative transcripts of the fibronectin gene after exposure to 6.37x10(-5) mol/L dexamethasone (9.19x10(-3)+/−1.2x10(-3)) was higher than for the control (4.61x10(-3)+/−1.54x10(-3)) and the 0.25x10(-5) mol/L group (6.20x10(-3)+/−1.93x10(-3)), and expression in the 1.27x10(-5) mol/L group (7.94x10(-3)+/−2.24x10(-3)) was also higher than for the control, P < 0.05. High concentrations of dexamethasone promoted fibronectin production after culture for 48 hours. CONCLUSIONS: Dexamethasone can increase invasiveness of A. fumigatus conidia by promoting fibronectin expression. This may partially explain why patients who are given large doses of glucocorticoids for extended periods are more susceptible to A. fumigatus infection.

[657]

- Enlace al Resumen / Link to its Summary
- Enlace al texto completo (gratuito o de pago) 1016/j.canep.2013.08.003
- Xu HL; Gao XR; Zhang W; Cheng JR; Tan YT; Zheng W; Shu XO; Xiang YB
PURPOSE: Translesion DNA synthesis (TLS) plays an important role in promoting replication through DNA lesions. Genetic polymorphisms in TLS genes may have potential roles in lung cancer development in humans. METHODS: We evaluated the association between genetic variants in six TLS genes and the risk and survival of lung cancer in a case-control study in China. Included in the study are 224 lung cancer patients and 448 healthy controls. RESULTS: Carriers of the G allele of POLkappa rs5744724 had significantly reduced risk of lung cancer (odds ratio (OR)=0.62, 95% confidence interval (CI): 0.44-0.89), comparing with those carrying the C allele, and the AA genotype of PCNA rs25406 was also associated with significantly decreased cancer risk compared with the major homozygote alleles (OR=0.47, 95% CI: 0.25-0.86). Haplotype analysis showed that subjects with the POLkappa C-G (rs5744533-rs5744724) haplotype had decreased risk of lung cancer (OR=0.69, 95% CI: 0.49-0.98), comparing with those carrying the C-C haplotype. Besides, the heterozygote of REV1 rs3087386 and rs3792136 were independent prognostic factors for lung cancer survival with hazard ratio (HR) 1.54 (95% CI: 1.12-2.12) and 1.44 (95% CI: 1.06-1.97) respectively. CONCLUSIONS: Our findings suggested that genetic variants in POLkappa and PCNA genes may play roles in the susceptibility of lung cancer, and REV1 gene may have roles in lung cancer survival in Chinese men.
SABR has shown good results in medically operable patients. No randomized data are available comparing SLR and SABR, and therefore, data from prospective studies were compared. Overall survival at 1 year was similar between patients treated with SABR and SLR (81-85.7 vs 92%); however, overall 3-year survival was higher following SLR (87.1 vs 45.1-57.1%). There was no statistically significant difference in local recurrence in patients treated with SABR compared with SLR (3.5-14.5 vs 4.8-20%). Both treatment modalities are associated with complications. Fatigue (31-32.6%), pneumonitis (2.1-12.5%) and chest wall pain (3.1-12%) were common following SABR; however, serious grade 3 and 4 toxicity were rare. Morbidity following SLR was reported between 7.3 and 33.7%. Thirty-day mortality following SABR was 0%, while predicted 30-day mortality following a lung resection, using the thoracoscore predictive model ranges between 1 and 2.6%. Treatment for early-stage NSCLC should be tailored to individual patients. SABR is an acceptable alternative to SLR in high-risk patients but comparative data are required.

[659]

**TÍTULO** / **TITLE:** - The Number of Resected Lymph Nodes (nLNs) Combined with Tumor Size as a Prognostic Factor in Patients with Pathologic N0 and Nx Non-Small Cell Lung Cancer.

**RESUMEN** / **SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES** / **AUTHORS:** - Yang M; Cao H; Guo X; Zhang T; Hu P; Du J; Liu Q

**INSTITUCIÓN** / **INSTITUTION:** - Institute of Oncology, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, P.R. China ; Department of Medical Oncology, Yantai Yuhuangding Hospital, Qingdao University School of Medicine, Yantai, P.R. China.

**RESUMEN** / **SUMMARY:** - BACKGROUND: The prognostic role of the number of resected lymph nodes (nLNs) in pathologic N0 (lymph node negative) and Nx (no lymph node examined) non-small cell lung cancer (NSCLC) patients remains uncertain. Guidelines for optimal nLNs have not been established. In the current study, we evaluated whether a higher number of resected lymph nodes (LNs) results in better survival in different tumor size categories among NSCLC patients without metastatic LNs.

**METHOD:** A retrospective study was conducted. Based on nLNs (LN = 0, 1-7, >7) and tumor size (Ta: \( \leq 3.5 \text{cm}, \ Tb: >3.5 \text{cm} \)) during surgery, patients were categorized into 6 groups (LN0Ta, LN0Tb, LN1-7Ta, LN1-7Tb, LN7-Ta and LN7-Tb). Survival and multivariate analyses were carried out to determine whether nLNs combined with tumor size was significant for overall survival (OS) or disease free survival (DFS) after adjusting for potential confounders. **RESULTS:** A total of 428 patients were enrolled in the study. Multivariate analysis demonstrated that nLNs, tumor size and pathological
stage were the independent prognosticators for OS and DFS. Data from our study suggested that lung cancer lymphadenectomy with more than 7 LNs removed should be considered a benchmark for surgery or pathology at an early stage. Survival was significantly better in the LN7-Ta group, compared with other 5 groups (p<0.001).

CONCLUSIONS: The combined predictor (nLNs combined with tumor size) is an independent prognostic factor and a reasonable stratification criterion in patients with pathologic N0 and Nx NSCLC. The validation of our finding is warranted in further investigation.

[660]
TÍTULO / TITLE: - Cisplatin in 5% Ethanol Eradicates Cisplatin-Resistant Lung Tumor by Killing Lung Cancer Side Population (SP) Cells and Non-SP Cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Niu Q; Wang W; Li Y; Ruden DM; Li Q; Wang F
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, No. 309 People’s Liberation Army Hospital Beijing, People’s Republic of China.
RESUMEN / SUMMARY: - Cancer side population (SP) cells with cancer stem cell-like properties are thought to be responsible for lung cancer chemotherapy resistance and currently no drug can efficiently target them. Breast cancer resistance protein (BRCP/ABCG2) is a major drug transporter in protecting lung cancer SP cells from cytotoxic agents. We showed that a low concentration of ethanol, which inhibits many membrane proteins, inhibits ABCG2 in lung cancer SP cells. Furthermore, cytotoxic cisplatin (DDP) in 5% (vol/vol) ethanol kills SP plus non-SP cancer cells better than either treatment alone in eradicating chemoresistant lung tumors. We found that 5% ethanol did not reduce ABCG2 protein levels, but significantly reduced ABCG2 protein function by a Hoechst 33342 extrusion assay, an ATPase activity assay, and transmission electron microscopy. Further, DDP in 5% ethanol (5% ethanol-DDP) induced apoptosis of the SP plus non-SP cancer cells both in vitro and in vivo. In DDP-resistant A549/DDP lung tumor-bearing Balb/C nude mice, intratumoral injection of 5% ethanol-DDP regressed tumors and significantly improved survivals compared with 5% ethanol, DDP alone, or control. Intratumoral injection of 5% ethanol-DDP helped eradicate tumors in 30% (3/10) of the mice after 4 weeks treatment. By killing SP and non-SP cancer cells, 5% ethanol-DDP could eradicate DDP-resistant lung tumor and extend survival, providing a novel way to improve chemoresistant lung cancer survival for clinic.

[661]
TÍTULO / TITLE: - Quality of life and personality traits in patients with malignant pleural mesothelioma and their first-degree caregivers.
Asbestos exposure causes significant pleural diseases, including malignant pleural mesothelioma (MPM). Taking into account the impact of MPM on emotional functioning and wellbeing, this study aimed to evaluate the quality of life and personality traits in patients with MPM and their first-degree caregivers through the World Health Organization Quality of Life-BREF (WHOQOL-BREF) and the Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF). The sample was composed of 27 MPM patients, 55 first-degree relatives enrolled in Casale Monferrato and Monfalcone (Italy), and 40 healthy controls (HC). Patients and relatives reported poorer physical health than the HC. Patients had a higher overall sense of physical debilitation and poorer health than relatives and the HC, more numerous complaints of memory problems and difficulties in concentrating, and a greater belief that goals cannot be reached or problems solved, while often claiming that they were more indecisive and inefficacious than the HC. First-degree relatives reported lower opinions of others, a greater belief that goals cannot be reached or problems solved, support for the notion that they are indecisive and inefficacious, and were more likely to suffer from fear that significantly inhibited normal activities than were HC. In multinomial regression analyses, partial models indicated that sex, physical comorbidities, and the True Response Inconsistency (TRIN-r), Malaise (MLS), and Behavior-Restricting Fears (BRF) dimensions of the MMPI-2-RF had significant effects on group differences. In conclusion, health care providers should assess the ongoing adjustment and emotional wellbeing of people with MPM and their relatives, and provide support to reduce emotional distress.

Lung cancer is the most common cancer in the world. Globally, the annual diagnosis rate of new cases is approximately 1.6 million. The latest figures for the UK show that there are approximately 39000 cases each year and that lung cancer accounts for about 22% of all cancer deaths (Cancer Research UK, 2013#).
The article will look at the latest national recommendations for managing and treating non-small cell lung cancer, which accounts for about 80% of lung cancers, as well as emerging therapies. It is not within the scope of this article to discuss each type and aspect of lung cancer in detail and further reading is encouraged.

[663]
**TÍTULO / TITLE:** - Pulmonary carcinoid presenting with cavitating lung infection and oligometastatic mediastinal disease.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Medford A; Bhatt N; Edey A

**INSTITUCIÓN / INSTITUTION:** - Consultant and Honorary Senior Clinical Lecturer in Interventional Pulmonology and Thoracic Medicine in the North Bristol Lung Centre, Southmead Hospital, Westbury-on-Trym, Bristol.

**RESUMEN / SUMMARY:** - A previously fit 25-year-old man presented with cavitating lung infection and evidence of cystic bronchiectasis. Computed tomography showed a 4.7cm soft tissue mass containing patchy calcification occluding the basal bronchus of the right lower lobe, resulting in atelectasis and marked distal airway dilatation with endoluminal air-fluid levels and mediastinal lymphadenopathy.

[664]
**TÍTULO / TITLE:** - Re-challenge chemotherapy with gemcitabine plus carboplatin in patients with non-small cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Khan K; Hanna GG; Campbell L; Scullin P; Hussain A; Eakin RL; McAleese J

**INSTITUCIÓN / INSTITUTION:** - Institute of Cancer Research/Royal Marsden Hospital, Downs Road, Sutton SM2 5PT, UK. khurum.khan@icr.ac.uk.

**RESUMEN / SUMMARY:** - Despite recent improvements to current therapies and the emergence of novel agents to manage advanced non-small cell lung cancer (NSCLC), the patients’ overall survival remains poor. Re-challenging with first-line chemotherapy upon relapse is common in the management of small cell lung cancer but is not well reported for advanced NSCLC. NSCLC relapse has been attributed to acquired drug resistance, but the repopulation of sensitive clones may also play a role, in which case re-challenge may be appropriate. Here, we report the results of re-challenge with gemcitabine plus carboplatin in 22 patients from a single institution who had previously received gemcitabine plus platinum in the first-line setting and had either
partial response or a progression-free interval of longer than 6 months. In this retrospective study, the charts of patients who underwent second-line chemotherapy for NSCLC in our cancer center between January 2005 and April 2010 were reviewed. All the patients who received a combination of gemcitabine and carboplatin for re-challenge were included in the study. These patients were offered second-line treatment on confirmation of clear radiological disease progression. The overall response rate was 15% and disease control rate was 75%. The median survival time was 10.4 months, with 46% of patients alive at 1 year. These results suggest that re-challenge chemotherapy should be considered in selected patients with radiological partial response or a progression-free survival of longer than 6 months to the initial therapy.

[665]

TÍTULO / TITLE: - Molecular epidemiology of epidermal growth factor receptor mutations in lung cancers in Indian population.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Mehta J
INSTITUCIÓN / INSTITUTION: - SRL Diagnostics, Centre of Excellence: Histopathology, Lower Parel, Mumbai, Maharashtra, India.
RESUMEN / SUMMARY: - Background: Lung cancer is the leading cause of cancer related mortality world-wide and amongst males in India. The discovery of tyrosine kinase inhibitors holds a ray of hope for a subset of lung cancer patients, which have activating epidermal growth factor receptor (EGFR) mutations. Much of the preliminary data on frequency of EGFR mutations emanated from Western studies, which reported EGFR mutation rates of 10-15%. However, studies from Asian countries report a much higher frequency of EGFR mutations, not only in the male population, but also in females. AIM: The object of this study was to share the author’s experience of EGFR mutation testing in 402 lung cancer patients as no large-scale study addressing the issue has been published from India. Materials and Methods: Formalin fixed paraffin embedded tissues were analyzed for EGFR exon 19 deletions and exon 21 point mutation by length analysis of fluorescently labeled polymerase chain reaction products on Applied Biosystems Inc. 310 genetic analyzer. Results: Out of 402 samples, 35 samples could not be analyzed because of poor deoxyribonucleic acid material. Thus of the remaining 367 cases analyzed, EGFR mutations were found in 118 patients (32%). Mutations were equally distributed between males (50%) and females (50%). Majority of the mutations were seen in adenocarcinoma subtype (90%). Exon 19 mutations accounted for 76% while exon 21 mutations accounted for 24% of the mutations. Summary: EGFR mutation frequency is higher in Indian population vis-a-vis
Caucasian population, but lower than that reported in the East Asian population. A significantly higher number of males also harbor EGFR mutations.
CYFRA21-1 were assessed in 150 patients with lung cancer, 100 patients with benign lung disease and 100 normal control subjects, and differences of expression were compared in each group, and joint effects of these tumor markers in the diagnosis of lung cancer were analyzed. Results: Serum CEA, CA19-9, NSE and CYFRA21-1 in patients with lung cancer were significantly higher than those with benign lung disease and normal controls (p<0.01). It is suggested that these four tumor markers combined together could produce a positive detection rate of 90.2%, significantly higher than that of any single test. Conclusion: Combination detection of CEA, CA19-9, NSE and CYFRA21-1 could significantly improve the sensitivity and specificity in diagnosis of lung cancer, and could be important in early detection.

[668]

TÍTULO / TITLE: - PIK3CA mutation in Chinese patients with lung squamous cell carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Yu J; Bai H; Wang Z; Wei Z; Ding X; Duan J; Yang L; Wu M; Wang Y; Wang J

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate PIK3CA mutation in Chinese patients with lung squamous cell carcinoma (LSCC) and explore their relationship with clinicopathological profiles. METHODS: Tumor samples from 123 cases of LSCC were included in this study. PIK3CA mutations in exon 9 and 20 were screened by pyrosequencing and confirmed by clone sequencing or amplification refractory mutation system (ARMS). Denaturing performance liquid chromatography (DHPLC) was employed for evaluation of EGFR mutation in exon 19, 21 and KRAS mutation. RESULTS: PIK3CA mutations were found in 3 (2.4%) patients. The mutation type included E545K, E452Q and H1047R. Of these three patients, one coupled with EGFR mutation, and the other two coupled with PIK3CA amplification. All the three patients shared the same clinicopathologic characteristics: male, less than 60 years old, had smoke history, stage III and carried wild-type KRAS. CONCLUSIONS: The frequency of PIK3CA mutation is low in Chinese patients with LSCC. The mutational status of PIK3CA is not mutually exclusive to EGFR mutation.

[669]
TÍTULO / TITLE: - CYFRA21-1 as a serum tumor marker for follow-up patients with squamous cell lung carcinoma and oropharynx squamous cell carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 2217/bmm.13.55

AUTORES / AUTHORS: - Liu L; Liu B; Zhu LL; Li Y

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, the Fourth Affiliated Hospital of Harbin Medical University, No 37, Yi Yuan Street, Nan Gang District, Harbin 150001, China. liulei110052@163.com

RESUMEN / SUMMARY: - AIM: To evaluate serum soluble fragments of cytokeratin 19 (i.e., CYFRA21-1) as a tumor marker for patients with squamous cell lung carcinoma (SCLC) and oropharynx squamous cell carcinoma (OSCC). PATIENTS & METHODS: A total of 152 patients with SCLC and OSCC, and 84 control patients were included in the study. CYFRA21-1 concentration was measured using electrochemiluminescence immunoassays. RESULTS: As the disease stages increased, concentrations and sensitivity of CYFRA21-1 increased significantly in patients with SCLC and OSCC. A significant difference in sensitivity between the pretherapeutic group and recurrence group of OSCC (p = 0.001) was observed, as well as for SCLC (p = 0.024). A positive correlation (p = 0.042) existed between CYFRA21-1 concentrations and cancer stage of SCLC and OSCC. There was no significant correlation between CYFRA21-1 concentrations and different organ types with squamous cell cancer (p = 0.51). CONCLUSION: The CYFRA21-1 assay demonstrated a greater sensitivity for recurrent stages of SCLC and OSCC, and may prove beneficial in the prediction of SCLC and OSCC recurrence at an earlier date.

[670]

TÍTULO / TITLE: - EGFR, KRAS, BRAF, and HER-2 molecular status in brain metastases from 77 NSCLC patients.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1002/cam4.82

AUTORES / AUTHORS: - Villalva C; Duranton-Tanneur V; Guilloteau K; Burel-Vandenbos F; Wager M; Doyen J; Levillain PM; Fontaine D; Blons H; Pedetour F; Karayan-Tapon L

INSTITUCIÓN / INSTITUTION: - INSERM U935, Poitiers University, Poitiers, France.

RESUMEN / SUMMARY: - The aim of this study was to determine the frequency of EGFR, KRAS, BRAF, and HER-2 mutations in brain metastases from non-small cell lung carcinomas (BM-NSCLC). A total of 77 samples of BM-NSCLC were included and 19 samples of BM from breast, kidney, and colorectal tumors were also studied as controls. These samples were collected from patients followed between 2008 and 2011 at Poitiers and Nice University Hospitals in France. The frequencies of EGFR,
KRAS, BRAF, and HER-2 mutations in BM-NSCLC were 2.6, 38.5, 0, and 0% respectively. The incidence of KRAS mutation was significantly higher in female and younger patients (P < 0.05). No mutations of the four genes were found in BM from breast or kidney. However, among six BM from colorectal tumors, we identified KRAS mutations in three cases and BRAF mutations in two other cases. This study is the largest analysis on genetic alterations in BM-NSCLC performed to date. Our results suggest a low frequency of EGFR mutations in BM-NSCLC whereas KRAS mutations are as frequent in BM-NSCLC as in primitive NSCLC. These results raise the question of the variability of the brain metastatic potential of NSCLC cells in relation to the mutation pattern.

[671] TÍTULO / TITLE: - Nutrition and exercise interventions for patients with lung cancer appear beneficial, but more studies are required.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kiss N; Isenring E
INSTITUCIÓN / INSTITUTION: - Peter MacCallum Cancer Care Centre, Melbourne, Australia.

[672] TÍTULO / TITLE: - Season of diagnosis and survival of advanced lung cancer cases - any correlation?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Oguz A; Unal D; Kurtul N; Aykas F; Mutlu H; Karagoz H; Cetinkaya A
INSTITUCIÓN / INSTITUTION: - Medical Oncology Department, Faculty of Medicine, Baskent University, Turkey E-mail: oguzarzu@yahoo.com.
RESUMEN / SUMMARY: - Introduction: The influence of season at diagnosis on cancer survival has been an intriguing issue for many years. Most studies have shown a possible correlation in between the seasonality and some cancer type survival. With short expected survival, lung cancer is an arena that still is in need of new prognostic factors and models. We aimed to investigate the effect of season of diagnosis on 3 months, 1 and 2 years survival rates and overall survival of non small cell lung cancer patients. Materials and Methods: The files of non small cell lung cancer patients that were stages IIIB and IV at diagnosis were reviewed retrospectively. According to diagnosis date, the patients were grouped into 4 season groups, autumn, winter, spring and summer. Results: A total of 279 advanced non small cell lung cancer patients’ files were reviewed. Median overall survival was 15 months in the entire population. Overall 3 months, 1 and 2 years survival rates were 91.0%, 58.2% and 31.2% respectively. The season of diagnosis was significantly correlated with 3 months
survival rates, being diagnosed in spring being associated with better survival. Also the season was significantly correlated with T stage of the disease. For 1 and 2 years survival rates and overall survival, the season of diagnosis was not significantly correlated. There was no correlation detected between season and overall survivals according to histological subtypes of non small cell lung cancer. Conclusion: As a new finding in advanced non small cell lung cancer patients, it can be concluded that being diagnosed in spring can be a favorable prognostic factor for short term survival.

[673]

**TÍTULO / TITLE:** Clinical significance and prognostic value of pentraxin-3 as serologic biomarker for lung cancer.

**RESUMEN / SUMMARY:** Purposes: Lung cancer is prevalent worldwide and improvements in timely and effective diagnosis are need. Pentraxin-3 as a novel serum marker for lung cancer (LC) has not been validated in large cohort studies. The aim of the study was to assess its clinical value in diagnosis and prognosis. Methods: We analyzed serum PTX-3 levels in a total of 1,605 patients with LC, benign lung diseases and healthy controls, as well as 493 non-lung cancer patients including 12 different types of cancers. Preoperative and postoperative data were further assessed in patients undergoing LC resection. The diagnostic performance of PTX-3 for LC and early-stage LC was assessed using receiver operating characteristics (ROC) by comparing with serum carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA 21-1). Results: Levels of PTX-3 in serum were significantly higher in patients with LC than all controls. ROC curves showed the optimum diagnostic cutoff was 8.03ng/mL (AUC 0.823, [95%CI 0.789-0.856], sensitivity 72.8%, and specificity 77.3% in the test cohort; 0.802, [95%CI 0.762-0.843], sensitivity 69.7%, and specificity 76.4% in the validate cohort). Similar diagnostic performance of PTX-3 was observed for early-stage LC. PTX-3 decreased following surgical resection of LC and increased with tumor recurrence. Significantly elevated PTX-3 levels were also seen in patients with non-lung cancers. Conclusions: The present data revealed that PTX-3 was significantly increased in both tissue and serum samples in LC patients. PTX-3 is a valuable biomarker for LC and improved identification of patients with LC and early-stage LC from those with non-malignant lung diseases.
Disease flare after discontinuation of crizotinib in anaplastic lymphoma kinase-positive lung cancer.

**RESUMEN / SUMMARY:** We report the case of a 50-year-old male former smoker. He was diagnosed as having lung adenocarcinoma and treated with induction chemoradiation therapy followed by surgery and adjuvant chemotherapy. Molecular testing revealed that his tumor had an echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement. Therefore, he was treated with crizotinib when his disease recurred. He achieved a partial response, which persisted for 10 months until progressive disease was confirmed. Crizotinib was continued for 1 month and the tumor size increased slightly. At that time, crizotinib was discontinued and he participated in a clinical trial of erlotinib +/- Met inhibitor; however, his disease progressed rapidly after discontinuation of crizotinib, and the diagnosis of disease flare was made. Readministration of crizotinib was started immediately; however, his disease progressed rapidly, and he died 2 days after starting crizotinib retreatment. Currently, the incidence of disease flare is unknown and it is impossible to predict who will experience it. Therefore, continuing crizotinib after disease progression may be a reasonable option to avoid disease flare.

Genetic Variation in BCL2 3'-UTR Was Associated with Lung Cancer Risk and Prognosis in Male Chinese Population.

**RESUMEN / SUMMARY:** OBJECTIVES: Bcl-2 is a critical apoptosis inhibitor with established carcinogenic potential, and can confer cancer cell resistance to therapeutic
treatments by activating anti-apoptotic cellular defense. We hypothesized that genetic variants of BCL2 gene may be associated with lung cancer susceptibility and prognosis.

METHODS: Three selected tagSNPs of BCL2 (rs2279115, rs1801018, and rs1564483) were genotyped in 1017 paired male Chinese lung cancer cases and controls by TaqMan assay. The associations of these variants with risk of lung cancer and overall survival of 242 male advanced non-small-cell lung cancer (NSCLC) patients were separately investigated. RESULTS: Compared with the BCL2 3’UTR rs1564483GG genotype, the rs1564483GA, AA, and GA+AA genotypes were associated with significantly decreased susceptibilities of lung cancer in male Chinese (adjusted OR = 0.78, 0.73, and 0.76, P = 0.016, 0.038, and 0.007, respectively), while rs1564483A allele has an inverse dose-response relationship with lung cancer risk (P trend = 0.010). These effects were more evident in the elders, smokers, and subjects without family history of cancer (P trend = 0.017, 0.043 and 0.005, respectively). Furthermore, advanced NSCLC males carrying BCL2 rs1564483 GA+AA genotypes had significantly longer median survival time (Long-rank P = 0.036) and decreased death risk (adjusted HR = 0.69, P = 0.027) than patients with rs1564483GG genotype. These effects were more obvious in patients with smoking, stage IIIA, and in patients without surgery but underwent chemotherapy or radiotherapy (adjusted HR = 0.68, 0.49, 0.67, 0.69, 0.50, respectively, all P<0.05). CONCLUSION: The BCL2 3’UTR rs1564483A allele was associated with a decreased lung cancer risk and better survival for advanced NSCLC in male Chinese, which may offer a novel biomarker for identifying high-risk population and predicting clinical outcomes.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zhang Y; Li S; Cao K; Feng Y; Zhang X; Xiao Y; Li J

INSTITUCIÓN / INSTITUTION: - Department of Traditional Chinese Medicine, General Hospital of People’s Liberation Army, Beijing 100853, China.

RESUMEN / SUMMARY: - OBJECTIVE: To observe the effect of decoction for reinforcing lung Qi on T-lymphocytic function, interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-alpha) in peripheral blood of patients with non-small cell lung cancer after operation with argon helium lancet in order to explore its mechanism. METHODS: A total of 76 patients suffering from non-small cell lung cancer without surgical indication were randomly divided into a treatment group treated with decoction for reinforcing lung Qi and argon helium lancet and a control group treated with argon helium lancet only to observe lymphocytic proliferation, detect the percentage of positive cells in the T-lymphocyte CD28 with flow cytometry and detect the expression of IL-2 and TNF-alpha in peripheral blood with enzyme linked immunosorbent assay.
RESULTS: Proliferation of T-lymphocytes and expression of CD28, IL-2 and TNF-alpha in peripheral blood after treatment in the treatment group were more obviously strengthened than those before treatment and those in the control group (all P < 0.05). CONCLUSION: The mechanism of using decoction for reinforcing lung Qi and argon helium lancet to treat lung cancer may be realized through promoting T-lymphocytic proliferation, up-regulating expression of CD28, IL-2 and TNF-alpha, and activating T-cells.

[677]
TÍTULO / TITLE: - A 52-year-old male patient with metastatic non-small-cell lung cancer and recurrent venous thromboembolism in unusual sites despite anticoagulation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - British Medical J (BMJ). %8?(3k+|3s http://bmj.com/search.dtl
AUTORES / AUTHORS: - Matikas A; Vardakis N; Souglakos J; Georgoulias V
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece.
RESUMEN / SUMMARY: - The link between cancer and venous thromboembolism is well known, with an annual incidence rate of venous thromboembolism between 0.5% and 20% depending on the primary site and background risk factors. Current guidelines suggest treatment with low-molecular-weight heparin over oral vitamin K antagonists. However, data regarding the management of recurrent venous thromboembolism when the patient is under treatment with anticoagulants are sparse. In this article we present a patient with multiple thromboembolic events in unusual sites despite anticoagulant treatment and we discuss the management options.

[678]
TÍTULO / TITLE: - Inhibition of nuclear factor-kappaB activity enhanced chemosensitivity to cisplatin in human lung adeno-carcinoma A549 cells under chemical hypoxia conditions.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Li F; Huang L; Su XL; Gu QH; Hu CP
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, Xiangya Hospital, Central South University, Changsha, Hunan 410007, China.
RESUMEN / SUMMARY: - BACKGROUND: Tumor hypoxia, one of the features of solid tumors, is associated with chemo-resistance. Recently, nuclear factor-kappaB (NF-kappaB) was found to be activated during hypoxia. However, the impact of NF-kappaB
activation on chemo-resistance during hypoxia remains unknown. METHODS: Human lung adenocarcinoma A549 cells were transfected with NF-kappaB p65siRNA and treated with cobalt chloride (CoCl2) to mimic hypoxia in the presence or absence of cisplatin. NF-kappaB expression was measured by Western blotting, immune-fluorescence and real-time PCR. Hypoxia-inducible factor-1alpha (HIF-1alpha) and Bcl-2 expression were determined by Western blotting. Cell apoptosis and survival with half-maximum inhibitory concentration (IC50) of cisplatin were determined by Annexin V-FITC/PI and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT), respectively. RESULTS: Exposure of A549 cells to CoCl2 increased nuclear HIF-1α protein expression, and enhanced NF-kappaB p65 protein nuclear accumulation (the mark of NF-kappaB activation) in a time and dose dependent manner. CoCl2 did not promote apoptosis in A549 cells; on the contrary, it reduced cisplatin-induced apoptosis and increased the IC50 of cisplatin. However, when we inhibited CoCl2-induced activation of NF-kappaB through NF-kappaB p65siRNA, cisplatin-induced apoptosis was increased and IC50 of cisplatin was reduced to levels similar to those in control cells. Meanwhile, CoCl2-induced Bcl-2 overexpression was down-regulated in the presence of cisplatin when NF-kappaB activity was inhibited. CONCLUSION: Up-regulating Bcl-2 might be involved in NF-kappaB activation induced resistance to cisplatin in A549 cells under CoCl2-induced chemical hypoxia.

[679]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Veldore VH; Rao RM; Kakara S; Pattanayak S; Tejaswi R; Sahoo R; Venkatawamy E; Prabhudesai SA; Krishnamoorthy N; Tejaswini BN; Hazarika D; Gangoli SA; Rahman SM; Naik R; Diwakar RB; Satheesh CT; Shashidhar SP; Patil SG; Ajai Kumar BS
INSTITUCIÓN / INSTITUTION: - Department of Molecular Pathology, Triesta Reference Laboratory, A unit of HCG Oncology Hospitals, Bangalore, Karnataka, India.
RESUMEN / SUMMARY: - Background: Epidermal growth factor receptor (EGFR) mutation plays a vital role in the prognosis of patients with lung cancer. However, there is a dearth of studies on EGFR mutation in Indian population. In this retrospective study conducted at a network of tertiary cancer care centers across India, we evaluated the proportion of EGFR mutation in patients with non-small-cell lung carcinomas (NSCLC). Materials and Methods: A total of 1036 cases of non-small lung cancer were assessed
for EGFR mutation status using Scorpion amplified refractory mutation system real time polymerase chain reaction method from fine needle aspiration cytology core biopsy, pleural fluid and cell blocks. For a few cases, macro dissection of tumor from H and E slides was also performed for EGFR analysis. EGFR Status was assessed for the most commonly known driver mutations in Exons 18, 19, 20 and 21, which contributes to a total of 29 somatic mutations including the resistance mutation T790M. Results: Around 39% of the cohort was female and 61% were male. Mutation was positive in 40.3% and negative (wild type) in 59.7%. There was 1.8% mutation in exon 18, 24.6% in exon 19, 1.6% in exon 20 and 12.8% in exon 21. 38.2% had a mutation in a single site and 1.1% had a mutation in two sites. Overall mutation was significant in females (50.5% vs. 33.9%) compared with males (chi² = 28.3, P < 0.001). Mutation was significant in exon 21 (16.8% vs. 10.3%, chi² = 9.44, P = 0.002) and exon 19 (30.7% vs. 20.7%, chi² = 13.2, P < 0.001) in females compared with males. Conclusion: EGFR is expressed differentially/mutated in patients with NSCLC. Further studies to unravel the predictors for acquired genetic alterations of EGFR are needed.
the signal intensities of the RT-PCR product), were also have high expression of ALK protein (IHC3+), and positive for FISH, except one failed in FISH. Variants 3a+3b (4/5, 80%) of EML4-ALK fusion gene were more common to have high abundance of EML4-ALK positive cells in tumor tissues than variant 1 (1/3, 33.3%). Meta-analysis of the published data of 2273 NSCLC patients revealed that variant 3 (23/44, 52.3%) was the most common type in Chinese population, while variant 1 (28/37, 75.7%) was most common in Caucasian. CONCLUSIONS: Among the three detection methods, RT-PCR could detect not only the presence of EML4-ALK fusion gene and their variant types, but also the abundance of EML4-ALK positive cells in NSCLC tumor tissues. The latter two factors might affect the treatment response to anti-ALK inhibitor. Including RT-PCR as a diagnostic test for ALK inhibitor treatment in the prospective clinical trials is recommended.

[681]
TÍTULO / TITLE: Proteomic analysis of pleural effusion from lung adenocarcinoma patients by shotgun strategy.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Sheng SH; Zhu HL
INSTITUCIÓN / INSTITUTION: Department of Respiratory Medicine, Huadong Hospital Affiliated to Fudan University, Shanghai, 200040, China.
RESUMEN / SUMMARY: PURPOSE: To construct a protein catalogue of malignant pleural effusion from lung adenocarcinoma patients and to screen the potential candidates of biomarkers for diagnostic value in human lung adenocarcinoma. METHOD: Five malignant pleural effusion samples of lung adenocarcinoma patients were collected from January 2009 to September. A composite sample was analyzed using shotgun strategy. Pleural effusion samples were separated by means of SDS-PAGE. Proteomic analysis was performed by 1D-LC-MS/MS, and then the proteins were identified using SEQUEST software and protein database search. RESULTS: Among 230 unique proteins, 123 proteins were identified with higher confidence levels (at least two unique peptide sequences matched). Most of these proteins have been reported in plasma. However, there are 7 proteins, including JUP protein, suprabasin, annexin A2, transforming growth factor-beta-induced protein ig-h3 (betaig-h3), V-set and immunoglobulin domain-containing protein 4 precursor, ifapsoriasin 2 and actin, cytoplasmic 1 have not been reported in serum. CONCLUSIONS: Seven proteins may represent potential candidates of biomarkers. Annexin A2 is of special interest since it may play a role in the regulation of intercellular adhesion and cell proliferation.

[682]
**TÍTULO / TITLE:** - Re-administration after the failure of gefitinib or erlotinib in patients with advanced non-small cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Song Z; Yu X; He C; Zhang B; Zhang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou 310022, China; ; Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Hangzhou 310022, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Few treatment options are available for advanced non-small cell lung cancer (NSCLC) patients who have failed of gefitinib or erlotinib treatment in second/third-line treatment. The aim of this study was to investigate the efficacy of re-administration of the same TKI after failure of gefitinib or erlotinib.

**PATIENTS AND METHODS:** The clinical data of 33 patients with advanced NSCLC were retrospectively analyzed. All of the patients were given the same TKI treatment after the failure of gefitinib or erlotinib. Survival analysis was evaluated by Kaplan-Meier method. RESULTS: Twenty patients (60.6%) were re-administration with gefitinib as the 2(nd) EGFR-TKI, and thirteen patients (39.4%) received erlotinib. One patient (3.0%) showed partial response (PR), 14 (42.4%) achieved stable disease (SD), and 18 (54.5%) had progressive disease (PD). The disease control rate was 45.5% and the median progression-free survival was 1.5 months (95% CI: 0.6-2.3 months). The PFS in patients who got disease control in the prior TKI was 2.2 and 1.2 months in the progression disease cases (P=0.29), the DCR was 54.5% and 27.3% in two group, respectively (P=0.26). CONCLUSIONS: Re-administration of TKI seems to be a potential therapeutic option for treatment of selected advanced NSCLC patients after failure of gefitinib or erlotinib, especially for the patients with NSCLC who once responded from the prior TKI treatment.

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**TÍTULO / TITLE:** - Comparison of haptoglobin and alpha1-Acid glycoprotein glycosylation in the sera of small cell and non-small cell lung cancer patients.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** - Postepy Hig Med Dosw (Online). 2013 Aug 8;67(0):828-36.

**AUTORES / AUTHORS:** - Ferens-Sieczkowska M; Kratz EM; Kosowska B; Passowicz-Muszynska E; Jankowska R

**INSTITUCIÓN / INSTITUTION:** - Department of Chemistry and Immunochemistry, Wroclaw Medical University, Wroclaw, Poland.

**RESUMEN / SUMMARY:** - Introduction: Cancer-related carbohydrate epitopes, which are regarded as potential diagnostic and prognostic biomarkers, are carried on the main
acute phase proteins. It is not clear, however, if the glycosylation profile is similar in different glycoproteins, or it is protein specific to some extent. The aim of the study was to compare fucosylation, alpha2,3 sialylation and expression of sialyl-Lewisx epitopes (sLex) in the serum as a whole, AGP and haptoglobin of small cell (SCLC) and non-small cell lung cancer (NSCLC) patients with respect to healthy subjects as well as the cancer stage and its histological type. Material and Methods: Thirty-three NSCLC, 13 SCLC patients and 20 healthy volunteers were included in the study. Carbohydrate epitopes were detected by means of their reactivity with specific lectins and monoclonal anti-sLex antibodies in direct or dual-ligand ELISA tests. Results: Significantly increased fucosylation was found in total serum in both cancer groups and in NSCLC haptoglobin. No difference was observed in SCLC haptoglobin or alpha1-acid glycoprotein in both cancer groups. Also alpha2,3 sialylation was elevated in total serum, but not in alpha1-acid glycoprotein. This type of sialylation was undetectable in haptoglobin by means of MAA reactivity, in both healthy and cancer subjects. Complete sLex antigens were overexpressed in total NSCLC serum and SCLC AGP, and their level was considerably lowered in cancer haptoglobin. Discussion: Typical acute phase proteins, haptoglobin and AGP, exhibit different glycosylation profiles in lung cancer. Alterations observed in haptoglobin reflected the disease process better than those in AGP. Comparison of haptoglobin and AGP glycosylation to that observed in total serum suggests that some efficient carriers of disease-altered glycoproteins still remain unidentified.
TÍTULO / TITLE: SAHA Treatment Reveals the Link between Histone Lysine Acetylation and Proteome in Nonsmall Cell Lung Cancer A549 Cells.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Wu Q; Xu W; Cao L; Li X; He T; Wu Z; Li W

INSTITUCIÓN / INSTITUTION: Central Laboratory, Affiliated Provincial Hospital, Anhui Medical University, Hefei, China.

RESUMEN / SUMMARY: Suberoylanilide hydroxamic acid (SAHA) is a well-known pan HDAC inhibitor, and its clinical application (Vorinostat) has been demonstrated to treat nonsmall cell lung cancer (NSCLS). Nevertheless, the impact of SAHA treatment on histone lysine acetylation and proteome in NSCLS cells still need further elucidate. In NSCLS A549 cells, by using stable isotope labeling for cell culture (SILAC)-based quantitative proteomics, biochemistry assay, and bioinformatic analysis, here we for the first time comprehensively identified and quantified histone lysine acetylation in A549 cells toward SAHA treatment. Despite the fact that SAHA treatment significantly increased histone lysine acetylation in specific sites, unexpectedly, some important “histone markers” showed markedly decreased acetylation level. Further quantitative proteome studies showed that among totally quantifiable 2818 nonredundant proteins, 1355 proteins were with increased level and 1463 with decreased level in response to SAHA treatment. Bioinformatic analysis further revealed that those quantifiable proteins were mainly involved in multiple biological functions and metabolic and enzyme-regulated pathways as well as protein complexes. By establishing the link between histone modification and whole proteome in response to SAHA treatment in NSCLS cells, this study therefore may deepen our understanding of HDAC inhibitor-mediated cancer therapeutics.

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TÍTULO / TITLE: Gene Expression Profile of the A549 Human Non-Small Cell Lung Carcinoma Cell Line following Treatment with the Seeds of Descurainia sophia, a Potential Anticancer Drug.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Kim BY; Lee J; Park SJ; Bang OS; Kim NS

INSTITUCIÓN / INSTITUTION: KM-Based Herbal Drug Research Group, Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon 305-811, Republic of Korea.
Descurainia sophia has been traditionally used in Korean medicine for treatment of diverse diseases and their symptoms, such as cough, asthma, and edema. Our previous results showed that ethanol extract of the seeds of D. sophia (EEDS) has a potent cytotoxic effect on human cancer cells. In this study, we reveal the molecular events that are induced by EEDS treatment in A549 human lung cancer cells. The dose-dependent effect of EEDS on gene expression was measured via a microarray analysis. Gene ontology and pathway analyses were performed to identify functional involvement of genes regulated by EEDS. From gene expression analyses, two major dose-dependent patterns were observed after EEDS treatment. One pattern consisted of 1,680 downregulated genes primarily involved in metabolic processes (FDR < 0.01). The second pattern consisted of 1,673 upregulated genes primarily involved in signaling processes (FDR < 0.01). Pathway activity analyses revealed that the metabolism-related pathways and signaling-related pathways were regulated by the EEDS in dose-dependent and reciprocal manners. In conclusion, the identified biphasic regulatory mechanism involving activation of signaling pathways may provide molecular evidence to explain the inhibitory effect of EEDS on A549 cell growth.

Role of induction therapy: surgical resection of non-small cell lung cancer after induction therapy.

Patients with Stage III non-small cell lung cancer are best managed by multimodality therapy. Patients with N2 disease can be treated with induction therapy (usually chemotherapy) followed by surgical resection. Patients whose medical comorbidities preclude surgery should be treated with definitive chemoradiotherapy. T3 or T4 tumors involving the superior sulcus or spine are best managed with induction chemoradiotherapy and surgical resection.

Lung cancer stem cells: a biological and clinical perspective.
INTRODUCTION: Lung cancer is the most lethal form of cancer in the world and despite significant therapeutic improvements that have been made, its survival rate still remains low. The latter is mainly due to the acquisition of resistance to systemic treatment regimens which, in turn, may be due to the presence of cancer stem cells (CSCs) within the primary tumors. CSCs constitute a subpopulation of cells that are highly tumorigenic and that exhibit biological properties similar to those of normal tissue stem cells, including an unlimited self-renewal capacity, an extensive proliferative capacity and a capacity to generate differentiated progeny. A better understanding of the signaling pathways that regulate lung CSC maintenance, proliferation, and tumorigenicity could thus lead to the design of improved approaches to lung cancer treatment. AIM: In this review we will discuss the current knowledge on lung CSCs, their biological properties and their putative clinical relevance. By employing currently available data, we will evaluate the prognostic value of several lung CSC markers. In addition, we will discuss the release of CSCs from tumor tissue into the blood circulation via epithelial-mesenchymal transition (EMT) as an important step towards acquiring a metastatic phenotype. Finally, we will provide an outlook into novel CSC-targeting approaches for achieving less invasive diagnostic procedures and improving long-term therapeutic options. CONCLUSION: Lung CSC research has gained considerable momentum to both basic and clinical applications, both aiming to identify a reliable panel of markers for lung CSCs and to clarify their function, with the final goal to develop a CSC-targeted therapy that will result in the complete elimination of CSCs for achieving significantly better long-time survival of lung cancer patients.

TÍTULO / TITLE: Therapeutic Potential of Andrographolide Isolated from the Leaves of Andrographis paniculata Nees for Treating Lung Adenocarcinomas.

RESUMEN / SUMMARY: Andrographolide is one of the major diterpene lactones found in Andrographis paniculata Nees and exhibits remarkable inhibitory effects on various cancers. In this study, the antipulmonary cancer effects of andrographolide were studied in a lung tumor mouse model induced by human vascular endothelial growth factor.
factor A 165 (hVEGF-A165). These results demonstrated that andrographolide significantly reduced the expression of hVEGF-A165 compared with a mock group in the Clara cells of the lungs. In addition, andrographolide also decreased tumor formation by reducing VEGF, EGFR, Cyclin A, and Cyclin B expression on the transcriptional and translational levels. These results indicated that andrographolide treatment on the overexpression of VEGF can arrest the cell cycle, which induced pulmonary tumors in transgenic mice. In conclusion, the antiangiogenesis and chemotherapeutic potential of andrographolide may provide a cure for pulmonary tumors in the future.

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expression levels of the integrin alpha2 and beta1 subunits were significantly elevated in IR cells. Knockdown of alpha2 expression or functional blockade of integrin alpha2beta1 resulted in a round morphology of IR cells, and abrogated their invasion in the collagen matrix, suggesting the molecule’s essential role in cell spread and invasion in 3D collagen. Epidermal growth factor receptor (EGFR) also presented enhanced expression and activation in IR cells. Treatment with EGFR tyrosine kinase inhibitor, PD168393, decreased the ratio of elongated cells and cell invasiveness. Signaling molecules, including extracellular signal-regulated kinase-1/2 (Erk1/2) and Akt, exhibited higher activation in IR cells. Inhibition of Akt activation by treating with phosphoinositide 3-kinase (PI3K) inhibitor LY294002 decreased IR cell invasion, whereas inhibition of Erk1/2 activation by mitogen-activated protein kinase kinase (MEK) inhibitor U0126 did not. Our results show that integrin alpha2beta1 and EGFR cooperatively promote higher invasiveness of IR-survived lung cancer cells, mediated in part by the PI3K/Akt signaling pathway, and might serve as alternative targets in combination with radiotherapy.

[692]

TÍTULO / TITLE: - Common and rare EGFR and KRAS mutations in a Dutch non-small-cell lung cancer population and their clinical outcome.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Kerner GS; Schuuring E; Sietsma J; Hiltermann TJ; Pieterman RM; de Leede GP; van Putten JW; Liesker J; Renkema TE; van Hengel P; Platteel I; Timens W; Groen HJ
INSTITUCIÓN / INSTITUTION: - University of Groningen, Department of Pulmonary Diseases, University Medical Center Groningen, Groningen, The Netherlands.
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RESUMEN / SUMMARY: - INTRODUCTION: In randomly assigned studies with EGFR TKI only a minor proportion of patients with NSCLC have genetically profiled biopsies. Guidelines provide evidence to perform EGFR and KRAS mutation analysis in non-squamous NSCLC. We explored tumor biopsy quality offered for mutation testing, different mutations distribution, and outcome with EGFR TKI. PATIENT AND METHODS: Clinical data from 8 regional hospitals were studied for patient and tumor characteristics, treatment and overall survival. Biopsies sent to the central laboratory were evaluated for DNA quality and subsequently analyzed for mutations in exons 18-21 of EGFR and exon 2 of KRAS by bidirectional sequence analysis. RESULTS: Tumors from 442 subsequent patients were analyzed. For 74 patients (17%) tumors were unsuitable for mutation analysis. Thirty-eight patients (10.9%) had EGFR mutations with 79% known activating mutations. One hundred eight patients (30%) had
functional KRAS mutations. The mutation spectrum was comparable to the Cosmic database. Following treatment in the first or second line with EGFR TKI median overall survival for patients with EGFR (n = 14), KRAS (n = 14) mutations and wild type EGFR/KRAS (n = 31) was not reached, 20 and 9 months, respectively. CONCLUSION: One out of every 6 tumor samples was inadequate for mutation analysis. Patients with EGFR activating mutations treated with EGFR-TKI have the longest survival.

[693]

TÍTULO / TITLE: Gremlin-1 associates with fibrillin microfibrils in vivo and regulates mesothelioma cell survival through transcription factor slug.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Tamminen JA; Parviainen V; Ronty M; Wohl AP; Murray L; Joenvaara S; Varjosaalo M; Lepparanta O; Ritvos O; Sengle G; Renkonen R; Myllarniemi M; Koli K
INSTITUCIÓN / INSTITUTION: 1] Research Programs Unit, Translational Cancer Biology, University of Helsinki, Helsinki, Finland [2] Transplantation Laboratory, Haartman Institute, University of Helsinki, Helsinki, Finland.
RESUMEN / SUMMARY: Malignant mesothelioma is a form of cancer that is highly resistant to conventional cancer therapy for which no major therapeutic advances have been introduced. Here, we identify gremlin-1, a known bone morphogenetic protein inhibitor crucial for embryonic development, as a potential therapeutic target for mesothelioma. We found high expression levels of gremlin-1 in the mesothelioma tumor tissue, as well as in primary mesothelioma cells cultured from pleural effusion samples. Downregulation of gremlin-1 expression by siRNA-mediated silencing in a mesothelioma cell line inhibited cell proliferation. This was associated with downregulation of the transcription factor slug as well as mesenchymal proteins linked to cancer epithelial-to-mesenchymal transition. Further, resistance to paclitaxel-induced cell death was associated with high gremlin-1 and slug expression. Treatment of gremlin-1-silenced mesothelioma cells with paclitaxel or pemetrexed resulted in efficient loss of cell survival. Finally, our data suggest that concomitant upregulation of fibrillin-2 in mesothelioma provides a mechanism for extracellular localization of gremlin-1 to the tumor microenvironment. This was supported by the demonstration of interactions between gremlin-1, and fibrillin-1 and -2 peptides as well as by colocalization of gremlin-1 to fibrillin microfibrils in cells and tumor tissue samples. Our data suggest that gremlin-1 is also a potential target for overcoming drug resistance in mesothelioma.

[694]
TÍTULO / TITLE: - Chemotherapy Outcomes by Histologic Subtypes of Non-Small-Cell Lung Cancer: Analysis of the Southwest Oncology Group Database for Antimicrotubule-Platinum Therapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kelly K; Chansky K; Mack PC; Lara PN Jr; Hirsch FR; Franklin WA; Wozniak AJ; Edelman MJ; Williamson SK; Gandara DR
INSTITUCIÓN / INSTITUTION: - University of California at Davis, Division of Hematology/Oncology, Sacramento, CA. Electronic address: karen.kelly@ucdmc.ucdavis.edu.
RESUMEN / SUMMARY: - OBJECTIVE: Histologic subtyping has been advocated to select chemotherapy for patients with advanced-stage non-small-cell lung cancer (NSCLC). To determine whether histologic subtype was associated with efficacy for the commonly used antimicrotubule (AMT) agents, paclitaxel, docetaxel, and vinorelbine plus a platinum compound, we examined the Southwest Oncology Group (SWOG) lung cancer database. METHODS: Data from 4 randomized trials (S9308, S9509, S9806, and S0003) administering an AMT agent plus platinum in patients receiving first-line treatment for advanced-stage NSCLC were analyzed. Overall survival (OS) and progression-free survival (PFS) comparisons were performed using Cox proportional hazard regression, adjusting for sex. Median survival times were estimated by Kaplan-Meier. RESULTS: Of 1146 patients included in this analysis, 640 had adenocarcinoma (56%), 220 had squamous cell carcinoma (19%), 121 had large cell carcinoma (11%), and 165 had NSCLC not otherwise specified (NOS) (14%). Median OS times by histologic subtypes were 8.5, 8.4, 8.2, and 9.6 months, respectively, and median PFS times were 4.2, 4.3, 4.3, and 4.6 months, respectively. No difference in OS or PFS was observed by histologic subtype and, specifically, between nonsquamous and squamous histologies. CONCLUSIONS: This pooled analysis from 4 SWOG trials using an AMT-platinum regimen did not show a difference in survival outcomes by histologic subtype. Because the majority of patients with advanced NSCLC continue to receive chemotherapy, defining molecular-based predictive markers of responsiveness is warranted.

[695]
TÍTULO / TITLE: - TLR9 signaling repressed tumor suppressor miR-7 expression through up-regulation of HuR in human lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 1186/1475-2867-13-90
BACKGROUND: Our recent evidence showed that Toll like receptor 9 (TLR9) signaling could enhance the growth and metastatic potential of human lung cancer cells through repressing microRNA-7 (miR-7) expression. Human antigen R (HuR) has been involved in stabilizing multiple mRNAs in cellular biology. However, whether HuR also contributed to the altered expression of miR-7 in TLR9 signaling stimulated human lung cancer cells remains to be elucidated. METHODS: The expression of HuR in human lung cancer 95D cells treated with TLR9 agonist CpG Oligonucleotides (ODNs) was detected by Real-time PCR and Western blot assay. To explore the possible role of HuR on miR-7 expression, eukaryotic expression vector encoding HuR was transiently transfected into 95D cells and then the expression of miR-7 was detected by Real-time PCR assay. Moreover, RNA interference, western blot, Real-time PCR, MTT assay, BrdU labeling, invasion assay and scratch assay were employed to examine the disrupt effect of HuR on miR-7 expression in human lung cancer cells treated with CpG ODNs. Finally, inhibitors for PI3K, Akt or Erk respectively, and western blot were performed to explore the possible signaling pathway related to HuR expression in CpG ODNs treated human lung cancer cells. RESULTS: Our data showed that TLR9 agonist CpG ODNs could induce the expression of HuR in human lung cancer cells. Moreover, overexpression of HuR could reduce the expression of miR-7 in lung cancer cells. Notably, down-regulation of HuR using RNA interference restored miR-7 expression in CpG ODNs treated lung cancer cells, accompanied by enhanced growth and metastatic potential. Finally, CpG ODNs could induce HuR expression through Akt pathway. CONCLUSION: Our findings indicated that HuR could act as regulator in regulating TLR9 signaling associated biological effect in human lung cancer cells, which might be helpful for the understanding of the potential role of HuR in tumor biology.

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TÍTULO / TITLE: Induction of apoptosis and cell cycle arrest in A549 human lung adenocarcinoma cells by surface encapping selenium nanoparticles: an effect enhanced by polysaccharides-protein complexes from Polyporus rhinocerus.

RESUMEN / SUMMARY: Surface-capping agents play key roles in cellular uptake and biological activity of functional nanomaterials. In the present study, functionalized selenium nanoparticles (SeNPs) have been successfully synthesized using Polyporus rhinocerus water-soluble polysaccharides-protein complexes (PRW) as the capping agent during the reduction of selenium salts. The acquired monodisperse, spherical...
PRW-SeNPs particles presented desirable size distribution and stability in the solution. Moreover, PRW surface decoration significantly enhanced the cellular uptake of SeNPs via endocytosis. Exposure to PRW-SeNPs significantly inhibited the growth of A549 cells through induction of apoptosis and G2/M phase arrest (IC50 = 4.06 +/- 0.25 microM) supported by an increase of sub-G1 and G2/M phase cell populations, DNA fragmentation and chromatin condensation. Caspase-3/8 activation induced by PRW-SeNPs indicated that the activation of death receptors was the main cause of PRW-SeNPs-induced apoptosis. Collectively, our results suggest that it is highly efficient to use PRW as a surface decorator of SeNPs to enhance its cellular uptake and anticancer efficacy, and the PRW-SeNPs is a potential chemopreventive agent for lung cancer therapy.

[697]
TÍTULO / TITLE: - Neferine from Nelumbo nucifera induces autophagy through the inhibition of PI3K/Akt/mTOR pathway and ROS hyper generation in A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Poornima P; Weng CF; Padma VV
INSTITUCIÓN / INSTITUTION: - Animal Tissue Culture and Molecular Genetics Laboratory, Department of Biotechnology, School of Biotechnology and Genetic Engineering, Bharathiar University, Coimbatore 641046, Tamilnadu, India.
RESUMEN / SUMMARY: - Previously we have reported that neferine from the medicinal plant Nelumbo nucifera, inhibited cancer cell proliferation by inducing apoptosis. The present study was focused on the action mechanism of neferine in inducing autophagy in lung cancer cells. Neferine markedly inhibited A549 cell proliferation in a dose dependent manner. Acidic vesicular accumulation was observed in neferine treated cells as an indication of autophagy. Neferine could induce the conversion of LC3B-I to LC3B-II without affecting the expression levels of PI3KCIII and Beclin1. It has been observed that neferine mediated autophagy is dependent on inhibition of PI3K/Akt/mTOR signaling by neferine. Neferine treatment could also lead to the ROS hypergeneration and depletion of cellular antioxidant, GSH. The results demonstrate that neferine-induced autophagy is mediated through ROS hypergeneration and mTOR inhibition. Taken together, the present study unveils a novel mechanism of action of neferine on lung cancer cells in the induction of autophagy.

[698]
TÍTULO / TITLE: - Axin gene methylation status correlates with radiosensitivity of lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yang LH; Han Y; Li G; Xu HT; Jiang GY; Miao Y; Zhang XP; Zhao HY; Xu ZF; Stoecker M; Wang E; Xu K; Wang EH
INSTITUCIÓN / INSTITUTION: - Department of Pathology, First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, Liaoning, China.
RESUMEN / SUMMARY: - BACKGROUND: We previously reported that Axin1 (Axin) is down-regulated in many cases of lung cancer, and X-ray irradiation increased Axin expression and inhibited lung cancer cells. The mechanisms, however, were not clear.
METHODS: Four lung cancer cell lines were used to detect the methylation status of Axin with or without X-ray treatment. Real-time PCR was used to quantify the expression of Axin, and western blot analysis was applied to measure protein levels of Axin, beta-catenin, Cyclin D1, MMP-7, DNMTs, MeCP2 and acetylated histones. Flow cytometric analysis, colony formation assay, transwell assay and xenograft growth experiment were used to study the biological behavior of the cells with hypermethylated or unmethylated Axin gene after X-ray treatment. RESULTS: Hypermethylated Axin gene was detected in 2 of 4 cell lines, and it correlated inversely with Axin expression. X-ray treatment significantly up-regulated Axin expression in H446 and H157 cells, which possess intrinsic hypermethylation of the Axin gene (P<0.01), but did not show up-regulation in LTE and H460 cells, which have unmethylated Axin gene. 2Gy X-ray significantly reduced colony formation (from 71% to 10.5%) in H157 cells, while the reduction was lower in LTE cells (from 71% to 20%). After X-ray irradiation, xenograft growth was significantly decreased in H157 cells (from 1.15 g to 0.28 g) in comparison with LTE cells (from 1.06 g to 0.65 g). Significantly decreased cell invasiveness and increased apoptosis were also observed in H157 cells treated with X-ray irradiation (P<0.01). Down-regulation of DNMTs and MeCP2 and up-regulation of acetylated histones could be detected in lung cancer cells.
CONCLUSIONS: X-ray-induced inhibition of lung cancer cells may be mediated by enhanced expression of Axin via genomic DNA demethylation and histone acetylation. Lung cancer cells with a different methylation status of the Axin gene showed different radiosensitivity, suggesting that the methylation status of the Axin gene may be one important factor to predict radiosensitivity of the tumor.

TÍTULO / TITLE: - Endobronchial lipoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Eren F; Candan T; Eren B; Comunoglu N; Comunoglu C
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Sevket Yilmaz Research and Training Hospital, Bursa, Turkey.
RESUMEN / SUMMARY: Endobronchial lipomas are rare benign tumours of the lung. The reported case was a 56-year-old man who visited the public hospital with complaints of chest pain and persistent cough. On bronchoscopy, a smooth-surfaced polypoid tumour obstructing the main bronchus in the left lobe was detected. The case was evaluated and surgical resection was performed. Histopathological investigation revealed that the tumour was an endobronchial lipoma; the tumour composed of mature fat tissue and was covered with bronchial epithelium.


RESUMEN / SUMMARY: Increasing evidence shows that dysregulation of microRNAs (miRNAs) is involved in malignant transformation. We investigated the clinical significance of miR-650 and its involvement in chemoresistance to docetaxel. Our results showed that the relative expression level of miR-650 was significantly higher in LAD tissues than in corresponding nontumor tissues and high level of miR-650 expression was found to be significantly associated with high incidence of lymph node metastasis, advanced clinical stage and poor prognosis of LAD patients. Univariate and multivariate analyses indicated that high miR-650 expression was an independent prognostic factor for survival. Also, we found that the level of miR-650 in LAD tissues was correlated with the response of patients to docetaxel-based chemotherapy. Silencing of miR-650 could increase the in vitro sensitivity of docetaxel-resistant LAD cells to docetaxel, while upregulation of miR-650 decreased the sensitivity of parental LAD cells to docetaxel both in vitro and in vivo. Additionally, silencing of miR-650 could enhance the caspase-3-dependent apoptosis, which might be correlated with the decreased ratio of Bcl-2/Bax. Further researches suggested that inhibitor of growth 4 (ING4) was a direct target of miR-650. Downregulated or upregulated ING4 expression could partially rescue the effects of miR-650 inhibitor or mimics in docetaxel-resistant or parental LAD cells. Furthermore, we found that ING4 was upregulated in docetaxel-responding LAD tissues, and its expression was inversely correlated with miR-650.
Thus, miR-650 is a novel prognostic marker in LAD and its expression is a potential indicator of chemosensitivity to docetaxel-based chemotherapy regimen.

[701]
TÍTULO / TITLE: - Autophagy Inhibition with Monensin Enhances Cell Cycle Arrest and Apoptosis Induced by mTOR or Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Choi HS; Jeong EH; Lee TG; Kim SY; Kim HR; Kim CH
INSTITUCIÓN / INSTITUTION: - Division of Pulmonology, Department of Internal Medicine, Korea Cancer Center Hospital, Seoul, Korea.
RESUMEN / SUMMARY: - BACKGROUND: In cancer cells, autophagy is generally induced as a pro-survival mechanism in response to treatment-associated genotoxic and metabolic stress. Thus, concurrent autophagy inhibition can be expected to have a synergistic effect with chemotherapy on cancer cell death. Monensin, a polyether antibiotic, is known as an autophagy inhibitor, which interferes with the fusion of autophagosome and lysosome. There have been a few reports of its effect in combination with anticancer drugs. We performed this study to investigate whether erlotinib, an epidermal growth factor receptor inhibitor, or rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, is effective in combination therapy with monensin in non-small cell lung cancer cells. METHODS: NCI-H1299 cells were treated with rapamycin or erlotinib, with or without monensin pretreatment, and then subjected to growth inhibition assay, apoptosis analysis by flow cytometry, and cell cycle analysis on the basis of the DNA contents histogram. Finally, a Western blot analysis was done to examine the changes of proteins related to apoptosis and cell cycle control. RESULTS: Monensin synergistically increases growth inhibition and apoptosis induced by rapamycin or erlotinib. The number of cells in the sub-G1 phase increases noticeably after the combination treatment. Increase of proapoptotic proteins, including bax, cleaved caspase 3, and cleaved poly(ADP-ribose) polymerase, and decrease of anti-apoptotic proteins, bcl-2 and bcl-xL, are augmented by the combination treatment with monensin. The promoters of cell cycle progression, notch3 and skp2, decrease and p21, a cyclin-dependent kinase inhibitor, accumulates within the cell during this process. CONCLUSION: Our findings suggest that concurrent autophagy inhibition could have a role in lung cancer treatment.

[702]
TÍTULO / TITLE: - beta-Escin Inhibits NNK-Induced Lung Adenocarcinoma and ALDH1A1 and RhoA/Rock Expression in A/J Mice and Growth of H460 Human Lung Cancer Cells.
Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1158/1940-6207.CAPR-13-0216

Autores / Authors: Patlolla JM; Qian L; Biddick L; Zhang Y; Desai D; Amin S; Lightfoot S; Rao CV

Institución / Institution: Center for Cancer Prevention and Drug Development, 975 NE 10th Street, BRC 1203, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104. cv-rao@ouhsc.edu; and Jagan M.R. Patlolla, E-mail: Jagan-Patlolla@ouhsc.edu.

Resumen / Summary: Lung cancer is the leading cause of cancer-related deaths. beta-Escin, a triterpene saponin isolated from horse chestnut seeds, was tested for inhibition of lung adenoma and adenocarcinoma induced by the tobacco carcinogen 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in female A/J mice; and its possible mode of action was evaluated using the H460 human lung cancer cell line. At 6 weeks of age, 35 mice were fed AIN-76ª-modified diet, and one week later, lung tumors were induced with a single intraperitoneal (i.p.) injection of 10 mumol NNK/mouse. Three weeks after the NNK treatment, groups of mice were fed either control or experimental diets containing 500 ppm for 20 weeks (10 control, 5 beta-escin) or 36 weeks (15 control, 5 beta-escin) and evaluated for lung tumor via histopathologic methods. Administration of 500 ppm beta-escin significantly suppressed lung tumor (adenoma + adenocarcinoma) formation by more than 40% (P < 0.0015) at 20 weeks and by 53.3% (P < 0.0001) at 37 weeks. beta-Escin inhibited NNK-induced lung adenocarcinoma formation by 65% (P < 0.001) at 20 weeks and by 53% (P < 0.0001) at 37 weeks. Immunohistochemical analysis revealed that lung tumors from mice exposed to beta-escin showed significantly reduced aldehyde dehydrogenase (ALDH1A1) and phospho-Akt (p-Akt) expression when compared with those in mice fed control diet. Aldefluor assay for ALDH revealed that among H460 lung cancer cells treated with different concentrations of beta-escin (0-40 mumol/L), the subpopulation of cells with elevated ALDH activity was inhibited significantly. Our findings suggest that beta-escin inhibits tobacco carcinogen-induced lung tumor formation by modulating ALDH1A1-positive cells and RhoA/Rock signaling. Cancer Prev Res; 6(10); 1140-9. ©2013 AACR.

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Título / Title: Personalized medicine: Lung Cancer leads the way.

Resumen / Summary: Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 4103/0019-509X.117005
Autore: Parikh P; Puri T

Título: Cytohistological correlation in diagnosis of lung tumors by using fiberoptic bronchoscopy: Study of 200 cases.

Resumen: Background: Examination of specimens obtained through flexible fiberoptic bronchoscope is an important and often the initial diagnostic technique performed in patients with suspected malignant lung lesion. Aims: To evaluate the correlation of cytological findings of bronchial washings, bronchial brushing and imprint smear of bronchial biopsy in the diagnosis of lung tumors, with histopathology of bronchial biopsy taking the latter as the confirmatory diagnostic test. Materials and Methods: A total of 200 patients with lung mass were included in the study. Bronchial brushings were obtained from all 200 cases. In the first 100 cases, pre-biopsy bronchial washing (washing collected before the brushing and biopsy procedure) while post-biopsy washing (washing at the end of the procedure) was procured in all 200 cases. Imprint smears of bronchial biopsy were prepared in 150 cases. Results: Sensitivity and specificity of brushing was 76.58% and 77.78% respectively and that of imprint smear was 81.35% and 78.12% respectively. Pre-biopsy and post-biopsy washing showed high specificity of 88.89%, but low sensitivity of 30.14 and 36.77% respectively. No significant difference was found in sensitivity between brushing and imprint smear (Chi-square; P = 0.4187); and between pre-biopsy and post-biopsy washing (Chi-square; P = 0.7982). However, there was a significant difference between sensitivity of brushing and washing (Chi-square; P = 0.0001). The sensitivity of combination of three cytological diagnostic techniques was 87.29%. Conclusion: Bronchial brushing and washing cytology in combination with imprint cytology aids in the diagnosis of lung tumors. Therefore, all these techniques may be used concurrently along with bronchial biopsy to diagnose lung tumors.

Autore: Bodh A; Kaushal V; Kashyap S; Gulati A

Institución: Department of Pathology, I.G.M.C., Shimla, Himachal Pradesh, India.

Resumen: Background: Examination of specimens obtained through flexible fiberoptic bronchoscope is an important and often the initial diagnostic technique performed in patients with suspected malignant lung lesion. Aims: To evaluate the correlation of cytological findings of bronchial washings, bronchial brushing and imprint smear of bronchial biopsy in the diagnosis of lung tumors, with histopathology of bronchial biopsy taking the latter as the confirmatory diagnostic test. Materials and Methods: A total of 200 patients with lung mass were included in the study. Bronchial brushings were obtained from all 200 cases. In the first 100 cases, pre-biopsy bronchial washing (washing collected before the brushing and biopsy procedure) while post-biopsy washing (washing at the end of the procedure) was procured in all 200 cases. Imprint smears of bronchial biopsy were prepared in 150 cases. Results: Sensitivity and specificity of brushing was 76.58% and 77.78% respectively and that of imprint smear was 81.35% and 78.12% respectively. Pre-biopsy and post-biopsy washing showed high specificity of 88.89%, but low sensitivity of 30.14 and 36.77% respectively. No significant difference was found in sensitivity between brushing and imprint smear (Chi-square; P = 0.4187); and between pre-biopsy and post-biopsy washing (Chi-square; P = 0.7982). However, there was a significant difference between sensitivity of brushing and washing (Chi-square; P = 0.0001). The sensitivity of combination of three cytological diagnostic techniques was 87.29%. Conclusion: Bronchial brushing and washing cytology in combination with imprint cytology aids in the diagnosis of lung tumors. Therefore, all these techniques may be used concurrently along with bronchial biopsy to diagnose lung tumors.

Título: Growth Inhibitory Effect of (E)-2,4-bis(p-hydroxyphenyl)-2-Butenal Diacetate through Induction of Apoptotic Cell Death by Increasing DR3 Expression in Human Lung Cancer Cells.
The Maillard Reaction Products (MRPs) are chemical compounds which have been known to be effective in chemoprevention. Death receptors (DR) play a central role in directing apoptosis in several cancer cells. In our previous study, we demonstrated that (E)-2,4-bis(p-hydroxyphenyl)-2-butenal, a MRP product, inhibited human colon cancer cell growth by inducing apoptosis via nuclear factor-kappaB (NF-kappaB) inactivation and G2/M phase cell cycle arrest. In this study, (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate, a new (E)-2,4-bis(p-hydroxyphenyl)-2-butenal derivative, was synthesized to improve their solubility and stability in water and then evaluated against NCI-H460 and A549 human lung cancer cells. (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate reduced the viability in both cell lines in a time and dose-dependent manner. We also found that (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate increased apoptotic cell death through the upregulation of the expression of death receptor (DR)-3 and DR6 in both lung cancer cell lines. In addition to this, the transfection of DR3 siRNA diminished the growth inhibitory and apoptosis inducing effect of (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate on lung cancer cells, however these effects of (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate was not changed by DR6 siRNA. These results indicated that (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate inhibits human lung cancer cell growth via increasing apoptotic cell death by upregulation of the expression of DR3.
demonstrated effective results regarding overall and progression-free survival, we have still failed to achieve long-term survival. Therefore, several strategies of applying locoregional therapy are under investigation. Aerosol chemotherapy is already under investigation and, taking this a step further, aerosol gene therapies with multiple delivery systems are being developed. Several efforts have demonstrated its efficiency and effectiveness, but there are still multiple factors that have to be considered and combined to achieve an overall more effective multifunctional treatment. In the current review, we present data regarding aerosol delivery systems, transporters, carriers, vectors, genes, toxicity, efficiency, specificity, lung microenvironment and delivery gene therapy systems. Finally, we present current studies and future perspectives.

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TÍTULO / TITLE: - Effects of MICA expression on the prognosis of advanced non-small cell lung cancer and the efficacy of CIK therapy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Chen Y; Lin G; Guo ZQ; Zhou ZF; He ZY; Ye YB

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Fujian Provincial Cancer Hospital, Fuzhou, Fujian Province, People’s Republic of China.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate the clinical significance of the expression of MHC class I chain-related gene A (MICA) in patients with advanced non-small cell lung cancer and explore the relationship between MICA expression and the efficacy of cytokine-induced killer cell (CIK) therapy for treating advanced non-small cell lung cancer. METHODS: We obtained data on 222 patients with advanced non-small cell lung cancer, including data on MICA expression, age, gender, ECOG score, pathological type, stage, treatment history (including 38 patients who were given autologous CIK cell infusion), and overall survival (OS). MICA expression in lung cancer tissue was evaluated by immunohistochemical staining. Analyses of MICA expression, and CIK therapy association with survival outcomes were performed using Cox proportional models, Kaplan-Meier methods, and the log-rank test. RESULT: s MICA was expressed in both membrane and cytoplasm. MICA expression correlated with the stage of lung cancer, ECOG score, gender and age. Multivariate COX regression analysis showed that the expression of MICA was an independent prognostic factor of advanced non-small cell lung cancer (p = 0.002). In subgroup analysis, we divided the 222 patients into CIK and control groups. In the CIK group, the medium OS (mOS) of patients with a high expression of MICA was longer than in those with low expression of MICA (27 months vs. 13 months). In the control group, the mOS in patients with a high expression of MICA was shorter than in patients with low MICA expression (9
months vs. 18 months). COX regression analysis showed that the MICA expression affects the effect of CIK therapy (p<0.0001). CONCLUSION: 1) The high expression of MICA is one of the indicators of a poor prognosis for advanced non-small cell lung cancer patients. 2) The high expression of MICA might be one of the predictive factors for successful CIK therapy.

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TÍTULO / TITLE: - Lung cancer: Maintenance therapy and precision medicine in NSCLC.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Rosell R; Karachaliou N
INSTITUCIÓN / INSTITUTION: - Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Carreterra del Canyet s/n, 08916 Badalona, Barcelona, España.

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TÍTULO / TITLE: - Estrogen receptor beta activation impairs mitochondrial oxidative metabolism and affects malignant mesothelioma cell growth in vitro and in vivo.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Manente AG; Valenti D; Pinton G; Jithesh PV; Daga A; Rossi L; Gray SG; O’Byrne KJ; Fennell DA; Vacca RA; Nilsson S; Mutti L; Moro L
INSTITUCIÓN / INSTITUTION: - Department Pharmaceutical Sciences, University of Piemonte Orientale ‘A. Avogadro’, Novara, Italy.

RESUMEN / SUMMARY: - Estrogen receptor (ER)-beta has been shown to possess a tumor suppressive effect, and is a potential target for cancer therapy. Using gene-expression meta-analysis of human malignant pleural mesothelioma, we identified an ESR2 (ERbeta coding gene) signature. High ESR2 expression was strongly associated with low succinate dehydrogenase B (SDHB) (which encodes a mitochondrial respiratory chain complex II subunit) expression. We demonstrate that SDHB loss induced ESR2 expression, and that activated ERbeta, by over-expression or by selective agonist stimulation, negatively affected oxidative phosphorylation compromising mitochondrial complex II and IV activity. This resulted in reduced mitochondrial ATP production, increased glycolysis dependence and impaired cell proliferation. The observed in vitro effects were phenocopied in vivo using a selective ERbeta agonist in a mesothelioma mouse model. On the whole, our data highlight an unforeseen interaction between ERbeta-mediated tumor suppression and energy metabolism that may be exploited to improve on the therapy for clinical management of malignant mesothelioma.
**TÍTULO / TITLE:** - Profile of lung cancer in predominantly bidi smoking rural population of northern Himachal Pradesh.

**RESUMEN / SUMMARY:**  - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Sharma PK; Bansal R

**INSTITUCIÓN / INSTITUTION:** - Department of Pharmacology, Dr R.P. Government Medical College, Kangra at Tanda (Himachal Pradesh), India. drdotsharma@gmail.com

**RESUMEN / SUMMARY:** - BACKGROUND: Lung cancer is a leading cause of morbidity and mortality among both genders. The histopathological patterns of lung cancer in different parts of India appear to be variable. OBJECTIVE: To study the profile of lung cancer in northern Himachal Pradesh. METHODS: Patients of all age groups and either gender with history and complaints suggestive of lung cancer were subjected to further investigations to study the histopathological types of lung cancer over a period of 14 months. RESULTS: Out of 105 histopathologically confirmed patients with lung cancer (mean age 62.7 +/- 11.6 years; 96 males), 89.5% were “ever smokers” and 82.9% were “current smokers”; 92% of current smokers were bidi smokers. Most common presenting complaints were chest pain (46.7%) and cough (35.2%). Mean duration of longest presenting complaint was 64 days. The histopathological types included squamous cell carcinoma (37.1%), adenocarcinoma (36.2%), small cell carcinoma (8.6%), un-classifiable (16.2%), and other types (1.9%). CONCLUSIONS: Majority of the lung cancer patients in northern Himachal Pradesh were bidi smoking males from rural areas and the incidence of adenocarcinoma and squamous cell carcinoma is almost equal.

[711]

**TÍTULO / TITLE:** - Nonsmall cell lung cancer therapy: insight into multitargeted small-molecule growth factor receptor inhibitors.

**RESUMEN / SUMMARY:**  - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Roy M; Luo YH; Ye M; Liu J

**INSTITUCIÓN / INSTITUTION:** - Molecular Biology Research Center, School of Life Science and State Key Laboratory of Medical Genetics of China, Central South University, Changsha, Hunan 410078, China.

**RESUMEN / SUMMARY:** - To date, lung cancer is the leading cause of cancer-related death worldwide, among which nonsmall cell lung cancer (NSCLC) comprises about 85%. Taking into account the side effects of surgery, radiation, platinum-based doublet
chemotherapy, and the growth self-sufficiency characteristic of cancer cells, drugs have been discovered toward growth factor receptor (GFR) to treat NSCLC. As expected, these drugs provide a greater benefit. To increase the efficacy of such growth factor receptor tyrosine kinase inhibitors (RTKIs), coinhibition of GFR signaling pathways and combination of inhibitors along with radiation or chemotherapy have drew intense insight. Although clinical trials about single-agent RTKIs or their combination strategies suggest their increase potency against cancer, they are not beyond adverse effects, and sometimes the effects are more deadly than chemotherapy. Nevertheless the hope for RTKIs may be proved true by further researches and digging deep into cancer therapeutics.

[712]

**TÍTULO / TITLE:** Quantitative analysis of tumor shrinkage due to chemotherapy and its implication for radiation treatment planning in limited-stage small-cell lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Radiat Oncol. 2013 Sep 16;8(1):216.

**AUTORES / AUTHORS:** Xia B; Wang JZ; Liu Q; Cheng JY; Zhu ZF; Fu XL

**RESUMEN / SUMMARY:** BACKGROUND: The optimal timing of chemoradiotherapy in limited-stage small-cell lung cancer (LS-SCLC) hasn’t been established, although evidence from studies supported that patients can benefit from early radiation therapy. The purpose of this study was to quantify tumor shrinkage in response to induction chemotherapy (IC), evaluate the impact of tumor shrinkage on radiation dosimetric parameters and determine its implication for the timing of radiation therapy for patients with LS-SCLC. METHODS: Twenty patients with LS-SCLC who were treated with IC followed by concomitant radiation therapy were investigated retrospectively. Ten patients received 1 cycle of IC, and 10 patients received 2 cycles of IC. Pre-IC CT imaging was coregistered with a simulation CT, and virtual radiation plans were created for pre- and post-IC thoracic disease in each case. The changes in the gross target volume (GTV), planning target volume (PTV) and dosimetric factors associated with the lungs, esophagus and heart were analyzed. RESULTS: The mean GTV and PTV for all of the patients decreased by 60.9% and 40.2%, respectively, which resulted in a significant reduction in the radiation exposure to the lungs, esophagus and heart. Changes in the PTV and radiation exposure of normal tissue were not significantly affected by the number of chemotherapy cycles delivered, although patients who received 2 cycles of IC had a greater decrease in GTV than those who received only 1 cycle of IC (69.6% vs. 52.1%, p = 0.273). CONCLUSIONS: Our data showed that targeting the tumor post-IC may reduce the radiation dose to normal tissue in patients with LS-SCLC. However, the benefit to the normal tissue was not increased by an additional cycle of IC. These findings suggest that the first cycle of chemotherapy is very important for tumor shrinkage and that initiating thoracic
radiation therapy at the second cycle of chemotherapy may be a reasonable strategy for timing of radiation therapy in LS-SCLC treatment.

[713]
**TÍTULO / TITLE:** Malignant pleural mesothelioma presenting with symptomatic brain metastases: report of a case.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** Marzullo A; Scattone A; Rossi R; Cimmino A; Punzi A; Corsi F; Cavone D; Lettini T; Serio G
**INSTITUCIÓN / INSTITUTION:** Department of Emergency and Organ Transplantation, Pathology Division, Medical School, University of Bari, Italy; gabriella.serio1@uniba.it.
**RESUMEN / SUMMARY:** We describe a unique case of brain metastases presenting as first symptom of a malignant mesothelioma (MM). MM is a highly aggressive tumor of the serous membrane that is generally believed to be rarely metastasizing. Recently, the reports of long surviving cases and larger literature reviews have suggested that cerebral metastases are not so uncommon. An extensive histochemical and immunohistochemical panel is needed to achieve a correct differential diagnosis, especially in the epithelioid type. Pathologists should be aware that brain metastases could have a mesothelial origin.

[714]
**TÍTULO / TITLE:** A year of anaplastic large cell kinase testing for lung carcinoma: Pathological and technical perspectives.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** Desai SS; Shah AS; Prabhash K; Jambhekar NA
**INSTITUCIÓN / INSTITUTION:** Department of Pathology, Tata Memorial Hospital and Advanced Centre for Training Research and Education, Mumbai, Maharashtra, India.
**RESUMEN / SUMMARY:** Background: An in-frame fusion protein between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic large cell kinase (ALK) genes is seen in some non-small cell lung cancer (NSCLC). EML4-ALK demonstrates constitutive kinase activity. These ALK-positive lung carcinomas have been shown to respond to ALK kinase inhibitors. ALK gene rearrangement is commonly detected using fluorescent in situ hybridization (FISH). Aims: To study the pathological features of ALK positive and negative NSCLC and evaluate the causes of uninterpretable FISH results. Materials and Methods: This is a retrospective, observational study. The molecular pathology records of patients on whom test for ALK had been performed in a period of
1 year (February 2012 to February 2013) were accessioned. A total 224 cases were
identified. Histological features were reviewed. The in situ hybridization was
performed using Vysis ALK Dual Color Break Apart Rearrangement Probe (Abbott
Molecular Inc.). Signal interpretation under the fluorescent microscope was performed
in accordance with College of American Pathologists guidelines. Results: Five patients
showed ALK gene rearrangement, 182 were negative and 37 cases were
uninterpretable. Five patients with ALK gene rearrangement had a mean age of 48
years and the male to female ratio was 2:3. In the ALK negative cases, the mean age
was 54 years and male to female ratio was 3.2:1. Histologically, amongst the
rearranged cases, three showed solid pattern, one showed acinar and one showed
acinar with signet ring cells on histology. Conclusion: The percentage of ALK gene
rearrangement was 2.7% (excluding the uninterpretable cases). These ALK positive
patients were relatively younger than ALK negative patients. Solid pattern on histology
was associated with ALK positivity. In a quarter of the uninterpretable results, the
material submitted was fixed and processed outside.

[715]

TÍTULO / TITLE: - Nuclear survivin and its relationship to DNA damage repair genes in
non-small cell lung cancer investigated using tissue array.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - PLoS One. 2013 Sep 16;8(9):e74161. doi:
10.1371/journal.pone.0074161.

Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0074161
AUTORES / AUTHORS: - Hu S; Qu Y; Xu X; Xu Q; Geng J; Xu J
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, The Third Affiliated
Hospital of Harbin Medical University, Harbin, China.
RESUMEN / SUMMARY: - PURPOSE: To investigate the predictive role and association of
nuclear survivin and the DNA double-strand breaks repair genes in non-small cell lung
cancer (NSCLC): DNA-dependent protein kinase catalytic subunit (DNA-PKcs), Ku
heterodimeric regulatory complex 70-KD subunit (Ku70) and ataxia-telangiectasia
mutated (ATM). METHODS: The protein expression of nuclear survivin, DNA-PKcs, Ku70
and ATM were investigated using immunohistochemistry in tumors from 256 patients
with surgically resected NSCLC. Furthermore, we analyzed the correlation between
the expression of nuclear survivin, DNA-PKcs, Ku70 and ATM. Univariate and multivariate
analyses were performed to determine the prognostic factors that signicantly inuced the
overall survival and disease-free survival of NSCLC. RESULTS: The expression of nuclear
survivin, DNA-PKcs, Ku70 and ATM was significantly higher in tumor tissues than in
normal tissues. By dichotomizing the specimens as expressing low or high levels of
nuclear survivin, nuclear survivin correlated signicantly with the pathologic stage (P =
0.009) and lymph node status (P = 0.004). The nuclear survivin levels were an
independent prognostic factor for both the overall survival and the disease-free survival in univariate and multivariate analyses. Patients with low Ku70 and DNA-PKcs expression had a greater benefit from radiotherapy than patients with high expression of Ku70 (P = 0.012) and DNA-PKcs (P = 0.02). Nuclear survivin expression positively correlated with DNA-PKcs (P<0.001) and Ku70 expression (P<0.001). CONCLUSIONS: Nuclear survivin may be a prognostic factor for overall survival in patients with resected stage I-III A NSCLC. DNA-PKcs and Ku70 could predict the effect of radiotherapy in patients with NSCLC. Nuclear survivin may also stimulates DNA double-strand breaks repair by its interaction with DNA-PKcs and Ku70.

[716]
TÍTULO / TITLE: Primary pulmonary rhabdomyosarcoma with brain metastases in a child: a case report with medico-legal implications.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Guo Y; Xie D; Yan J; Yin G; Wu L
INSTITUCIÓN / INSTITUTION: - Department of Forensic Science, School of Basic Medical Sciences, Central South University, Changsha 410013, Hunan, China.
RESUMEN / SUMMARY: Rhabdomyosarcoma (RMS) is a rare type of soft tissue sarcoma that mainly affects children. RMS in childhood commonly occurs in the head and neck, followed by the genitourinary tract. Primary pulmonary rhabdomyosarcoma (PPR) is extremely rare. We report a 31-month-old girl who had PPR with brain metastasis. The girl with wheezing and cough of 3 weeks and vomiting of 1 day was referred to a county hospital. At 9:00 a.m., a chest X-ray showed an abnormal shadow on a chest radiogram. Four hours later, in the process of computed tomography (CT) scan her condition deteriorated dramatically, while resuscitation efforts were unsuccessful. CT showed a solid mass in the right middle lung lobe. Subsequent autopsy revealed a large tumour located in the right middle lung lobe. Surprisingly, a mass of haematoma appearance was found in the left occipital lobe. Histological and immunohistochemical investigations of the masses established the diagnosis of PPR with brain metastasis. Herniation of brain, caused by the brain metastasis, was ascertained as the cause of death. The morphological and pathological findings are presented; the difficulty to diagnose PPR and the medico-legal implications are discussed.

[717]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
Nuclear atypia is one of the most important morphological features used to diagnose malignant neoplasms. The potential molecular alteration that causes nuclear atypia remains unknown. P53 and p16INK4A play crucial roles in cell cycle checkpoints and repairing DNA damage to maintain integrity of the genome. Thus, inactivation of p53 and p16INK4A has been hypothesized to alter the chromatin structure and result in nuclear atypia. This study examined 201 primary lung cancers for the immunohistochemical expression of p53 and p16INK4A, and analyzed potential associations with the essential elements of nuclear atypia, such as nuclear size, circularity of the outline, and the density and granularity of chromatin. Tumors that expressed high levels of p53 had larger nuclei with higher chromatin density and distorted nuclear outlines. Tumors that expressed low levels of p16INK4 had larger nuclei with distorted nuclear outlines. Thus, alterations in p53 and p16INK4A may be the potential cause of nuclear atypia in neoplastic cells.

TÍTULO / TITLE: - Association between XRCC1 and XRCC3 Polymorphisms with Lung Cancer Risk: A Meta-Analysis from Case-Control Studies.
RESUMEN / SUMMARY: - Many studies have reported the association of X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln, Arg194Trp, Arg280His, -77T>C, and X-ray repair cross-complementing group 3 (XRCC3) T241M polymorphisms with lung cancer risk, but the results remained controversial. Hence, we performed a meta-analysis to investigate the association between lung cancer risk and XRCC1 Arg399Gln (14,156 cases and 16,667 controls from 41 studies), Arg194Trp (7,426 cases and 9,603 controls from 23 studies), Arg280His (6,211 cases and 6,763 controls from 16 studies), -77T>C (2,487 cases and 2,576 controls from 5 studies), and XRCC3 T241M (8,560 cases and 11,557 controls from 19 studies) in different inheritance models. We found that -77T>C polymorphism was associated with increased lung cancer risk (dominant model: odds ratio [OR] = 1.45, 95% confidence interval [CI] = 1.27-1.66, recessive model: OR = 1.73, 95% CI = 1.14-2.62, additive model: OR = 1.91, 95% CI = 1.24-1.94) when all the
eligible studies were pooled into the meta-analysis. In the stratified and sensitive analyses, significantly decreased lung cancer risk was observed in overall analysis (dominant model: OR = 0.83, 95% CI = 0.78-0.89; recessive model: OR = 0.90, 95% CI = 0.81-1.00; additive model: OR = 0.82, 95% CI = 0.74-0.92), Caucasians (dominant model: OR = 0.82, 95% CI = 0.76-0.87; recessive model: OR = 0.89, 95% CI = 0.80-0.99; additive model: OR = 0.81, 95% CI = 0.73-0.91), and hospital-based controls (dominant model: OR = 0.81, 95% CI = 0.76-0.88; recessive model: OR = 0.89, 95% CI = 0.79-1.00; additive model: OR = 0.80, 95% CI = 0.71-0.90) for XRCC3 T241M. In conclusion, this meta-analysis indicates that XRCC1 -77T>C shows an increased lung cancer risk and XRCC3 T241M polymorphism is associated with decreased lung cancer risk, especially in Caucasians.


[720] - Safety and efficacy of first-line bevacizumab combination therapy in Chinese population with advanced non-squamous NSCLC: data of subgroup analyses from MO19390 (SAiL) study.
non-small cell lung cancer (NS-NSCLC). SAiL (MO19390), an open-label, multicenter, single-arm study, evaluated the safety and efficacy of first-line bevacizumab-based treatment in clinical practice. This report presents the results of a subgroup analysis of Chinese patients enrolled in SAiL. METHODS: Chemo-naive Chinese patients with locally advanced, metastatic or recurrent NSCLC were randomized to receive Bev 15 mg/kg every 3 weeks plus carboplatin + paclitaxel for maximum of six cycles, followed by single-agent bevacizumab until disease progression. The primary endpoint was safety. Secondary endpoints included time to progression and overall survival. RESULTS: The Chinese intent-to-treat (ITT) population consists of 198 Chinese patients, among whom 107 (54 %) were non-smokers and 90 (45.5 %) were female. The median cycle of bevacizumab administration was 10 and median duration of bevacizumab treatment was 29.5 weeks. Only eight cases of severe adverse events were observed in the study, which were deemed to be related to bevacizumab. The incidence of AEs over grade 3 in Chinese ITT patients was generally low (<9 %). No new safety signals were reported. Objective response rate in 195 evaluable Chinese patients was 68.8 %, including four complete responses (2.1 %). Time to disease progression (TTP) and overall survival were 8.8 and 18.5 months, respectively. CONCLUSIONS: The safety and efficacy of first-line bevacizumab-based treatment in Chinese population with advanced NS-NSCLC are consistent with those in previous studies as well as in Asian subgroup population from SAiL study. No new safety signals were reported.
The patients underwent whole body PET-CT scan, MRI brain and pulmonary function test (PFT with DLCO). The SBRT schedules included 48 Gy in 6 fractions for peripherally located and 48 Gy in 8 fractions for centrally located tumors. Response and toxicity were assessed in 3 monthly follow up visits. Results: The median duration of follow up was 18 months (range 8-44 months). The median age of the patients was 70 years (range 63-82 years) and the median tumor diameter was 4 cm (range 2.8-5.0 cm). The mean PTV volume was 165 cc (range 127.3-193.9 cc). The mean dose to the PTV was 99.5% (range 97.7-102.1%). After 3 months, 7 patients had complete metabolic response and 1 patient had partial metabolic response. Overall survival at 1.5 years was 87.5%. One patient had grade 2 pneumonitis. No toxicities of grade 3 or higher were identified.

Conclusion: SBRT for early stage NSCLC resulted in excellent local control with minimal toxicity and can be considered as a treatment option in properly selected patients.

[722]

TÍTULO / TITLE: - Effect of folic Acid and vitamin B12 on pemetrexed antifolate chemotherapy in nutrient lung cancer cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Yang TY; Chang GC; Hsu SL; Huang YR; Chiu LY; Sheu GT

INSTITUCIÓN / INSTITUTION: - Institute of Medicine, Chung Shan Medical University, No. 110, Sec 1, Jianguo N. Road, Taichung 402, Taiwan ; Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, No. 160, Sec 3, Chung-Kang, Taichung 407, Taiwan.

RESUMEN / SUMMARY: - Pemetrexed (MTA) is a multitargeted antifolate drug approved for lung cancer therapy. Clinically, supplementation with high doses of folic acid (FA) and vitamin B12 (VB12) lowers MTA cytotoxicities. An antagonistic effect of FA/VB12 on MTA efficacy has been proposed. However, patients who receive FA/VB12 show better tolerance to MTA with improved survival. The aims of this study are to investigate the modulation of FA and VB12 on MTA drug efficacy in human nonsmall cell lung cancer (NSCLC) cell lines. The sensitivities of cells, apoptosis, and MTA-regulated proteins were characterized to determine the possible effects of high doses of FA and VB12 on MTA efficacy. MTA has the lowest efficacy under 10% serum conditions. However, supplementation with FA and VB12 individually and additively reversed the insensitivity of NSCLC cells to MTA treatment with 10% serum. The enhanced sensitivities of cells following FA/VB12 treatment were correlated with increasing apoptosis and were specific to MTA but not to 5-fluorouracil (5-FU). Enhanced sensitivity was also associated with p21(WAF1/Cip1) expression level. Our results revealed no antagonistic effect of high doses of FA/VB12 on MTA efficacy in
cancer cells grown in nutrient medium. Furthermore, these data may partially explain why supplementation of FA and VB12 resulted in better survival in MTA-treated patients.

[723]
TÍTULO / TITLE: Lack of Association of a Common Polymorphism in the 3'-UTR of Interleukin 8 with Non Small Cell Lung Cancer in Kashmir.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Pandith AA; Bhat BA; Naykoo NA; Qasim I; Rasool R; Aziz SA; Shah ZA
INSTITUCIÓN / INSTITUTION: Department of Immunology and Molecular Medicine, Sher i Kashmir institute of Medical Sciences Srinagar, India E-mail: imty82@gmail.com.
RESUMEN / SUMMARY: Background: Chronic inflammation is considered as an important factor in the pathogenesis of lung cancer. The presence of inflammatory cells and higher levels of pro-inflammatory cytokines in the tumor microenvironment and their surrounding tissues is gaining much importance in research. Materials and Methods: One hundred ninety NSCLC cases and 200 age, smoking and sex matched controls were evaluated for association of IL-8 -251 (rs4073) and IL-8 -845 (rs2227532) in our population. Restriction fragment length polymorphism (RFLP) was used followed by direct sequencing for the detection of SNPs. Results: The IL-8 -845 polymorphism was not found in our population. No significant association was observed between the IL-8 -251 AT genotypes and IL-8 -25 AA genotypes and NSCLC (p=0.05) in our population. The IL-8 -251 A allele was also non-significant (p=0.05) in NSCLC patients. Conclusions: In conclusion, this report reveals lack of association between IL-8 - 251 A/T polymorphism and NSCLC in our Kashmir Valley population.

[724]
TÍTULO / TITLE: Sodium arsenite and arsenic trioxide differently affect the oxidative stress, genotoxicity and apoptosis in A549 cells: An implication for the paradoxical mechanism.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Jiang X; Chen C; Zhao W; Zhang Z
INSTITUCIÓN / INSTITUTION: Department of Environmental Health, West China School of Public Health, Sichuan University, Chengdu 610041, PR China.
RESUMEN / SUMMARY: Although arsenic toxicity greatly depends on its chemical forms, few studies have taken into account the paradoxical phenomenon which is manifested
by that sodium arsenite (NaAsO2) acts as a potent carcinogen but arsenic trioxide (As2O3) serves as an effective therapeutic agent. In this study, we compared the in vitro effects of NaAsO2 and As2O3 on cell viability, colony formation, cell cycle progression, apoptosis, genotoxicity and oxidative stress in human lung adenocarcinoma A549 cells. Our results demonstrated that both NaAsO2 and As2O3 caused oxidative stress, genotoxicity, cytotoxicity, cell cycle arrest as well as apoptosis, while As2O3 induced higher production of reactive oxygen species (ROS) with a more remarkable decrease in superoxide dismutase (SOD) activities and intracellular levels of glutathione (GSH) than NaAsO2. Moreover, the degree of DNA damage, chromosomal breakage, cell cycle arrest and apoptosis in As2O3-treated cells were more severe than those in NaAsO2-treated cells. These findings suggest that differential effects and mechanisms of NaAsO2 and As2O3 may be responsible for the paradoxical effects of arsenic on the carcinogenesis and anticancer function.

[725]

TÍTULO / TITLE: - Cancer-testis gene expression is associated with the methylenetetrahydrofolate reductase 677 C>T polymorphism in non-small cell lung carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Senses KM; Gonen M; Barutcu AR; Kalaylioglu Z; Isbilen M; Konu O; Chen YT; Altorki NK; Gure AO

RESUMEN / SUMMARY: - BACKGROUND: Tumor-specific, coordinate expression of cancer-testis (CT) genes, mapping to the X chromosome, is observed in more than 60% of non-small cell lung cancer (NSCLC) patients. Although CT gene expression has been unequivocally related to DNA demethylation of promoter regions, the underlying mechanism leading to loss of promoter methylation remains elusive. Polymorphisms of enzymes within the 1-carbon pathway have been shown to affect S-adenosyl methionine (SAM) production, which is the sole methyl donor in the cell. Allelic variants of several enzymes within this pathway have been associated with altered SAM levels either directly, or indirectly as reflected by altered levels of SAH and Homocysteine levels, and altered levels of DNA methylation. We, therefore, asked whether the five most commonly occurring polymorphisms in four of the enzymes in the 1-carbon pathway associated with CT gene expression status in patients with NSCLC. METHODS: Fifty patients among a cohort of 763 with NSCLC were selected based on CT gene expression status and typed for five polymorphisms in four genes known to affect SAM generation by allele specific q-PCR and RFLP. RESULTS: We identified a significant association between CT gene expression and the MTHFR 677 CC genotype, as well as the C allele of the SNP, in this cohort of patients. Multivariate analysis revealed that the genotype and allele strongly associate with CT gene
expression, independent of potential confounders. CONCLUSIONS: Although CT gene expression is associated with DNA demethylation, in NSCLC, our data suggests this is unlikely to be the result of decreased MTHFR function.

[726]

TÍTULO / TITLE: Tagging of Genomic STAT3 and STAT1 with Fluorescent Proteins and Insertion of a Luciferase Reporter in the Cyclin D1 Gene Provides a Modified A549 Cell Line to Screen for Selective STAT3 Inhibitors.

RESUMEN / SUMMARY: Signal transducer and activator of transcription 3 (STAT3) is an oncogenic protein that is constitutively activated in numerous cancer cell lines and human cancers. Another STAT family member, STAT1, possesses cancer-inhibitory properties and can promote apoptosis in tumor cells upon activation. To better characterize these important cancer related genes, we tagged STAT3 and STAT1 loci with fluorescent protein (FP) sequences (RFP and GFP respectively) by targeted integration via zinc finger nuclease (ZFN) - mediated homologous recombination in A549 cells that express aberrantly activated STAT3. We inserted the FP transgenes at the N-terminus of the STAT3 locus and at the C-terminus of the STAT1 locus. The integration resulted in endogenous expression of fluorescent STAT3 and STAT1 chimeric fusion proteins. When stimulated with IL-6 or IFN-gamma, the cells showed robust nuclear translocation of RFP-STAT3 or STAT1-GFP, respectively. Pre-incubation of cells with a known specific STAT3 inhibitor showed that IFN-gamma-induced translocation of STAT1-GFP was not impaired. STAT3 activates multiple downstream targets such as genes involved in cell cycle progression - e.g. cyclin D1. To detect changes in expression of endogenous cyclin D1, we used ZFN technology to insert a secreted luciferase reporter behind the cyclin D1 promoter and separated the luciferase and cyclin D1 coding regions by a 2⁸ sequence to induce a translational skip. The luciferase insertion was made in the RFP-STAT3/STAT1-GFP cell line to have all three reporters in a single cell line. Addition of a STAT3 inhibitor led to suppression of cyclin D1 promoter activity and cell growth arrest. The triple-modified cell line provides a simple and convenient method for high-content screening and pre-clinical testing of potential STAT3 inhibitors in live cells while ensuring that the STAT1 pathway is not affected. This approach of reporting endogenous gene activities using ZFN technology could be applied to other cancer targets.

[727]
TÍTULO / TITLE: - The Cost-Utility Analysis of PET-Scan in Diagnosis and Treatment of Non-Small Cell Lung Carcinoma in Iran.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Akbari Sari A; Ravaghi H; Mobinizadeh M; Sarvari S

INSTITUCIÓN / INSTITUTION: - Deptartment of Health Management and Economics, Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran.

RESUMEN / SUMMARY: - BACKGROUND: PET scan is a non-invasive, complex and expensive medical imaging technology that is normally used for the diagnosis and treatment of various diseases including lung cancer. OBJECTIVES: The purpose of this study is to assess the cost effectiveness of this technology in the diagnosis and treatment of non-small cell lung carcinoma (NSCLC) in Iran. MATERIALS AND METHODS: The main electronic databases including The Cochrane Library and Medline were searched to identify available evidence about the performance and effectiveness of technology. A standard decision tree model with seven strategies was used to perform the economic evaluation. Retrieved studies and expert opinion were used to estimate the cost of each treatment strategy in Iran. The costs were divided into three categories including capital costs (depreciation costs of buildings and equipment), staff costs and other expenses (including cost of consumables, running and maintenance costs). The costs were estimated in both IR-Rials and US-Dollars with an exchange rate of 10,000 IR Rials per one US Dollar according to the exchange rate in 2008. RESULTS: The total annual running cost of a PET scan was about 8850 to 13000 million Rials, (0.9 to 1.3 million US$). The average cost of performing a PET scan varied between 3 and 4.5 million Rials (300 to 450US$). The strategies 3 (mediastinoscopy alone) and 7 (mediastinoscopy after PET scan) were more cost-effective than other strategies, especially when the result of the CT-scan performed before PET scan was negative. CONCLUSION: The technical performance of PET scan is significantly higher than similar technologies for staging and treatment of NSCLC. In addition, it might slightly improve the treatment process and lead to a small level of increase in the quality adjusted life year (QALY) gained by these patients making it cost-effective for the treatment of NSCLC.

TÍTULO / TITLE: - Efficacy and safety of metronomic administration of paclitaxel for advanced recurrent non-small-cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Noronha V; Patil VM; Joshi A; Prabhash K

INSTITUCIÓN / INSTITUTION: Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India.

RESUMEN / SUMMARY: Context: There are limited effective therapeutic options in the relapsed setting for non-small cell lung cancer (NSCLC) or in the first line for platinum-ineligible patients. Aim: To evaluate the safety and efficacy of a metronomic schedule of paclitaxel administered weekly in relapsed refractory NSCLC or upfront in patients not eligible for platinum-based chemotherapy. Settings and Design: Retrospective analysis of a prospectively collected database from the medical oncology department at Tata Memorial Hospital in Mumbai, India. Materials and Methods: Patients with recurrent and treatment-naive platinum-ineligible advanced NSCLC were treated with weekly paclitaxel at 80 mg/m² with palliative intent. Restaging scans were obtained every two months. Chemotherapy was continued until progressive disease, intolerable side effects, or decision of the patient. Statistical Analysis Used: SPSS version 16 was used for analysis. Simple percentages were used for descriptive statistics. Progression-free survival (PFS) was calculated from date of start of paclitaxel till the date of progression, change of therapy due to any reason, or death due to any cause. Overall survival (OS) was calculated from date of start of paclitaxel to death. The Kaplan Meier method was used for estimation of survival. Results: There were 37 patients over eight months. The median age was 59 years, with a male-to-female ratio of 5:1. Two patients received paclitaxel in the first line, 18 patients in second line, nine in third line, five in fourth line, and three were in fifth line. 73% patients had received prior platinum and 48.6% patients had Eastern Cooperative Oncology Group performance status (ECOG PS) >2. The median number of weekly cycles delivered was 14. The response rate was 35% [complete remission (CR): 2.7%, partial remission (PR): 32.4%, stable disease (SD): 32.4%, progressive disease (PD): 27%], the median PFS was four months, and the estimated median OS was seven months. Chemotherapy was well tolerated. The most frequent grade 3 toxicities included anemia: 8%, neutropenia: 5.4%, and sensory neuropathy: 8%. There were no grade 4 toxicities and no episodes of febrile neutropenia. Conclusions: Weekly low-dose continuous metronomic-type scheduling of paclitaxel is safe and effective for relapsed refractory NSCLC and in the first line in platinum-ineligible patients.

TÍTULO / TITLE: Correction: Functional disruption of macrophage migration inhibitory factor (MIF) suppresses proliferation of human h460 lung cancer cells by caspase-dependent apoptosis.

After publication of the original article [1] it came to the authors attention that an incomplete version of figure three was published with the article. The complete figure and new figure legend are presented in this correction article.

TÍTULO / TITLE: Completely resected n0 non-small cell lung cancer: prognostic factors affecting long-term survival.
RESUMEN / SUMMARY: Background. Although early stage non-small cell lung cancer (NSCLC) has an excellent outcome and correlated with good long-term survival, up to 15 percent of patients still relapse postoperatively and die. This study is conducted to identify prognostic factors that may affect the long-term survival in completely resected N0 NSCLC. Methods. Medical records of 124 patients with completely resected N0 NSCLC were retrospectively reviewed. Prognostic factors affecting long-term survival were analyzed by the Kaplan-Meier method and Cox proportional hazards analysis. Results. Overall five-year survival rate was 48 percent. Multivariable analysis revealed stage of disease, tumor necrosis, tumor recurrence, brain metastasis, adrenal metastases, and skin metastases as significant prognostic factors affecting long-term survival. The hazard ratio (HR) of tumor necrosis, tumor recurrence, brain metastasis, adrenal metastases, and skin metastases was 2.0, 2.3, 7.6, 4.1, and 8.3, respectively, and all P values were less than 0.001. Conclusions. Our study shows stage of disease, tumor necrosis, tumor recurrence, brain metastasis, adrenal metastasis, and skin metastasis as the independent prognostic factors of long-term survival in pathological N0 NSCLC. Early stage NSCLC patients without nodal involvement or presented with tumor necrosis should benefit from adjuvant chemotherapy, and sites of metastasis could predict the long-term survival as described.

TÍTULO / TITLE: Results of diagnostic dilemma between lung cancer and sputum negative pulmonary tuberculosis: a retrospective study.
RESUMEN / SUMMARY: Background. Although early stage non-small cell lung cancer (NSCLC) has an excellent outcome and correlated with good long-term survival, up to 15 percent of patients still relapse postoperatively and die. This study is conducted to identify prognostic factors that may affect the long-term survival in completely resected N0 NSCLC. Methods. Medical records of 124 patients with completely resected N0 NSCLC were retrospectively reviewed. Prognostic factors affecting long-term survival were analyzed by the Kaplan-Meier method and Cox proportional hazards analysis. Results. Overall five-year survival rate was 48 percent. Multivariable analysis revealed stage of disease, tumor necrosis, tumor recurrence, brain metastasis, adrenal metastases, and skin metastases as significant prognostic factors affecting long-term survival. The hazard ratio (HR) of tumor necrosis, tumor recurrence, brain metastasis, adrenal metastases, and skin metastases was 2.0, 2.3, 7.6, 4.1, and 8.3, respectively, and all P values were less than 0.001. Conclusions. Our study shows stage of disease, tumor necrosis, tumor recurrence, brain metastasis, adrenal metastasis, and skin metastasis as the independent prognostic factors of long-term survival in pathological N0 NSCLC. Early stage NSCLC patients without nodal involvement or presented with tumor necrosis should benefit from adjuvant chemotherapy, and sites of metastasis could predict the long-term survival as described.
AUTORES / AUTHORS: - Dasgupta P; Chakrabarti A; Halder D; Acharyya S; Gangopadhyay S

INSTITUCIÓN / INSTITUTION: - Department of Radiotherapy, RG Kar Medical College and Hospital, Kolkata 700004.

RESUMEN / SUMMARY: - Diagnostic dilemma owing to radiological similarities between smear negative pulmonary tuberculosis and bronchogenic lung cancer pose a critical problem of late detection of the later with all its impact on the life of the victims. The aim of the study was to assess the magnitude and consequence of diagnostic dilemma between lung cancer and smear negative pulmonary tuberculosis. The retrospective observational study was conducted in the radiotherapy department of RG Kar Medical College and Hospital, Kolkata, West Bengal involving the lung cancer patients reported from February, 2009 to March, 2011. Out of the 76 lung cancer patients, 39.47% had exposure to anti tuberculosis treatment (ATT) before the actual diagnosis of lung cancer. Significantly higher proportion of rural patients was put on the ATT compared to their urban counterpart. Duration of symptoms before arrival was found significantly more among those who got ATT. Presence of any history of tuberculosis within the family was found to have significant association with the exposure to ATT before diagnosis as lung cancer. So in conclusion the treating physician must think twice before stamping a case as smear negative tuberculosis based on the radiological findings. High index of suspicion should also be maintained during treatment and follow-up of both smear positive and smear negative pulmonary tuberculosis as because the lung cancer may be preceded by or coexist with pulmonary tuberculosis.

[732]


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Chen L; Caldero SG; Gmitro S; Smith ML; De Petris G; Zarka MA

INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, Arizona; Department of Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio.

RESUMEN / SUMMARY: - BACKGROUND: The cytological diagnosis of malignant mesothelioma (MM) on serous effusion is challenging due to significant morphologic overlap with reactive mesothelial cells and adenocarcinoma. One of the morphologic features of MM in effusion cytology, small orangiophilic squamous-like cells (SOSLC), has received little attention. To the best of the authors’ knowledge, the current study is the first to assess the sensitivity and specificity of SOSLC in serous effusion.
specimens from histology-proven MM cases along with those of reactive mesothelial and adenocarcinoma cases. METHODS: A total of 130 cases of pleural (86 cases) and peritoneal (44 cases) effusion cytology cases (30 with histology-proven MM, 41 with adenocarcinoma, and 59 with reactive mesothelial cells) were studied. The presence or absence of SOSLC was recorded in each case. RESULTS: The cytological diagnoses of the 30 histology-proven MM cases included 1) atypical mesothelial cells, favor reactive (4 cases); 2) atypical mesothelial cells, suspicious for or cannot exclude mesothelioma (18 cases); and 3) positive for MM (8 cases). SOSLC were found in 10 of the 30 MM effusion cases (33.3%), 1 of the 41 adenocarcinoma cases (2.4%), and 5 of the 59 reactive mesothelial cell cases (8.5%). SOSLC were more likely to be present in MM effusions compared with either adenocarcinoma (P < .0001) or reactive mesothelial cell (P < .02) effusions. All 10 cases of MM with SOSLC were from pleural fluids. One case of peritoneal serous adenocarcinoma had SOSLC and 5 cases of reactive mesothelial cells in peritoneal fluid were found to have SOSLC. CONCLUSIONS: Although not sensitive, the presence of SOSLC is quite specific for MM in pleural fluid cytology specimens. Finding this morphological feature in pleural fluid should alert the pathologist to a possible diagnosis of MM. Cancer (Cancer Cytopathol) 2013. © 2013 American Cancer Society.
INSTITUCIÓN / INSTITUTION: - Department of Biology, University of Padova, via U. Bassi 58/B, Padova 35131, Italy. lucia.celotti@unipd.it.

RESUMEN / SUMMARY: - Perturbations during the cell DNA-Damage Response (DDR) can originate from alteration in the functionality of the microRNA-mediated gene regulation, being microRNAs (miRNAs), small non-coding RNAs that act as post-transcriptional regulators of gene expression. The oncogenic miR-27\(^a\) is over-expressed in several tumors and, in the present study, we investigated its interaction with ATM, the gene coding for the main kinase of DDR pathway. Experimental validation to confirm miR-27\(^a\) as a direct regulator of ATM was performed by site-direct mutagenesis of the luciferase reporter vector containing the 3'UTR of ATM gene, and by miRNA oligonucleotide mimics. We then explored the functional miR-27\(^a\)/ATM interaction under biological conditions, i.e., during the response of A549 cells to ionizing radiation (IR) exposure. To evaluate if miR-27\(^a\) over-expression affects IR-induced DDR activation in A549 cells we determined cell survival, cell cycle progression and DNA double-strand break (DSB) repair. Our results show that up-regulation of miR-27\(^a\) promotes cell proliferation of non-irradiated and irradiated cells. Moreover, increased expression of endogenous mature miR-27\(^a\) in A549 cells affects DSB rejoining kinetics early after irradiation.

[735]

TÍTULO / TITLE: - Effect of DNA methylation inhibitor on RASSF1A genes expression in non-small cell lung cancer cell line A549 and A549DDP.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1186/1475-2867-13-91

AUTORES / AUTHORS: - Mengxi D; Qian W; Nan W; Xiaoguang X; Shijun L

RESUMEN / SUMMARY: - BACKGROUND: Ras association domain family 1\(^a\) gene (RASSF1A) is a candidate suppressor gene. Lack of RASSF1A expression was found in lung cancer. High DNA methylation at the promoter region is the main reason for inactivating RASSR1A transcription. METHODS: In this study, we examined RASSF1A’s methylation status and its mRNA expression level between non-small cell lung cancer cell line A549 and anti-Cisplatin cell strain A549DDP. Furthermore, methylation of A549DDP was reversed by treatment of 5-Aza-2[prime] - deoxycytidine (5-Aza-cdR), a DNA methyltransferase inhibitor. RESULTS: We found that RASSF1A’s methylation status and its mRNA expression were obvious differences between A549 and A549DDP. 5-Aza-CdR treatment remarkably reduced cell viability of A549DDP. Moreover, 5-Aza-CdR treatment induced A549DDP cell apoptosis in a dose dependent manner with declining cell percentage in S and G2/M stage, and increasing proportion in G0/G1 stage. Cell motility was blocked in G0/G1 stage. All of A549DDP cells showed unmethylated expression, its high methylation status was reversed in a dose-dependent manner within a certain range. CONCLUSIONS: The abnormal gene
methylation status of RASSF1A is a molecular biomarker in lung cancer diagnosis, treatment and prognosis.

[736]


**RESUMEN** - Enlace al Resumen / Link to its Summary


**AUTORES** - Neri A; Stewart SL; Angell W

**INSTITUCIÓN** - Centers for Disease Control and Prevention, Comprehensive Cancer Control Branch, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Public Health Promotion, 4770 Buford Hwy, MS K-57, Atlanta, GA 30341, USA. ANeri@cdc.gov

**RESUMEN** - INTRODUCTION: Radon is the second leading cause of lung cancer among smokers and the leading cause among nonsmokers. The US Environmental Protection Agency recommends that every home be tested for radon. Comprehensive Cancer Control (CCC) programs develop cancer coalitions that coordinate funding and resources to focus on cancer activities that are recorded in cancer plans. Radon tests, remediation, and radon mitigation techniques are relatively inexpensive, but it is unclear whether coalitions recognize radon as an important carcinogen. METHODS: We reviewed 65 cancer plans created from 2005 through 2011 for the terms “radon,” “radiation,” or “lung.” Plan activities were categorized as radon awareness, home testing, remediation, supporting radon policy activities, or policy evaluation. We also reviewed each CCC program’s most recent progress report. Cancer plan content was reviewed to assess alignment with existing radon-specific policies in each state. RESULTS: Twenty-seven of the plans reviewed (42%) had radon-specific terminology. Improving awareness of radon was included in all 27 plans; also included were home testing (n=21), remediation (n=11), support radon policy activities (n=13), and policy evaluation (n=1). Three plans noted current engagement in radon activities. Thirty states had radon-specific laws; most (n=21) were related to radon professional licensure. Eleven states had cancer plan activities that aligned with existing state radon laws. CONCLUSION: Although several states have radon-specific policies, approximately half of cancer coalitions may not be aware of radon as a public health issue. CCC-developed cancer coalitions and plans should prioritize tobacco control to address lung cancer but should consider addressing radon through partnership with existing radon control programs.

[737]

**TÍTULO** - Clinical features and prognostic factors in elderly koreans with advanced non-small-cell lung cancer in a tertiary referral hospital.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 4046/trd.2013.75.2.52

AUTORES / AUTHORS: Kim SW; Kim MY; Lee YP; Ryu YJ; Lee SJ; Lee JH; Chang JH; Shim SS

INSTITUCIÓN / INSTITUTION: Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ewha Medical Center and Ewha Medical Research Institute, Ewha Womans University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: BACKGROUND: More than half of cases for advanced non-small-cell lung cancer (NSCLC) occur in elderly patients with a median age at diagnosis of 70 years. The aim of our study was to examine the clinical features and prognostic factors contributing to mortality in elderly patients with advanced NSCLC. METHODS: Following a retrospective review of clinical data, 122 patients aged 70 years and over with a histopathological diagnosis of locally advanced (stage IIIB, n=32) and metastatic (stage IV, n=90) NSCLC between 2005 and 2011 were enrolled. RESULTS: The median age was 76 years (interquartile range, [IQR], 72-80 years), and 85 (70%) patients were male. Fifty-seven (46%) patients had never smoked, and 17 (19%) were in a malnourished state with a body mass index (BMI) of <18.5 kg/m(2). The initial treatments included chemotherapy (40%) and radiotherapy (7%), but 57% of the patients received supportive care only. The 1-year survival rate was 32%, and the 3-year survival rate was 4%, with a median survival duration of 6.2 months (IQR, 2.5-15.3 months). Male gender (hazard ratio [HR], 2.2; 95% confidence interval [CI], 1.3-3.9; p=0.005), low BMI (HR, 2.3; 95% CI, 1.3-3.9; p=0.004), and supportive care only (HR, 1.9; 95% CI, 1.2-2.9; p=0.007) were independent predictors of shorter survival based on a Cox proportional hazards model. CONCLUSION: Elderly patients with advanced NSCLC had a poor prognosis, particularly male patients, those with a low BMI, and those who received supportive care only.

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[738]

TÍTULO / TITLE: Emoein elicits cytotoxicity in human lung adenocarcinoma A549 cells through inducing apoptosis.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

●● Enlace al texto completo (gratuito o de pago) 1007/s10787-013-0186-4

AUTORES / AUTHORS: Li WY; Ng YF; Zhang H; Guo ZD; Guo DJ; Kwan YW; Leung GP; Lee SM; Yu PH; Chan SW

INSTITUCIÓN / INSTITUTION: Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China.

RESUMEN / SUMMARY: This study investigated the mechanism of the cytotoxic effect of emodin, an active anthraquinone, on human lung adenocarcinoma A549 cells. In vitro growth inhibition and suppression on colony forming were used to evaluate the effects
of emodin on A549 cells. Emodin’s ability in changing the expressions of apoptosis-related genes was studied by real-time RT-PCR. Emodin could significantly inhibit the growth of A549 cells with IC50 = 16.85 μg/ml (~60 μM). It also concentration-dependently inhibited the colony-forming ability of A549 cells with IC50 = 7.60 μg/ml (~30 μM). Hallmarks of apoptosis, such as single-strand DNA breakage and DNA fragmentation, were observed in A549 cells treated with emodin. Emodin (72 h) treatment could up-regulate the gene expression of FASL (p < 0.05) and down-regulate the gene expression of C-MYC (p < 0.01), but induce no significant changes in the gene expressions of MCL1, GAPDH, BAX and CCND1. These results suggest that emodin could induce growth inhibition and apoptosis in A549 cells through modifying the extrinsic apoptotic pathways and the induction of cell cycle arrest.

[739]

TÍTULO / TITLE: - Clinical outcome of primary small cell carcinoma of the urinary bladder.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Hou CP; Lin YH; Chen CL; Chang PL; Tsui KH
INSTITUCIÓN / INSTITUTION: - Department of Urology, Chang Gung Memorial Hospital-Linko, Taiwan, Republic of China ; College of Medicine, Chang Gung University, Taiwan, Republic of China.

RESUMEN / SUMMARY: - PURPOSE: Primary small cell carcinoma of the urinary bladder is a rare malignant disease. It accounts for less than 1% of all urinary bladder carcinomas. The purpose of this study is to review the clinical features, the treatment modalities, and the overall survival of these patients. We also compare the clinical outcomes between patients of bladder small cell carcinoma (SCC) and bladder urothelial carcinoma (UC). MATERIALS AND METHODS: We reviewed the charts of patients with bladder tumors from January 1995 to December 2012 in the Chang Gung Memorial Hospital. A total of 2421 malignant bladder tumor patients were reviewed and there were 18 patients who were diagnosed with primary bladder SCC. The patients’ characteristics, including age, gender, smoking history, presented symptoms, tumor size, locations, clinical stages, treatment modalities, pathology appearance, recurrence conditions, and survival conditions were all recorded. We also compared the clinical outcomes and the overall survival rates between patients with bladder SCC and those with UC. RESULTS: Bladder SCC accounted for about 0.74% of all bladder malignancies in our institution. The mean age at diagnosis was 70.67 years, and the male-to-female ratio was 2.6:1. Thirteen patients had a history of cigarette smoking. All patients presented with symptoms of gross hematuria, and three of them had bladder tamponade requiring blood clot evacuation by cystoscopy. Only one patient had T1 disease, ten patients had stage III disease, and seven patients had lymph node
or distant metastasis (stage IV disease). The mean tumor size was 4.29 cm in diameter. For the majority (61.11%) of patients, SCC coexisted with UC components. The average survival time was 10.92 months. Patients with bladder SCC had worse overall survival rates than those of stage III and stage IV bladder UC. Performing radical cystectomy does not significantly improve their overall survival rates. None of the clinicopathologic parameters, including the presence of coexisting nonsmall cell carcinoma component (P = 0.831), receiving radical cystectomy (P = 0.194), distant metastasis (P = 0.062), and gender (P = 0.564), were significantly associated with survival. CONCLUSION: SCC of the urinary bladder is a rare condition, and standard treatment outlines have not been well established. Most of the presented cases have a very poor prognosis. Prospective, multi-institutional, randomized studies are required to assess better treatment modalities. To the best of our knowledge, this is the largest reported case analysis of primary bladder SCC in a Taiwanese population.

[740]
**TÍTULO / TITLE:** - Down-Regulation of SIX3 is Associated with Clinical Outcome in Lung Adenocarcinoma.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Mo ML; Okamoto J; Chen Z; Hirata T; Mikami I; Bosco-Clement G; Li H; Zhou HM; Jablons DM; He B

**INSTITUCIÓN / INSTITUTION:** - School of Life Sciences, Tsinghua University, Beijing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Lung cancer is a common cancer and the leading cause of cancer-related death worldwide. SIX3 is a human homologue of the highly conserved sine oculis gene family essential during embryonic development in vertebrates, and encodes a homeo-domain containing transcription factor. Little is known about the role of SIX3 in human tumorigenesis. This study is to assess the expression/function of SIX3 and the significance of SIX3 as a prognostic biomarker in lung adenocarcinoma. METHODS: Quantitative real-time RT-PCR was used to analyze SIX3 mRNA expression and quantitative methylation specific PCR (MSP) was used to examine promoter methylation. MTS and colony formation assays were performed to examine cell proliferation. Wound healing assays were used to assess cell migration, and microarrays were utilized to examine genes regulated by SIX3 in lung cancer cells. Association of SIX3 expression levels with clinical outcomes of patients with lung adenocarcinoma was evaluated using the Kaplan-Meier method and a multivariate Cox proportional hazards regression model. RESULTS: SIX3 was down-regulated in lung adenocarcinoma tissues compared to their matched adjacent normal tissues, and this down-regulation was associated with methylation of the SIX3 promoter. SIX3 was also methylation-silenced in lung cancer cell lines. Restoration of SIX3 in lung cancer cells
lacking endogenous SIX3 suppressed cell proliferation and migration, and downregulated a number of genes involved in proliferation and metastasis such as S100P, TGFB3, GINS3 and BAG1. Moreover, SIX3 mRNA expression was associated with significantly improved overall survival (OS) and progression-free survival (PFS) in adenocarcinoma patients and patients with bronchioloalveolar carcinoma (BAC) features. CONCLUSIONS: SIX3 may play an important role as a novel suppressor in human lung cancer. SIX3 has potential as a novel prognostic biomarker for patients with lung adenocarcinomas.
gene are associated with female non-smokers with adenocarcinoma and regarded as a prognostic biomarker for assessing overall survival of patients with lung adenocarcinoma.

[742]

**TÍTULO / TITLE:** - Association Between Environmental Tobacco Smoke Exposure and Lung Cancer Susceptibility: Modification by Antioxidant Enzyme Genetic Polymorphisms.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Fathy M; Hamed M; Youssif O; Fawzy N; Ashour W

**INSTITUCIÓN / INSTITUTION:** - Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Cairo, Egypt, muna_fathy@hotmail.com.

**RESUMEN / SUMMARY:** - BACKGROUND: Environmental tobacco smoke (ETS) is the primary etiologic factor responsible for lung cancer. However, only 10-15% of smokers develop lung cancer, suggesting a genetic role in modifying individual susceptibility to lung cancer. Antioxidant enzymes and genetic polymorphisms should be considered. AIM: The present study aimed to evaluate the role of antioxidant enzyme activity and genetic polymorphisms in modifying the susceptibility to lung cancer among individuals exposed to ETS. SUBJECTS AND METHODS: A total of 150 male subjects were divided into three groups: 50 lung cancer patients, 50 chronic smokers, and 50 passive smokers. Genotyping of microsomal epoxide hydrolase (mEH) exon 3 (Tyr113Hist) and exon 4 (Hist139Arg) polymorphisms were done by the polymerase chain reaction-restriction fragment length polymorphism technique. MnSOD (Val16Ala) polymorphism was detected by the real time-TaqMan assay. Erythrocyte MnSOD activity was measured spectrophotometrically. RESULTS: ETS-exposed individuals (both active and passive smokers) who carried the His allele of mEH exon 3 have a 2.9-fold increased risk of lung cancer (odds ratio [OR] 2.9, P < 0.001). In addition, ETS-exposed carriers of the Arg allele of mEH exon 4 have a 2.1-fold increased risk of lung cancer (OR 2.1, P = 0.024). However, no association between the MnSOD Val16Ala polymorphism and lung cancer was detected among ETS-exposed individuals (OR 1.6, P = 0.147), although the lung cancer group had significantly lower MnSOD activity than the chronic or passive smoker groups (P = 0.03). CONCLUSIONS: Exons 3 and 4 polymorphisms of the mEH gene may contribute to lung cancer susceptibility through disturbed antioxidant balance. However, this was not the case with the MnSOD Val16Ala single-nucleotid polymorphism. Antioxidant enzymes may modulate the influence of ETS exposure on lung cancer risk.

[743]

**TÍTULO / TITLE:** - LKB1/AMPK/mTOR Signaling Pathway in Non-small-cell Lung Cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Han D; Li SJ; Zhu YT; Liu L; Li MX
INSTITUCIÓN / INSTITUTION: - Respiratory Diseases Research Center, Department of Respiratory Medicine, The Second Affiliated Hospital of Medical College, Xi’an Jiaotong University, Xi’an, China E-mail: manxiangli@hotmail.com.
RESUMEN / SUMMARY: - Links between cancer and metabolism have been suggested for a long time but compelling evidence for this hypothesis came from the recent molecular characterization of the LKB1/AMPK signaling pathway as a tumor suppressor axis. Besides the discovery of somatic mutations in the LKB1 gene in certain type of cancers, a critical emerging point was that the LKB1/AMPK axis remains generally functional and could be stimulated by pharmacological molecules such as metformin in cancer cells. In addition, AMPK plays a central role in the control of cell growth, proliferation and autophagy through the regulation of mTOR activity, which is consistently deregulated in cancer cells. Targeting of AMPK/mTOR is thus an attractive strategy in the development of therapeutic agents against non-small-cell lung cancer (NSCLC). In this review, the LKB1/AMPK/mTOR signaling pathway is described, highlighting its protective role, and opportunities for therapeutic intervention, and clinical trials in NSCLC.

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[744]

TÍTULO / TITLE: - Evaluation of EGFR and RTK Signaling in the Electrotaxis of Lung Adenocarcinoma Cells under Direct-Current Electric Field Stimulation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Tsai HF; Huang CW; Chang HF; Chen JJ; Lee CH; Cheng JY
INSTITUCIÓN / INSTITUTION: - Institute of Biophotonics, National Yang-Ming University, Taipei, Taiwan; Research Center for Applied Sciences, Academia Sinica, Taipei, Taiwan; Biophotonics & Molecular Imaging Research Center, National Yang-Ming University, Taipei, Taiwan.
RESUMEN / SUMMARY: - Physiological electric field (EF) plays a pivotal role in tissue development and regeneration. In vitro, cells under direct-current electric field (dcEF) stimulation may demonstrate directional migration (electrotaxis) and long axis reorientation (electro-alignment). Although the biophysical models and biochemical signaling pathways behind cell electrotaxis have been investigated in numerous normal cells and cancer cells, the molecular signaling mechanisms in CL1 lung adenocarcinoma cells have not been identified. Two subclones of CL1 cells, the low invasive CL1-0 cells and the highly invasive CL 1-5 cells, were investigated in the present study. CL1-0 cells are non-electrotactic while the CL 1-5 cells are anodally electrotactic and have high expression level of epidermal growth factor receptor (EGFR), in this study, we
investigated the generally accepted hypothesis of receptor tyrosine kinase (RTK) activation in the two cell lines under dcEF stimulation. Erbitux, a therapeutic drug containing an anti-EGFR monoclonal antibody, cetuximab, was used to investigate the EGFR signaling in the electrotaxis of CL 1-5 cells. To investigate RTK phosphorylation and intracellular signaling in the CL1 cells, large amount of cellular proteins were collected in an airtight dcEF stimulation device, which has advantages of large culture area, uniform EF distribution, easy operation, easy cell collection, no contamination, and no medium evaporation. Commercial antibody arrays and Western blotting were used to study the phosphorylation profiles of major proteins in CL1 cells under dcEF stimulation. We found that electrotaxis of CL 1-5 cells is serum independent and EGFR independent. Moreover, the phosphorylation of Akt and S6 ribosomal protein (rpS6) in dcEF-stimulated CL1 cells are different from that in EGF-stimulated cells. This result suggests that CL1 cells’ response to dcEF stimulation is not through EGFR-triggered pathways. The new large-scale dcEF stimulation device developed in the present work will aid the sample preparation for protein-based experiments.

[745]

TÍTULO / TITLE: Anticancer Activity of Novel Daphnane Diterpenoids from Daphne genkwa through Cell-Cycle Arrest and Suppression of Akt/STAT/Src Signalings in Human Lung Cancer Cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Jo SK; Hong JY; Park HJ; Lee SK

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea.

RESUMEN / SUMMARY: - Although the immense efforts have been made for cancer prevention, early diagnosis, and treatment, cancer morbidity and mortality has not been decreased during last forty years. Especially, lung cancer is top-ranked in cancer-associated human death. Therefore, effective strategy is strongly required for the management of lung cancer. In the present study, we found that novel daphnane diterpenoids, yuanhualine (YL), yuanhuahine (YH) and yuanhuagine (YG) isolated from the flower of Daphne genkwa (Thymelaeaceae), exhibited potent anti-proliferative activities against human lung A549 cells with the IC50 values of 7.0, 15.2 and 24.7 nM, respectively. Flow cytometric analysis revealed that the daphnane diterpenoids induced cell-cycle arrest in the G0/G1 as well as G2/M phase in A549 cells. The cell-cycle arrests were well correlated with the expression of checkpoint proteins including the up-regulation of cyclin-dependent kinase inhibitor p21 and p53 and down-regulation of cyclin A, cyclin B1, cyclin E, cyclin dependent kinase 4, cdc2,
phosphorylation of Rb and cMyc expression. In the analysis of signal transduction molecules, the daphnane diterpenoids suppressed the activation of Akt, STAT3 and Src in human lung cancer cells. The daphnane diterpenoids also exerted the potent anti-proliferative activity against anticancer-drug resistant cancer cells including gemcitabine-resistant A549, gefitinib-, erlotinib-resistant H292 cells. Synergistic effects in the growth inhibition were also observed when yuanhualine was combined with gemcitabine, gefitinib or erlotinib in A549 cells. Taken together, these findings suggest that the novel daphnane diterpenoids might provide lead candidates for the development of therapeutic agents for human lung cancers.

[746] TÍTULO / TITLE: - Curcumin Induces Autophagy via Activating the AMPK Signaling Pathway in Lung Adenocarcinoma Cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Xiao K; Jiang J; Guan C; Dong C; Wang G; Bai L; Sun J; Hu C; Bai C
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The Second Xiangya Hospital, Central South University, China.
RESUMEN / SUMMARY: - Curcumin is a major yellow pigment and active component of turmeric widely used as dietary spice and herbal medicine. This compound has been reported to be a promising antitumor agent, although the underlying molecular mechanisms are not fully understood yet. In this study, we reported that curcumin inhibited growth of lung adenocarcinoma cells, but had no cytotoxic activity to IMR-90 normal lung fibroblast cells. Curcumin induced autophagy in the A549 human lung adenocarcinoma cell line, evidenced by LC3 immunofluorescence analysis and immunoblotting assays on LC3 and SQSTM1. Moreover, the autophagy inhibitor 3-MA partly blocked the inhibitory effect of curcumin on the growth of A549 cells. Curcumin markedly increased the phosphorylation of AMP-activated protein kinase (AMPK) and acetylCoA carboxylase in A549 cells. At last, pharmacological blockade of the AMPK signaling pathway by compound C and genetic disruption of the AMPK signaling pathway with siRNA-mediated AMPKalpha1 knockdown impaired the autophagy-inducing effect of curcumin. Collectively, our data suggests that curcumin induces autophagy via activating the AMPK signaling pathway and the autophagy is important for the inhibiting effect of curcumin in lung adenocarcinoma cells.

[747] TÍTULO / TITLE: - Pleomorphic adenoma of lateral nasal wall presenting with epiphora.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ulkumen B; Kaplan Y; Dogru N
INSTITUCIÓN / INSTITUTION: - Department of Otorhinolaryngology of Ozel Batman Dunya Hospital, Batman, Turkey. drburak@gmail.com

RESUMEN / SUMMARY: - We report a rare case of pleomorphic adenoma arising from the lateral nasal wall which was incidentally detected at a very early stage. A 38-year-old man presented to the ophthalmology department with a 2-year history of epiphora from the left eye. He was referred to otorhinolaryngology department as a candidate for endoscopic dacryocystorhinostomy. Nasal endoscopy revealed a polypoid mass on the left lateral nasal wall arising near the uncinate process and protruding into the middle meatus. Endoscopic excision of the mass and a concomitant endoscopic dacryocystorhinostomy and functional endoscopic sinus surgery were done. Histopathological examination was compatible with pleomorphic adenoma having tumour-negative surgical margins. He was free from the disease 24 months after the surgery.

[748]

TÍTULO / TITLE: - Xiao-Ai-Ping, a TCM Injection, Enhances the Antigrowth Effects of Cisplatin on Lewis Lung Cancer Cells through Promoting the Infiltration and Function of CD8(+) T Lymphocytes.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Li W; Yang Y; Ouyang Z; Zhang Q; Wang L; Tao F; Shu Y; Gu Y; Xu Q; Sun Y

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, 22 Hankou Road, Nanjing 210093, China.

RESUMEN / SUMMARY: - Objectives. To investigate how Xiao-Ai-Ping injection, a traditional Chinese medicine and an ancillary drug in tumor treatment, enhances the antitumor effects of cisplatin on Lewis lung cancer (LLC) cells. Methods. LLC-bearing mice were daily intraperitoneally injected with various doses of cisplatin, Xiao-Ai-Ping, or cisplatin plus Xiao-Ai-Ping, respectively. Body weight and tumor volumes were measured every three days. Results. Combination of Xiao-Ai-Ping and cisplatin yielded significantly better antigrowth and proapoptotic effects on LLC xenografts than sole drug treatment did. In addition, we found that Xiao-Ai-Ping triggered the infiltration of CD8(+) T cells, a group of cytotoxic T cells, to LLC xenografts. Furthermore, the mRNA levels of interferon- gamma (ifn- gamma ), perforin-1 (prf-1), and granzyme B (gzmb) in CD8(+) T cells were significantly increased after combination treatment of Xiao-Ai-Ping and cisplatin. In vitro studies showed that Xiao-Ai-Ping markedly upregulated the mRNA levels of ifn- gamma , prf-1, and gzmb in CD8(+) T cells in a concentration-dependent manner, suggesting that Xiao-Ai-Ping augments the function of CD8(+) T
cells. Conclusions. Xiao-Ai-Ping promotes the infiltration and function of CD8(+) T cells and thus enhances the antigrowth effects of cisplatin on LLC xenografts, which provides new evidence for the combination of Xiao-Ai-Ping and cisplatin in clinic in China.

[749]

[RESUMEN / SUMMARY] - Enlace al Resumen / Link to its Summary
[AUTORES / AUTHORS] - Dey SK; Jha S; Ghosh I; Bhattacharya SK; Das A; Gangopadhyay S
[INSTITUCIÓN / INSTITUTION] - Department of Chest Medicine, Calcutta National Medical College, Kolkata.

[RESUMEN / SUMMARY] - Lung cancer is the most common cancer in the world since 1988, both in terms of incidence and mortality among both men and women. Approximately half of the cases of lung cancer now occur in developing countries compared to 1980. Tobacco smoking is by far the predominant risk factor for lung cancer. A knowledge, attitude and practice of smoking among 132 cases of lung cancer in this study was undertaken. Amongst 113 ever smokers, out of 132 cases, 91.18% of males and 36.36% of female subjects continued smoking despite knowing the harmful effects of tobacco, displayed over the cigarette or bidi packets. In these group squamous cell carcinoma was the most common type followed by adenocarcinoma. Among the never smokers adenocarcinoma was the commonest type, females accounting for 75% of the cases, though a good number was observed among male ever smokers, signifying the changing histological types of lung cancer today.

[750]

[RESUMEN / SUMMARY] - Enlace al Resumen / Link to its Summary
[AUTORES / AUTHORS] - Rimner A; Rosenzweig KE
[INSTITUCIÓN / INSTITUTION] - Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;

[751]

RESUMEN / SUMMARY: - The inability to deliver MAbs to intracellular targets still remains a limitation to their application in cancer therapy and diagnosis. Selective targeting of MAbs to oncoproteins in cancer cells while avoiding their accumulation in normal cells may reduce some of the well-documented adverse effects accompanying antibody therapy. One of the remarkable characteristics of malignant cells is the alteration in the biological properties of the cellular plasma membrane. Taking advantage of this alteration, we hope to selectively deliver self-associated MAb nanoparticles to cancer cells while reducing their accumulation in normal cells. We hypothesized that self-associated MAb nanoparticles can be preferentially taken up by non-small lung cancer cells in comparison to normal cells due to the absence or dysfunction of tight junctions (TJ) in confluent cancer cells and increased permeability of the cancer cell membrane. Self-associated bevacizumab nanoparticles were prepared and characterized for particle size and biochemical stability. Fluorescence microscopy, TEM, and flow cytometry revealed that these bevacizumab nanoparticles were internalized by A549 cells three times more than MRC-5 cells. Macropinocytosis and energy-dependent pathways were elucidated to be involved in their uptake by A549 cells. Further, uptake was by nonspecific interaction with cell membrane. Results obtained from this study suggest that self-associated MAb nanoparticles can be selectively delivered to cancer cells.

[752]

TÍTULO / TITLE: - The Joint Effect of hOGG1, APE1, and ADPRT Polymorphisms and Cooking Oil Fumes on the Risk of Lung Adenocarcinoma in Chinese Non-Smoking Females.

RESUMEN / SUMMARY: - The human 8-oxoguanine DNA glycosylase 1 (hOGG1), apurinic/apyrimidinic endonuclease 1 (APE1), and adenosine diphosphate ribosyl transferase (ADPRT) genes play an important role in the DNA base excision...
repair pathway. Single nucleotide polymorphisms (SNPs) in critical genes are suspected to be associated with the risk of lung cancer. This study aimed to identify the association between the polymorphisms of hOGG1 Ser326Cys, APE1 Asp148Glu, and ADPRT Val762Ala, and the risk of lung adenocarcinoma in the non-smoking female population, and investigated the interaction between genetic polymorphisms and environmental exposure in lung adenocarcinoma. METHODS: We performed a hospital-based case-control study, including 410 lung adenocarcinoma patients and 410 cancer-free hospital control subjects who were matched for age. Each case and control was interviewed to collect information by well-trained interviewers. A total of 10 ml of venous blood was collected for genotype testing. Three polymorphisms were analyzed by the polymerase chain reaction-restriction fragment length polymorphism technique. RESULTS: We found that individuals who were homozygous for the variant hOGG1 326Cys/Cys showed a significantly increased risk of lung adenocarcinoma (OR = 1.54; 95% CI: 1.01-2.36; P = 0.045). When the combined effect of variant alleles was analyzed, we found an increased OR of 1.89 (95% CI: 1.24-2.88, P = 0.003) for lung adenocarcinoma individuals with more than one homozygous variant allele. In stratified analyses, we found that the OR for the gene-environment interaction between Ser/Cys and Cys/Cys genotypes of hOGG1 codon 326 and cooking oil fumes for the risk of lung adenocarcinoma was 1.37 (95% CI: 0.77-2.44; P = 0.279) and 2.79 (95% CI: 1.50-5.18; P = 0.001), respectively. CONCLUSIONS: The hOGG1 Ser326Cys polymorphism might be associated with the risk of lung adenocarcinoma in Chinese non-smoking females. Furthermore, there is a significant gene-environment association between cooking oil fumes and hOGG1 326 Cys/Cys genotype in lung adenocarcinoma among female non-smokers.

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**RESUMEN** / SUMMARY: - Enlace al Resumen / Link to its Summary


**AUTORES** / AUTHORS: - Bi H; Hou J; Zhang X; Zhang C; Yue L; Wen X; Liu D; Shi H; Yuan J; Liu J; Liu B

**INSTITUCIÓN** / INSTITUTION: - State Key Laboratory of Molecular Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100191, China.

**RESUMEN** / SUMMARY: - The exact influence of statins on gefitinib resistance in human non-small cell lung cancer (NSCLC) cells with KRAS mutation alone or KRAS/PI3CA and KRAS/PTEN comutations remains unclear. This work found that transfection of mutant KRAS plasmids significantly suppressed the gefitinib cytotoxicity in Calu3 cells (wild-type KRAS). Gefitinib disrupted the Kras/PI3K and Kras/Raf complexes in Calu3 cells,
whereas not in Calu3 KRAS mutant cells. These trends were corresponding to the expression of pAKT and pERK in gefitinib treatment. Atorvastatin (1 μM) plus gefitinib treatment inhibited proliferation, promoted cell apoptosis, and reduced the AKT activity in KRAS mutant NSCLC cells compared with gefitinib alone. Atorvastatin (5 μM) further enhanced the gefitinib cytotoxicity through concomitant inhibition of AKT and ERK activity. Atorvastatin could interrupt Kras/PI3K and Kras/Raf complexes, leading to suppression of AKT and ERK activity. Similar results were also obtained in comutant KRAS/PTEN or KRAS/PIK3CA NSCLC cells. Furthermore, mevalonate administration reversed the effects of atorvastatin on the Kras/Raf and Kras/PI3K complexes, as well as AKT and ERK activity in both A549 and Calu1 cells. The in vivo results were similar to those obtained in vitro. Therefore, mutant KRAS-mediated gefitinib insensitivity is mainly derived from failure to disrupt the Kras/Raf and Kras/PI3K complexes in KRAS mutant NSCLC cells. Atorvastatin overcomes gefitinib resistance in KRAS mutant NSCLC cells irrespective of PIK3CA and PTEN statuses through inhibition of HMG-CoA reductase-dependent disruption of the Kras/Raf and Kras/PI3K complexes.

[754]

**TÍTULO / TITLE:** miR-203 Inhibits Cell Proliferation and Migration of Lung Cancer Cells by Targeting PKCalpha.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Wang C; Wang X; Liang H; Wang T; Yan X; Cao M; Wang N; Zhang S; Zen K; Zhang C; Chen X

**INSTITUCIÓN / INSTITUTION:** Jiangsu Engineering Research Center for microRNA Biology and Biotechnology, State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, Jiangsu, China.

**RESUMEN / SUMMARY:** PKCalpha (protein kinase C alpha, PRKCA) is an important protein involved in several steps of signaling pathways in lung cancer, and microRNAs (miRNAs) have also been shown to participate in lung carcinogenesis. However, it is not clear how PKCalpha and miRNAs are correlated in the disease. In this report, we aimed to identify novel miRNAs that target PKCalpha and to study their biological function. Using bioinformatics analysis, we predicted one novel candidate, miR-203, and found differential expression patterns of miR-203 and PKCalpha in human lung cancer tissues. Moreover, we experimentally validated miR-203 as a direct regulator of PKCalpha. Finally, we demonstrated that the targeting of PKCalpha by miR-203 played a critical role in regulating cell proliferation, apoptosis and migration in lung cancer cells. In summary, this study identifies a novel miRNA that targets PKCalpha and
illustrates that the downregulation of PKCalpha by miR-203 modulates biological processes in lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hamalisto S; Pouwels J; de Franceschi N; Saari M; Ivarsson Y; Zimmermann P; Brech A; Stenmark H; Ivaska J
INSTITUCIÓN / INSTITUTION: - Center for Biotechnology, University of Turku, Turku, Finland.
RESUMEN / SUMMARY: - Recently, we demonstrated that integrin adhesion to the extracellular matrix at the cleavage furrow is essential for cytokinesis of adherent cells. Here, we report that tight junction protein ZO-1 (Zonula Occludens-1) is required for successful cytokinesis in NCI-H460 cells plated on fibronectin. This function of ZO-1 involves interaction with the cytoplasmic domain of alpha5-integrin to facilitate recruitment of active fibronectin-binding integrins to the base of the cleavage furrow. In the absence of ZO-1, or a functional ZO-1/alpha5beta1-integrin complex, proper actin-dependent constriction between daughter cells is impaired and cells fail cytokinesis. Super-resolution microscopy reveals that in ZO-1 depleted cells the furrow becomes delocalized from the matrix. We also show that PKCepsilon-dependent phosphorylation at Serine168 is required for ZO-1 localization to the furrow and successful cell division. Altogether, our results identify a novel regulatory pathway involving the interplay between ZO-1, alpha5-integrin and PKCepsilon in the late stages of mammalian cell division.

TÍTULO / TITLE: - Molecular Imaging of Nonsmall Cell Lung Carcinomas Expressing Active Mutant EGFR Kinase Using PET with [(124)I]-Morpholino-IPQA.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yeh SH; Lin CF; Kong FL; Wang HE; Hsieh YJ; Gelovani JG; Liu RS
INSTITUCIÓN / INSTITUTION: - National PET/Cyclotron Center, Department of Nuclear Medicine, Taipei Veterans General Hospital, Taiwan ; Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan ; Biophotonic and Molecular Imaging Research Center, National Yang-Ming University, Taipei, Taiwan ; Taiwan Mouse Clinic, National Comprehensive Mouse Phenotyping and Drug Testing Center, Taiwan.
RESUMEN / SUMMARY: Mutations in the kinase domain of epidermal growth factor receptor (EGFR) have high levels of basal receptor phosphorylation and are associated with clinical responsiveness to Iressa in patients with nonsmall cell lung cancer (NSCLC). This study aimed to assess the feasibility of morpholino-[(124)I]IPQA derivative as an in vivo PET imaging tool for the expression of different EGFR mutants in NSCLC. In vitro radiotracer accumulation and washout studies demonstrated a rapid accumulation and progressive retention after washout of morpholino-[(131)I]IPQA derivative in high EGFR-expressing H1299 NSCLC derivative cell lines (L858R and E746-A750 del cell lines), but not in EGFR-transfected H1299 cell line and vector-transfected H1299 cell line. Using the morpholino-[(124)I]IPQA derivative, we obtained noninvasive microPET images of EGFR activity in L858R and E746-A750 del subcutaneous tumor xenografts, but not in subcutaneous tumor xenografts grown form control cell line. Different EGFR mutant (activity) tumors have a different morpholino-[ ( *) I]IPQA derivative uptake. However, it still needs to modify the structure of IPQA to increase its water solubility and reduce hepatobiliary clearance. Morpholino-[(124)I]IPQA derivative may be a potential probe for selection of the candidate patients suffering from NSCLC for the small molecule tyrosine kinase inhibitor therapy (e.g., Iressa) in the future.

[759]

TÍTULO / TITLE: Synchronous left atrial myxoma and adenosquamous lung carcinoma.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Liu HC; Chen XF; Yu YM; Jiang GN

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China.

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[760]

TÍTULO / TITLE: Epithelial-mesenchymal transition leads to crizotinib resistance in H2228 lung cancer cells with EML4-ALK translocation.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Kim HR; Kim WS; Choi YJ; Choi CM; Rho JK; Lee JC

INSTITUCIÓN / INSTITUTION: Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Republic of Korea.

RESUMEN / SUMMARY: Epithelial-mesenchymal transition (EMT) is associated with reduced sensitivity to many chemotherapeutic drugs, including EGFR tyrosine kinase
inhibitors. Here, we investigated if this reduced sensitivity also contributes to resistance to crizotinib, an ALK inhibitor of lung cancer that exhibits the EML4-ALK translocation. We established a crizotinib-resistant subline (H2228/CR), which was derived from the parental H2228 cell line by long-term exposure to increasing concentrations of crizotinib. Characteristics associated with EMT, including morphology, EMT marker proteins, and cellular mobility, were analyzed. Compared with H2228 cells, the growth of H2228/CR cells was independent of EML4-ALK, and H2228/CR cells showed cross-resistance to TAE-684 (a second-generation ALK inhibitor). Phenotypic changes to the spindle-cell shape were noted in H2228/CR cells, which were accompanied by a decrease in E-cadherin and increase in vimentin and AXL. In addition, H2228/CR cells showed increased secretion and expression of TGF-beta1. Invasion and migration capabilities were dramatically increased in H2228/CR cells. Applying TGF-beta1 treatment to parental H2228 cells for 72 h induced reversible EMT, leading to crizotinib resistance, but this was reversed by the removal of TGF-beta1. Suppression of vimentin in H2228/CR cells by siRNA treatment restored sensitivity to crizotinib. Furthermore, these resistant cells remained highly sensitive to the Hsp90 inhibitors, similar to the parental H2228 cells. In conclusion, we suggest EMT is possibly involved in acquired resistance to crizotinib, and that HSP90 inhibitors could be a promising option for the treatment of EMT.
KRAS rules out ALK and EGFR, and KRAS may therefore form part of an efficient pathway in a testing algorithm. Currently, KRAS itself remains undruggable despite decades of effort, but attention has recently focused on inhibition of the Ras-contingent downstream signalling. Selumetinib (AZD6244; ARRY-142886) is an oral, tight-binding, uncompetitive inhibitor of mitogen-activated protein kinase kinases (MEK) 1 and 2, downstream of KRAS, with preclinical evidence of synergistic activity with docetaxel in KRAS-mutant cancers and currently in clinical development. The Ras/RAF/MEK/ERK pathway is frequently deregulated in cancer and a number of inhibitors that target this pathway are currently in clinical development. Recently, in a randomised, phase II trial selumetinib plus docetaxel has proven to improve progression free survival compared to docetaxel alone in previously treated patients with advanced KRAS-mutant NSCLC.

[762]
TÍTULO / TITLE: - Feasibility of complete video-assisted thoracoscopic surgery following neoadjuvant therapy for locally advanced non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Huang J; Xu X; Chen H; Yin W; Shao W; Xiong X; He J
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; ; Guangzhou Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, Guangzhou 510120, China.
RESUME N / SUMMARY: - OBJECTIVE: To explore the feasibility of complete video-assisted thoracoscopic surgery (c-VATS) following neoadjuvant therapy (chemotherapy, targeted therapy and radiotherapy, either alone or in combination) for the treatment of patients with non-small cell lung cancer (NSCLC). METHODS: The clinical data of 43 NSCLC patients undergoing c-VATS following neoadjuvant therapy were retrospectively analyzed, including the preoperative functional indicators, staging, concurrent diseases, surgical techniques, operation time, number of lymph nodes dissected and postoperative drainage time and quantity, postoperative hospital stay, postoperative complications, and survival. RESULTS: From January 2006 to March 2012, a total of 43 patients with stage II A-IIIB NSCLC were included in this study (IIIA: 27 cases, 62.8%; IIIB: 11 cases, 25.6%), including 32 males (74.4%) and 11 females (25.6%). Forty-two patients were operated successfully, 28 underwent pulmonary lobectomies (including 9 bronchial sleeve resections), 5 had double lobectomies, 5 had wedge resections, and 4 had total pneumonectomies. Seven patients were referred to undergo Hybrid VATS (7/42, 16.7%). The mean length of the operation was 160.48 +/- 16.52 min (range, 130-
180 min); the intraoperative blood loss was 253.57±/117.08 mL; the number of lymph nodes dissected was 16.88±/10.93; the postoperative drainage time was 1-7 d (mean: 2.62±/0.96 d); and the postoperative hospital stay was 3-7 d (mean: 5.45±/1.30 d). The incidence of postoperative complications was 9.5% (4/42), and the perioperative mortality was 2.4% (1/42). The 1-, 2-, and 3-year overall survival rates were 94%, 79%, and 65%, respectively. CONCLUSIONS: c-VATS following neoadjuvant therapy is safe and feasible for the treatment of locally advanced NSCLC.

[763]
TÍTULO / TITLE: - WT1 promotes cell proliferation in non-small cell lung cancer cell lines through up-regulating cyclin D1 and p-pRb in vitro and in vivo.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Xu C; Wu C; Xia Y; Zhong Z; Liu X; Xu J; Cui F; Chen B; Roe OD; Li A; Chen Y
INSTITUCIÓN / INSTITUTION: - Department of Cardiovascular Surgery, The First Affiliated Hospital of Soochow University, Soochow, Jiangsu, China.
RESUMEN / SUMMARY: - The Wilms’ tumor suppressor gene (WT1) has been identified as an oncogene in many malignant diseases such as leukaemia, breast cancer, mesothelioma and lung cancer. However, the role of WT1 in non-small-cell lung cancer (NSCLC) carcinogenesis remains unclear. In this study, we compared WT1 mRNA levels in NSCLC tissues with paired corresponding adjacent tissues and identified significantly higher expression in NSCLC specimens. Cell proliferation of three NSCLC cell lines positively correlated with WT1 expression; moreover, these associations were identified in both cell lines and a xenograft mouse model. Furthermore, we demonstrated that up-regulation of Cyclin D1 and the phosphorylated retinoblastoma protein (p-pRb) was mechanistically related to WT1 accelerating cells to S-phase. In conclusion, our findings demonstrated that WT1 is an oncogene and promotes NSCLC cell proliferation by up-regulating Cyclin D1 and p-pRb expression.

[764]
TÍTULO / TITLE: - The role of DNA methylation as biomarkers in the clinical management of lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fleischhacker M; Dietrich D; Liebenberg V; Field JK; Schmidt B
INSTITUCIÓN / INSTITUTION: Molecular Biology Laboratory, Schwerpunkt Pneumologie, Universitätsklinik und Poliklinik für Innere Medizin I, Universitätsklinikum Halle (Saale), Ernst-Grube-Str. 40, 06120 Halle/Saale, Germany. michael.fleischhacker@uk-halle.de.

RESUMEN / SUMMARY: It is now widely accepted that cancer is caused by complex interactions between genetic and epigenetic factors and the environment. Only in the last 20 years, DNA methylation has been recognized as an epigenetic mechanism, which plays a major role during the development and progression of cancers. Accordingly, DNA methylation profiling provides a useful source for biomarkers in distinct clinical questions; for example, risk stratification, diagnosis, staging, prognosis and therapy-response prediction. In the last 10 years, not only has an increase in the number of papers published on this subject been seen, but also an impressive technological advancement allowing for the highly sensitive and accurate quantification of DNA methylation biomarkers in challenging sample types. However, the development of a suitable biomarker with appropriate assay technology is not trivial. This is especially true for the choice of biomarkers used for the management of early diagnosis of lung cancer.

[765]

TÍTULO / TITLE: Low-dose CT scan screening for lung cancer: comparison of images and radiation doses between low-dose CT and follow-up standard diagnostic CT.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Ono K; Hiraoka T; Ono A; Komatsu E; Shigenaga T; Takaki H; Maeda T; Ogusu H; Yoshida S; Fukushima K; Kai M

INSTITUCIÓN / INSTITUTION: Faculty of Nursing at Higashigaoka, Tokyo Healthcare University, 2-5-1, Higashigaoka, Meguro, Tokyo, Japan.

RESUMEN / SUMMARY: OBJECTIVES: This study aim to compare image quality and radiation doses between low-dose CT and follow-up standard diagnostic CT for lung cancer screening. METHODS: In a single medical institution, 19 subjects who had been screened for lung cancer by low-dose CT before going through follow-up standard diagnostic CT were randomly selected. Both CT image sets for all subjects were independently evaluated by five specialized physicians. RESULTS: There were no significant differences between low-dose CT screening and follow-up standard diagnostic CT for lung cancer screening in all 11 criteria. The concordance rate for the diagnoses was approximately 80% (p < 0.001) for all categories. Agreement of the evaluation of all categories in the final diagnosis exceeded 94% (p < 0.001). Five physicians detecting and characterizing the pulmonary nodules did not recognized the difference between low-dose CT screening and follow-up standard diagnostic CT. With low-dose CT, the effective dose ranged between 1.3 and 3.4 mSv, whereas in the follow-up diagnostic CT, the effective dose ranged between 8.5 and 14.0 mSv.
CONCLUSION: This study suggests that low-dose CT can be effectively used as a follow-up standard diagnostic CT in place of standard-dose CT in order to reduce the radiation dose.

[766]

TÍTULO / TITLE: - Therapeutic pulmonary artery stenting for metastatic bronchial carcinoid.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - British Medical J (BMJ). %8?(3k+)]3s http://bmj.com/search.dtl
  ●● Enlace al texto completo (gratuito o de pago) 1136/bcr-2013-201123
AUTORES / AUTHORS: - Vawdrey DB; Fitzsimmons S; Veldtman GR; Carpenter JP
INSTITUCIÓN / INSTITUTION: - Wessex Cardiothoracic Centre, Southampton, UK.
RESUMEN / SUMMARY: - We present a case of a middle-aged man with a 3-month history of progressive shortness of breath and peripheral oedema. Ten years prior to this, he had undergone a left pneumonectomy for metastatic bronchial carcinoid. Clinical examination revealed significant right heart failure, supported by transthoracic echocardiography. CT pulmonary angiogram revealed the cause to be marked progression of the bronchial carcinoid causing severe external compression of right pulmonary artery (RPA). In view of the distressing symptoms, a palliative endovascular intervention to the RPA was attempted to relieve obstruction, improve blood flow through the right lung and offload the right ventricle. This was performed under general anaesthesia involving interventional cardiology and radiology specialists together with a specialist anaesthetic team with extensive experience of managing carcinoid patients. The result was a marked improvement in symptoms and right heart function and the patient was discharged 2 days later.

[767]

TÍTULO / TITLE: - Steroidal Cardiac Na+/K+ ATPase Inhibitors Exhibit Strong Anti-Cancer Potential in Vitro and in Prostate and Lung Cancer Xenografts in Vivo.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dimas K; Papadopoulou N; Baskakis C; Prousis KC; Tsakos M; Alkahtani S; Honisch S; Lang F; Calogeropoulou T; Alevizopoulos K; Stournaras C
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, University of Crete Medical School, GR-71110, Heraklion, Greece, Tel/Fax +302810 394563/394530. cstourn@med.uoc.gr.
RESUMEN / SUMMARY: - Sodium potassium pump (Na+/K+ ATPase) is a validated pharmacological target for the treatment of congestive heart failure. Recent data with inotropic drugs such as digoxin & digitoxin (digitalis) suggest a potent anti-cancer
action of these drugs and promote Na+/K+ ATPase as a novel therapeutic target in cancer. However, digitalis have narrow therapeutic indices, are pro-arrhythmic and are considered non-developable drugs by the pharmaceutical industry. On the contrary, a series of recently-developed steroidal inhibitors showed better pharmacological properties and clinical activities in cardiac patients. Their anti-cancer activity however, remained unknown. In this study, we synthesized seventeen steroidal cardiac inhibitors and explored for the first time their anti-cancer activity in vitro and in vivo. Our results indicate potent anti-cancer actions of steroidal cardiac inhibitors in multiple cell lines from different tumor panels including multi-drug resistant cells. Furthermore, the most potent compound identified in our studies, the 3-[*-3-pyrrolidinyl]oxime derivative 3, showed outstanding potencies (as measured by GI50, TGI and LC50 values) in most cells in vitro, was selectively cytotoxic in cancer versus normal cells showing a therapeutic index of 31.7 and exhibited significant tumor growth inhibition in prostate and lung xenografts in vivo. Collectively, our results suggest that previously described cardiac Na+/K+ ATPase inhibitors have potent anti-cancer actions and may thus constitute strong re-purposing candidates for further cancer drug development.

[768]

**TÍTULO / TITLE:** Silent rupture of aortic aneurysm mimicking lung malignancy.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Wijesinghe SN; Yasaratne BM; Madegedara RM

**INSTITUCIÓN / INSTITUTION:** Department of Radiology, Teaching Hospital, Kandy, Sri Lanka.

**RESUMEN / SUMMARY:** Extra-pulmonary diseases may mimic pulmonary lesions on chest radiography. We report a case of a silent rupture of an atherosclerotic thoracic aortic aneurysm with peripheral thrombus formation, that closely mimicked a complicated lung malignancy.

[769]

**TÍTULO / TITLE:** Cardiac involvement of lung cancer mimicking myocardial infarction.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Kardiol Pol. 2013;71(9):994. doi: 10.5603/KP.2013.0245

**AUTORES / AUTHORS:** Ciurus T; Maciejewski M; Lelonek M

**INSTITUCIÓN / INSTITUTION:** Medical University of Lodz. mlelonek@poczta.fm

[770]
TÍTULO / TITLE: - Respiratory epithelial adenomatoid hamartoma: a rare nasopharyngeal mass lesion.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Koc G; Altay C; Paker I; Sarsilmaz A; Erdogan N; Oyar O

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Ataturk Training and Research Hospital, 35140 Basinsitesi, Izmir, Turkey. ggulkoc@gmail.com.

RESUMEN / SUMMARY: - Respiratory epithelial adenomatoid hamartoma (REAH) is a rare and nonneoplastic lesion of upper respiratory tract characterized by an abnormal mixture of tissues which are peculiar to the involved anatomic region. The most common site reported is nasal cavity and its nasopharyngeal origin is extremely rare. The lesion can be confused with a variety of benign and malignant entities. In this article, we report a 22-year-old female case of REAH of posterior nasopharyngeal wall. The clinical and radiological features of the lesion are discussed in the light of literature data.

[771]

TÍTULO / TITLE: - Influence of erbanxiao solution on inhibiting angiogenesis in stasis toxin stagnation of non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Liu J; Liu Y

INSTITUCIÓN / INSTITUTION: - The First Clinical College of Nanjing University of Chinese Medicine, Nanjing 210029, China.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate the effects and mechanisms of Erbanxiao solution in inhibiting tumor angiogenesis. METHODS: We observed the effects and mechanisms of Chinese medicines on inhibiting tumor angiogenesis and studied the theories and results of treatment. Sixty patients with lung cancer were randomized into two groups (n = 30). Patients in the control group were given compound Kushen injection, and patients in the treatment group were given Erbanxiao solution. The effect of Erbanxiao solution on vascular endothelium growth factor (VEGF), basic fibroblast growth factor (bFGF), and tumor necrosis factor-alpha (TNF-alpha) was observed. RESULTS: The effective rate of the treatment group was 60% while the control group was 36%. There was a significant difference between the two groups (P < 0.05). VEGF, bFGF, and TNF-alpha levels of the two groups were significantly different before and after treatment (P < 0.01). These Traditional Chinese Medicines significantly inhibited tumor angiogenesis, possibly by changing levels of VEGF, bFGF, and TNF-alpha. CONCLUSION: It is necessary to further explore the
potential of Traditional Chinese Medicine in the treatment of angiogenesis in tumor patients.

[772]

TÍTULO / TITLE: Exophthalmos as a first manifestation of the systemic spread of small cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Obuchowska I; Pawluczuk B; Mariak Z
INSTITUCIÓN / INSTITUTION: Department of Ophthalmology, Medical University of Bialystok. iwonaobu@wp.pl
RESUMEN / SUMMARY: Small cell lung cancer is characterized by rapid growth and early metastases. The most frequent locations of the secondary lesions include adrenal glands, brain, liver, and skeleton. On initial diagnosis, up to 70% of patients with small cell lung cancer have metastases. Metastases to the eye or orbit developed approximately 0.7-12% of patients with lung cancer. Clinical signs and symptoms of orbital metastases may include exophthalmos, diplopia, pain, limited ocular motility, blurred vision, swollen eyelid, conjunctival hyperemia and edema, increased ocular pressure and papilledema. Here, we report a rare case of exophthalmos as the first manifestation of a metastatic tumor of orbit due to small cell lung cancer.

[773]

TÍTULO / TITLE: Pleuropulmonary blastoma.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Anand R; Narula MK; Chadha R; Chander J; Jain M
INSTITUCIÓN / INSTITUTION: Department of Radiodiagnosis, Lady Hardinge Medical College, New Delhi 110001.
RESUMEN / SUMMARY: Pleuropulmonary blastoma is a rare and aggressive malignant tumour that affects young children. A case of pleuropulmonary blastoma has been presented in a 9-year-old male child who was initially diagnosed and treated as pulmonary tuberculosis. Computed tomography of chest revealed a large heterogeneously enhancing mass with calcification in left hemithorax and left pleural effusion. The mass was seen to invade mediastinum and left hemidiaphragm. Thoracotomy revealed unresectable tumour involving both lobes of left lung with invasion of mediastinum and left hemidiaphragm. Biopsy confirmed type II pleuropulmonary blastoma and the child was treated with chemotherapy and radiotherapy.
TÍTULO / TITLE: NF-kappaB regulates mesenchymal transition for the induction of non-small cell lung cancer initiating cells.
RESUMEN / SUMMARY: The epithelial-to-mesenchymal transition (EMT) is a de-differentiation process that has been implicated in metastasis and the generation of cancer initiating cells (CICs) in solid tumors. To examine EMT in non-small cell lung cancer (NSCLC), we utilized a three dimensional (3D) cell culture system in which cells were co-stimulated with tumor necrosis factor alpha (TNF) and transforming growth factor beta (TGFbeta). NSCLC spheroid cultures display elevated expression of EMT master-switch transcription factors, TWIST1, SNAI1/Snail1, SNAI2/Slug and ZEB2/Sip1, and are highly invasive. Mesenchymal NSCLC cultures show CIC characteristics, displaying elevated expression of transcription factors KLF4, SOX2, POU5F1/Oct4, MYCN, and KIT. As a result, these putative CIC display a cancer “stem-like” phenotype by forming lung metastases under limiting cell dilution. The pleiotropic transcription factor, NF-kappaB, has been implicated in EMT and metastasis. Thus, we set out to develop a NSCLC model to further characterize the role of NF-kappaB activation in the development of CICs. Here, we demonstrate that induction of EMT in 3D cultures results in constitutive NF-kappaB activity. Furthermore, inhibition of NF-kappaB resulted in the loss of TWIST1, SNAI2, and ZEB2 induction, and a failure of cells to invade and metastasize. Our work indicates that NF-kappaB is required for NSCLC metastasis, in part, by transcriptionally upregulating master-switch transcription factors required for EMT.

[775] TÍTULO / TITLE: The HDAC inhibitor, MPT0E028, enhances erlotinib-induced cell death in EGFR-TKI-resistant NSCLC cells.
RESUMEN / SUMMARY: The HDAC inhibitor, MPT0E028, enhances erlotinib-induced cell death in EGFR-TKI-resistant NSCLC cells.
AUTORES / AUTHORS: Chen MC; Chen CH; Wang JC; Tsai AC; Liou JP; Pan SL; Teng CM
INSTITUCIÓN / INSTITUTION: Pharmacological Institute, College of Medicine, National Taiwan University, Taipei, Taiwan.
Epidermal growth factor receptor (EGFR), which promotes cell survival and division, is found at abnormally high levels on the surface of many cancer cell types, including many cases of non-small cell lung cancer. Erlotinib (Tarceva), an oral small-molecule tyrosine kinase inhibitor, is a so-called targeted drug that inhibits the tyrosine kinase domain of EGFR, and thus targets cancer cells with some specificity while doing less damage to normal cells. However, erlotinib resistance can occur, reducing the efficacy of this treatment. To develop more effective therapeutic interventions by overcoming this resistance problem, we combined the histone deacetylase inhibitor, MPT0E028, with erlotinib in an effort to increase their antitumor effects in erlotinib-resistant lung adenocarcinoma cells. This combined treatment yielded significant growth inhibition, induced the expression of apoptotic proteins (PARP, gammaH2AX, and caspase-3), increased the levels of acetylated histone H3, and showed synergistic effects in vitro and in vivo. These effects were independent of the mutation status of the genes encoding EGFR or K-Ras. MPT0E028 synergistically blocked key regulators of the EGFR/HER2 signaling pathways, attenuating multiple compensatory pathways (e.g., AKT, extracellular signal-regulated kinase, and c-MET). Our results indicate that this combination therapy might be a promising strategy for facilitating the effects of erlotinib monotherapy by activating various networks. Taken together, our data provide compelling evidence that MPT0E028 has the potential to improve the treatment of heterogeneous and drug-resistant tumors that cannot be controlled with single-target agents.

TÍTULO / TITLE: A synthetic curcumin derivative hydrazinobenzoylcurcumin induces autophagy in A549 lung cancer cells.
RESUMEN / SUMMARY: Abstract Context: Curcumin exhibits growth-suppressive activity against a variety of cancer cells, but low bioavailability restricts its application in chemotherapeutic trials. Nowadays, a growing number of curcumin derivatives or analogs are known, hoping to replace curcumin and circumvent this problem. Hydrazinobenzoylcurcumin (HBC) has been synthesized and identified as a potent inhibitor of cell proliferation in previous reports. Objective: This study presents a novel mechanism of cell autophagy induced by HBC in the human non-small lung epithelial carcinoma (A549) cells. Materials and methods: Cells were cultured and treated with HBC at different concentrations (10-80 μM) and at different time periods (1-24 h). Microscopic analysis was used to detect the morphology changes and autophagolysosomes of A549 cells. An acridine orange staining assay was conducted to
evaluate the autophagolysosomes and autophagic vacuoles was analyzed by monodansylcadaverine (MDC) and GFP-LC3 transfection analysis. Western blotting was used to assess the conversion of microtubule-associated protein light chain 3 (LC3). Results: HBC could induce A549 cells autophagolysosomes formation in a dose and time-dependent manner and the inhibitory rate of HBC (80 µM) on the viability of A549 cells reached 76.68 ± 5.81% after 24 h of treatment. Autophagic vacuoles increased in a concentration-dependent manner in HBC-treated cell. Furthermore, conversion of LC3-I to LC3-II, accumulation of GFP-tagged LC3 positive intracellular vacuoles and increased fusion of autophagosomes with lysosomes suggested the occurrence of autophagy. Conclusion: Our data indicate that HBC induced A549 cell autophagy, which is a novel cell death mechanism induced by curcumin derivatives.

TÍTULO / TITLE: - Characterization of indoor dust from Brazil and evaluation of the cytotoxicity in A549 lung cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Deschamps E; Weidler PG; Friedrich F; Weiss C; Diabate S

INSTITUCIÓN / INSTITUTION: - Environmental Agency Feam, Fumec University, Belo Horizonte, Brazil, deschamps.deschamps@gmail.com.

RESUMEN / SUMMARY: - Over the past decade, ambient air particulate matter (PM) has been clearly associated with adverse health effects. In Brazil, small and poor communities are exposed to indoor dust derived from both natural sources, identified as blowing soil dust, and anthropogenic particles from mining activities. This study investigates the physicochemical and mineralogical composition of indoor PM10 dust samples collected in Minas Gerais, Brazil, and evaluates its cytotoxicity and inflammatory potential. The mean PM10 mass concentration was 206 µg/m3. The high dust concentration in the interior of the residences is strongly related to blowing soil dust. The chemical and mineralogical compositions were determined by ICP-OES and XRD, and the most prominent minerals were clays, Fe-oxide, quartz, feldspars, Al(hydr)oxides, zeolites, and anatase, containing the transition metals Fe, Cr, V, Ni, Cu, Zn, Ti, and Mn as well as the metalloid As. The indoor dust samples presented a low water solubility of about 6 %. In vitro experiments were carried out with human lung alveolar carcinoma cells (A549) to study the toxicological effects. The influence of the PM10 dust samples on cell viability, intracellular formation of reactive oxygen species (ROS), and release of the pro-inflammatory cytokine IL-8 was analysed. The indoor dust showed little effects on alamarBlue reduction indicating unaltered mitochondrial activity. However, significant cell membrane damage, ROS production, and IL-8 release were detected in dependence of dose and time. This study will support the implementation of mitigation actions in the investigated area in Brazil.
CXCR4, but not CXCR7, discriminates metastatic behavior in non-small cell lung cancer cells.

Chemokines have been implicated as key contributors of non-small cell lung cancer (NSCLC) metastasis. However, the role of CXCR7, a recently discovered receptor for CXCL12 ligand, in the pathogenesis of NSCLC is unknown. To define the relative contribution of chemokine receptors to migration and metastasis we generated human lung A549 and H157 cell lines with stable knockdown of CXCR4, CXCR7, or both. Cancer cells exhibited chemotaxis to CXCL12 that was enhanced under hypoxic conditions, associated with a parallel induction of CXCR4, but not CXCR7. Interestingly, neither knockdown cell line differed in the rate of proliferation, apoptosis or cell adherence; however, in both cell lines, CXCL12-induced migration was abolished when CXCR4 signaling was abrogated. In contrast, inhibition of CXCR7 signaling did not alter cellular migration to CXCL12. In an in vivo heterotopic xenograft model using A549 cells, expression of CXCR4, but not CXCR7, on cancer cells was necessary for the development of metastases. In addition, cancer cells knocked-down for CXCR4 (or both CXCR4 and CXCR7) produced larger and more vascular tumors as compared to wild-type or CXCR7 knock-down tumors, an effect that was attributable to cancer cell-derived CXCR4 out competing endothelial cells for available CXCL12 in the tumor microenvironment. These results indicate that CXCR4, not CXCR7, expression engages CXCL12 to mediate NSCLC metastatic behavior. Implications: Targeting CXCR4-mediated migration and metastasis may be a viable therapeutic option in NSCLC.
Accumulating evidence indicates that epithelial-to-mesenchymal transition (EMT) might be a key event for cancer progression. The upregulation of Snail1, one of the most extensively studied EMT regulators, has been implicated in cancer metastasis, but the underlying mechanisms remain unclear. This study aims to identify that Snail1 targets regulating EMT-associated cancer cell migration. Human lung carcinoma A549 cells were treated with transforming growth factor beta 1 (TGF-beta1), and EMT-associated phenotypic and functional alterations were monitored. TGF-beta1 induced typical EMT-like morphological changes, ‘cadherin switching’ and cell migration in A549 cells. TGF-beta1 stimulation induced rapid and persistent upregulation of Snail1. Moreover, Snail1 upregulation was required for EMT-associated cell migration. Several metastasis suppressors with putative Snail1-binding sites in their promoters were dramatically repressed in A549 cells during TGF-beta1-induced EMT. Gain- and loss-of Snail1 function experiments demonstrated that scavenger receptor class A member 5 (SCARA5) was negatively regulated by Snail1. Importantly, SCARA5 downregulation was essential for EMT-induced migration in A549 cells. The chromatin immunoprecipitation assay revealed that Snail1 could bind to the E-box elements in SCARA5 promoter, implying that SCARA5 is a direct Snail1 target modulating cancer cell mobility during EMT. In addition, we showed that DNA methyltransferase 1 was physically associated with Snail1 to silence SCARA5 expression with an unidentified DNA methylation-independent mechanism, suggesting the complexity of Snail1-mediated epigenetic regulation. Collectively, our data demonstrated that EMT-regulator Snail1 suppresses the expression of SCARA5 to promote cancer progression, highlighting the possibility to target Snail1 and SCARA5 for cancer treatment.
intrinsic apoptotic pathway, associated with a strong NF-kappaB inhibition. In contrast, both Co-ASS and Co-EPM showed only a modest cytostatic activity against epithelioid MPM cells. Co-EPM induced an increase of senescent cells, while Co-ASS did not; the different outcomes were traced back to the organic (aspirin-like) portion of the molecule. Both Co-EPM and Co-ASS significantly reduced reactive oxygen/nitrogen species (ROS/RNS), and in turn nitrites, suggesting that the hexacarbonyldicobalt moiety may deliver CO within the cell, acting as a CO-releasing molecule (CO-RM). In perspective, Co-ASS would be better considered as a CO-NSAID agent (a CO-releasing molecule retaining the NSAID properties similar to NO- and H2S-NSAIDs) than as an antitumor drug candidate.

[781]

TÍTULO / TITLE: Interferon-beta Produces Synergistic Combinatory Anti-Tumor Effects with Cisplatin or Pemetrexed on Mesothelioma Cells.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Li Q; Kawamura K; Yang S; Okamoto S; Kobayashi H; Tada Y; Sekine I; Takiguchi Y; Shingyouji M; Tatsumi K; Shimada H; Hiroshima K; Tagawa M

INSTITUCIÓN / INSTITUTION: Division of Pathology and Cell Therapy, Chiba Cancer Center Research Institute, Chiba, Japan ; Department of Molecular Biology and Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan.

RESUMEN / SUMMARY: Interferons (IFNs) have been tested for the therapeutic effects in various types of malignancy, but mechanisms of the anti-tumors effects and the differential biological activities among IFN members are dependent on respective cell types. In this study, we examined growth inhibitory activities of type I and III IFNs on 5 kinds of human mesothelioma cells bearing wild-type p53 gene, and showed that type I IFNs but not type III IFNs decreased the cell viabilities. Moreover, growth inhibitory activities and up-regulated expression levels of the major histocompatibility complexes class I antigens were greater with IFN-beta than with IFN-alpha treatments. Cell cycle analyses demonstrated that type I IFNs increased S- and G2/M-phase populations, and subsequently sub-G1-phase fractions. The cell cycle changes were also greater with IFN-beta than IFN-alpha treatments, and these data collectively showed that IFN-beta had stronger biological activities than IFN-alpha in mesothelioma. Type I IFNs-treated cells increased p53 expression and the phosphorylation levels, and activated apoptotic pathways. A combinatory use of IFN-beta and cisplatin or pemetrexed, both of which are the current first-line chemotherapeutic agents for mesothelioma, produced synergistic anti-tumor effects, which were also evidenced by increased sub-G1-phase fractions. These data demonstrated firstly to our knowledge that IFN-beta produced
synergistic anti-tumor effects with cisplatin or pemetrexed on mesothelioma through up-regulated p53 expression.

[782]
TÍTULO / TITLE - CK2 Inhibitor CX-4945 Blocks TGF-beta1-Induced Epithelial-to-Mesenchymal Transition in A549 Human Lung Adenocarcinoma Cells.
RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS - Kim J
INSTITUCIÓN / INSTITUTION - Laboratory of Translational Therapeutics, Pharmacology Research Center, Division of Drug Discovery Research, Korea Research Institute of Chemical Technology, Yuseong-gu, Daejeon, Republic of Korea.
RESUMEN / SUMMARY - BACKGROUND: The epithelial-to-mesenchymal transition (EMT) is a major phenotype of cancer metastasis and invasion. As a druggable cancer target, the inhibition of protein kinase CK2 (formally named to casein kinase 2) has been suggested as a promising therapeutic strategy to treat EMT-controlled cancer metastasis. This study aimed to evaluate the effect of the CK2 inhibitor CX-4945 on the processes of cancer migration and invasion during the EMT in A549 human lung adenocarcinoma cells. MATERIALS AND METHODS: The effect of CX-4945 on TGF-beta1-induced EMT was evaluated in A549 cells treated with TGF-beta1 (5 ng/ml) and CX-4945. The effect of CX-4945 on TGF-beta1-induced cadherin switch and activation of key signaling molecules involved in Smad, non-Smad, Wnt and focal adhesion signaling pathways were investigated by Western blot analysis, immunocytochemistry and reporter assay. Additionally, the effect of CX-4945 on TGF-beta1-induced migration and invasion was investigated by wound healing assay, Boyden chamber assay, gelatin zymography, and the quantitative real-time PCR. RESULTS: CX-4945 inhibits the TGF-beta1-induced cadherin switch and the activation of key signaling molecules involved in Smad (Smad2/3, Twist and Snail), non-Smad (Akt and Erk), Wnt (beta-catenin) and focal adhesion signaling pathways (FAK, Src and paxillin) that cooperatively regulate the overall process of EMT. As a result, CX-4945 inhibits the migration and invasion of A549 cells accompanied with the downregulation of MMP-2 and 9. CONCLUSIONS: Clinical evaluation of CX-4945 in humans as a single agent in solid tumors and multiple myeloma has established its promising pharmacokinetic, pharmacodynamic, and safety profiles. Beyond regression of tumor mass, CX-4945 may be advanced as a new therapy for cancer metastasis and EMT-related disorders.

[783]
Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 7150/ijms.6538

Autores / Authors: Dong W; Qiu C; Shen H; Liu Q; Du J

Institución / Institution: 1. Institute of Oncology, Shandong Provincial Hospital affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan, 250021 P.R. China; ; 2. Department of Thoracic Surgery, Shandong Provincial Hospital affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan, 250021 P.R. China.

Resumen / Summary: Research in recent years has revealed that embryonic stem cells (ESCs) could generate obvious antitumor effects in both vitro and vivo. In vitro, ESCs could secrete soluble factors that are capable of blocking cancer cells proliferation, moreover, embryonic microenvironments could effectively inhibit tumorigenesis and metastasis; while in vivo, administration of ESCs in tumor-bearing mice could generate significant antitumor effects by indirectly activating the antitumor immune system. In this study, non-small cell lung cancer cells (Lewis Lung Carcinoma cells, LLCs) and ESCs were co-injected together into mice, after that subcutaneous tumor growth was monitored, cellular and humoral immune responses were detected, and different control groups were set to compare the results in different conditions. Our results suggested that compared to be injected alone, ESCs co-injected with cancer cells could inhibit cancer cell growth more efficiently in vivo, with more CD8+ lymphocytes generated in both peripheral circulation and spleen, and with higher serum anticancer cytokine level (interleukin (IL)-2 and interferon (IFN)-gamma). We conclude that the boosted antitumor effects induced by ESCs and cancer cells co-injection may be both the effects of antitumor factors secreted by ESCs and immune responses induced by ESCs in vivo.

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Resumen / Summary: Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0070672

Autores / Authors: Lam TK; Moore SC; Brinton LA; Smith L; Hollenbeck AR; Gierach GL; Friedman ND

Institución / Institution: Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland, United States of America.

Resumen / Summary: Worldwide, lung cancer in never-smokers is ranked the seventh most common cause of cancer death; however, the etiology of lung cancer in never-
smokers is unclear. We investigated associations for body mass index (BMI) at various ages, waist circumference, hip circumference, and physical activity with lung cancer in 158,415 never-smokers of the NIH-AARP Diet and Health Study. Multivariable hazard ratios (HR) and 95% confidence intervals (CI) were estimated from Cox proportional hazards models. Over 11 years of follow-up, 532 lung cancer cases occurred. The risk estimate for obese (BMI≥30 kg/m²) participants at baseline was 1.21 (95%CI = 0.95-1.53) relative to those with a normal BMI between 18.5<BMI<25.0. Overweight (25.0<BMI<30.0) at age 18 (HROverweight-vs-normal = 1.51;95%CI = 1.01-2.26) and time spent sitting (HRSitting-vs<3 hrs = 1.32;95%CI = 1.00-1.73) was each associated with lung cancer after adjustment for baseline BMI, as was waist (HRQ4-vs-Q1 = 1.75;95%CI = 1.09-2.79) and hip circumference (HRQ4-vs-Q1 = 0.62;95%CI = 0.39-0.99), after mutual adjustment for each other and baseline BMI. No associations were observed for vigorous activity or television watching. In summary, using a large prospective cohort study, we found no evidence that BMI at baseline or middle age was associated with decreased lung cancer risk in never smokers. If anything, we observed some evidence for positive associations with a larger BMI or waist circumference.

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[785]
TÍTULO / TITLE: - Expression of metallothionein and Nrf2 pathway genes in lung cancer and cancer-surrounding tissues.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Liang GY; Lu SX; Xu G; Liu XD; Li J; Zhang DS
RESUMEN / SUMMARY: - BACKGROUND: Nuclear factor (erythroid-derived 2)-like (Nrf2) and metallothionein have been implicated in carcinogenesis. This study investigated the expression of Nrf2 and of Nrf2-targeted genes (NQO1 and GCLC) and the genes for the metallothionein (MT) isoforms (MT-1ª and MT-2ª) in human lung cancer and cancer-surrounding tissues. METHODS: Surgically removed lung cancer samples (n = 80) and cancer-surrounding tissues (n = 38) were collected from Zunyi Medical College Hospital, China. Total RNA was extracted, purified, and used for real-time reverse transcription-PCR analysis of interested genes. RESULTS: Expression of the Nrf2-targeted genes NQO1 and GCLC tended to be higher (30 to 60%) in lung cancers, but was not significantly different from that in peri-cancer tissues. By contrast, expression of the genes for M)-1ª, MT-2ª, and the metal transcription factor MTF-1 were three-fold to four-fold lower in lung cancers. CONCLUSION: In surgical samples of lung cancer, MT expression was generally downregulated, whereas Nrf2 expression tended to be upregulated. These changes could play an integral role in lung carcinogenesis.

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[786]
**TÍTULO / TITLE:** Standardizing surgical treatment in malignant pleural mesothelioma.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Rice D

**INSTITUCIÓN / INSTITUTION:** University of Texas M.D. Anderson Cancer Center, Houston, TX, USA.

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**TÍTULO / TITLE:** Quantitative proteomic analysis of human lung tumor xenografts treated with the ectopic ATP synthase inhibitor citreoviridin.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Wu YH; Hu CW; Chien CW; Chen YJ; Huang HC; Juan HF

**INSTITUCIÓN / INSTITUTION:** Institute of Molecular and Cellular Biology, Department of Life Science, National Taiwan University, Taipei, Taiwan.

**RESUMEN / SUMMARY:** ATP synthase is present on the plasma membrane of several types of cancer cells. Citreoviridin, an ATP synthase inhibitor, selectively suppresses the proliferation and growth of lung cancer without affecting normal cells. However, the global effects of targeting ectopic ATP synthase in vivo have not been well defined. In this study, we performed quantitative proteomic analysis using isobaric tags for relative and absolute quantitation (iTRAQ) and provided a comprehensive insight into the complicated regulation by citreoviridin in a lung cancer xenograft model. With high reproducibility of the quantitation, we obtained quantitative proteomic profiling with 2,659 proteins identified. Bioinformatics analysis of the 141 differentially expressed proteins selected by their relative abundance revealed that citreoviridin induces alterations in the expression of glucose metabolism-related enzymes in lung cancer. The up-regulation of enzymes involved in gluconeogenesis and storage of glucose indicated that citreoviridin may reduce the glycolytic intermediates for macromolecule synthesis and inhibit cell proliferation. Using comprehensive proteomics, the results identify metabolic aspects that help explain the antitumorigenic effect of citreoviridin in lung cancer, which may lead to a better understanding of the links between metabolism and tumorigenesis in cancer therapy.

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**TÍTULO / TITLE:** Immunomodifiers in combination with conventional chemotherapy in small cell lung cancer: a phase II, randomized study.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 2147/DDDT.S43184

AUTORES / AUTHORS: - Zarogoulidis K; Ziogas E; Boutsikou E; Zarogoulidis P; Darwiche K; Kontakiotis T; Tsakiridis K; Porpodis K; Latsios D; Chatzizisi O; Karapantzos I; Li Q; Kyriazis G

INSTITUCIÓN / INSTITUTION: - Pulmonary Department, “G Papanikolaou” General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the effect of immunotherapy on response, survival, and certain immune markers in patients with small cell lung cancer (SCLC) who are receiving chemotherapy. PATIENTS AND METHODS: Patients with SCLC (n = 164) were assigned to receive either chemotherapy alone (group A) or a combination of chemotherapy and immunotherapy as follows: interferon alpha (IFN-alpha; 3 million IU) 3 times per week (group B); IFN-gamma (3 million IU) 3 times per week (group C); and IFN-alpha and IFN-gamma (1.5 million IU of each) 3 times per week (group D). Chemotherapy was the same for all groups and consisted of eight cycles with carboplatin 5.5 mg/m(2) intravenously on day 1, ifosfamide 3.5 mg/m(2) intravenously on day 1, and etoposide 200 mg/m(2) total dose taken orally on days 1 through 3, every 28 days. Patients completing chemotherapy were restaged, and those who were found to have limited disease received primary site and prophylactic cranial irradiation. Immunotherapy was continued throughout these treatments and during the follow-up period. Blood was taken before each course of chemotherapy and during follow-up to measure CD3+ lymphocytes, CD3+CD4+ lymphocytes, CD3+CD8+ lymphocytes, natural killer cells, and natural killer T cells. RESULTS: Differences in response and survival were not significantly different when all patients were considered. However, among patients with limited disease, Kaplan-Meier analysis disclosed a survival benefit for group B (P < 0.05). The analysis of immunologic measurements revealed that the improvement of immune markers was always accompanied by clinical improvement, whereas deterioration of all markers was accompanied by disease progression (result not statistically significant except for group C; P < 0.05). CONCLUSION: Among cytokines used in the study, only IFN-alpha seems to confer a survival benefit to patients with SCLC with limited disease. However, immunotherapy remains a challenge in the treatment of lung neoplasms and should be further explored.

[789]

TÍTULO / TITLE: - Clinical significance of incidental thyroid nodules identified on low-dose CT for lung cancer screening.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

BACKGROUND: Incidental thyroid nodules (ITNs) are defined as newly encountered nodules identified on imaging performed for an unrelated purpose. In practice, ITNs are often detected on chest computed tomography (CT). We investigated the prevalence and clinical significance of ITNs detected on low-dose chest CT (LDCT) for lung cancer screening.

METHODS: We retrospectively reviewed the electronic medical records of patients with no history of thyroid disease who underwent LDCT for lung cancer screening between March 2009 and February 2012 at Jeju National University Hospital (Korea).

RESULTS: Among 1,941 patients that underwent LDCT, 55 (2.8%) were found to have ITNs. Seven (12.7%) of those cases were malignant. The positive and negative predictive values of chest LDCT for the detection of incidental malignant thyroid nodules were 26.9% and 73.4%, respectively. Factors considered to be predictive of malignancy on LDCT were a mean attenuation value of 55 HU or more (p = 0.036) and the presence of dense calcifications (p = 0.048).

Sex, age, location of the nodule, longest diameter of the lesion, AP/T (anteroposterior/transverse dimension) ratio, margins, density, presence of punctate calcifications, and thyroid enlargement had no significant predictive value in discriminating benign and malignant nodules. On multivariate analyses, a mean attenuation value above 55 was the only statistically significant feature (p = 0.048).

CONCLUSIONS: A mean attenuation value greater than 55 HU on LDCT may be a useful predictive factor for differentiating malignant from benign lesions. Therefore, a careful assessment of the thyroid gland is necessary for patients undergoing LDCT for lung cancer screening.

TÍTULO / TITLE: Amrubicin: potential in combination with cisplatin or carboplatin to treat small-cell lung cancer.

RESUMEN / SUMMARY: Small-cell lung cancer (SCLC) is the most aggressive form of lung cancer characterized by early metastasis and high mortality. In recent years, monotherapy and combination therapy of amrubicin with cisplatin or carboplatin has been actively studied and shown promise for the treatment of extensive disease SCLC (ED-SCLC). In this article, we summarize clinical trials of both monotherapy and combination therapy with amrubicin conducted in Japan, the USA, and the European Union. The results suggest that the clinical outcome of amrubicin therapy may be
associated with genetic variations in patients. Further study of combination regimens in patients of different ethnicities is warranted.
In 2 of 22 (9%) dogs, VATS was converted to OT. All dogs survived to discharge from the hospital. There were no significant differences between the VATS and OT groups with regard to most variables. Surgery time was significantly longer for VATS than for OT (median, 120 vs 95 minutes, respectively). Conclusions and Clinical Relevance—In medium- to large-breed dogs, short-term outcomes for dogs that underwent VATS for lung lobectomy were comparable to those of dogs that underwent OT. Further studies are required to evaluate the effects of surgical approach on indices of postoperative pain and long-term outcomes.

[793]
TÍTULO / TITLE: - Multimodality therapy for malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Weder W; Opitz I
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.

[794]
TÍTULO / TITLE: - Radical pleurectomy and photodynamic therapy for malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Friedberg JS
INSTITUCIÓN / INSTITUTION: - University of Pennsylvania, Philadelphia, PA 19104, USA.

[795]
TÍTULO / TITLE: - The development of targeted therapy in small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang Y; He J
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou 510120, China.
RESUMEN / SUMMARY: - Small cell lung cancer (SCLC) is a highly aggressive cancer usually with distal metastasis and very poor prognosis. Chemotherapy is the treatment of choice for SCLC in all stages and an initial good response, but there is a high chance of disease relapse with an overall poor median survival for both stages. With increasing translational research and a better understanding of the molecular basis of cancer, a number of molecular targets have been identified in various preclinical studies. Targeted drugs have less toxicity than chemotherapy drugs, but no targeted agents have been approved for use in the treatment of SCLC patients to date. This review focuses on targeted therapies in SCLC.

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TÍTULO / TITLE: - Targeted therapy for squamous cell lung cancer.
RESUMEN / SUMMARY: - Enlace al texto completo (gratuito o de pago) 2217/lmt.12.40
AUTORES / AUTHORS: - Liao RG; Watanabe H; Meyerson M; Hammerman PS
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA ; Cancer Program, Broad Institute, Cambridge, MA, USA.
RESUMEN / SUMMARY: - Lung squamous cell carcinoma (SqCC) is the second most common subtype of non-small-cell lung cancer and leads to 40,000-50,000 deaths per year in the USA. Management of non-small-cell lung cancer has dramatically changed over the past decade with the introduction of targeted therapeutic agents for genotypically selected individuals with lung adenocarcinoma. These agents lead to improved outcomes, and it has now become the standard of care to perform routine molecular genotyping of lung adenocarcinomas. By contrast, progress in lung SqCC has been modest, and there has yet to be a successful demonstration of targeted therapy in this disease. Here, we review exciting work from ongoing genomic characterization and biomarker validation efforts that have nominated several likely therapeutic targets in lung SqCCs. These studies suggest that targeted therapies are likely to be successful in the treatment of lung SqCCs and should be further explored in both preclinical models and in clinical trials.

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TÍTULO / TITLE: - Advances in personalized therapy for lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kim ES; Pandya KJ
INSTITUCIÓN / INSTITUTION: - University of Rochester, James P. Wilmot Cancer Center, The Department of Medicine, 601 Elmwood Ave, Box 704, Rochester, NY 14642, USA +1 585 273 4150; eric_kim@urmc.rochester.edu.

RESUMEN / SUMMARY: - Introduction: Personalized medicine based on tumor characteristics is transforming the management of lung cancer. This review provides an overview of clinically approved strategies to personalize treatment for lung cancer as well as evolving strategies in various stages of clinical development. Areas covered: Selecting therapy based on various tumor characteristics such as histology and presence of specific molecular alterations will be covered. This review will only discuss the role of targeted agents in personalizing care for lung cancer but also the strategies to personalize traditional chemotherapeutic agents. Expert opinion: Advances in genomic medicine to identify key genetic alterations with subsequent development of matching targeted agents are rapidly changing the management of lung cancer. Being able to target key driver molecular aberrations is certainly exciting and clinically meaningful, but only for a limited period of time. Intratumoral heterogeneity is a major contributor to therapy resistance, a substantial roadblock to durable response. Better understanding of resistance mechanism is at least as important as identifying new targetable genetic changes to effectively advance personalized therapy for lung cancer. Finally, optimization of biopsy specimens and rigorous validation steps to ensure reliability of diagnostic methods would be critical in moving forward.

[798]


RESUMEN / SUMMARY: - Link to its Summary


AUTORES / AUTHORS: - Momparler RL

INSTITUCIÓN / INSTITUTION: - Departement de Pharmacologie, Centre de Recherche du CHU Sainte-Justine, Universite de Montreal, Montreal, QC, Canada.

RESUMEN / SUMMARY: - Epigenetic analysis shows that many genes that suppress malignancy are silenced by aberrant DNA methylation in lung cancer. Many of these genes are interesting targets for reactivation by the inhibitor of DNA methylation, decitabine (5-aza-2’-deoxycytidine, DAC). A pilot study on intense dose DAC showed promising results in patients with metastatic non-small cell lung cancer (NSCLC). However, subsequent clinical studies using low dose DAC were not very effective against NSCLC and interest in this therapy diminished. Recently, interesting responses were observed in a patient with NSCLC following treatment with a combination of the related inhibitor of DNA methylation, 5-azacytidine, and an inhibitor of histone deacetylation. This finding has generated a renewed interest in the epigenetic therapy
of lung cancer. Preclinical studies indicate that DAC has remarkable chemotherapeutic potential for tumor therapy. This epigenetic agent has a delayed and prolonged epigenetic action on tumor cells. This delayed action should be taken into consideration in the design and evaluation of clinical studies on DAC. Future research should be directed at finding the optimal dose-schedule of DAC for the treatment of NSCLC.

[799]

TÍTULO / TITLE - Bayesian inference supports a location and neighbour-dependent model of DNA methylation propagation at the MGMT gene promoter in lung tumours.

RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS - Bonello N; Sampson J; Burn J; Wilson IJ; McGrown G; Margison GP; Thorncroft M; Crossbie P; Povey AC; Santibanez-Koref M; Walters K

INSTITUCIÓN / INSTITUTION - School of Mathematics and Statistics, University of Sheffield, Sheffield S3 7RH, UK.

RESUMEN / SUMMARY - We exploit model-based Bayesian inference methodologies to analyse lung tumour-derived methylation data from a CpG island in the O6-methylguanine-DNA methyltransferase (MGMT) promoter. Interest is in modelling the changes in methylation patterns in a CpG island in the first exon of the promoter during lung tumour development. We propose four competils of methylation state propagation based on two mechanisms. The first is the location-dependence mechanism in which the probability of a gain or loss of methylation at a CpG within the promoter depends upon its location in the CpG sequence. The second mechanism is that of neighbour-dependence in which gain or loss of methylation at a CpG depends upon the methylation status of the immediately preceding CpG. Our data comprises the methylation status at 12 CpGs near the 5’ end of the CpG island in two lung tumour samples for both alleles of a nearby polymorphism. We use approximate Bayesian computation, a computationally intensive rejection-sampling algorithm to infer model parameters and compare models without the need to evaluate the likelihood function. We compare the four proposed models using two criteria: the approximate Bayes factors and the distribution of the Euclidean distance between the summary statistics of the observed and simulated datasets. Our model-based analysis demonstrates compelling evidence for both location and neighbour dependence in the process of aberrant DNA methylation of this MGMT promoter CpG island in lung tumours. We find equivocal evidence to support the hypothesis that the methylation patterns of the two alleles evolve independently.

$!998.95$! TATATAT - J Theor Biol
Background: To understand cartilage oligomeric matrix protein (COMP) mechanism network from human normal adjacent tissues to lung adenocarcinoma. METHODS: COMP complete different activated (all no positive correlation, Pearson CC < 0.25) and uncomplete (partly no positive correlation except COMP, Pearson CC < 0.25) network were identified in higher lung adenocarcinoma compared with lower human normal adjacent tissues from the corresponding COMP-stimulated (>/=0.25) or inhibited (Pearson CC</=0.25) overlapping molecules of Pearson correlation coefficient (CC) and GRNInfer, respectively. COMP complete different activated and inhibited (all no positive correlation, Pearson CC < 0.25) mechanisms networks of higher lung adenocarcinoma and lower human normal adjacent tissues were constructed by integration of Pearson CC, GRNInfer and GO. As visualized by integration of GO, KEGG, GenMAPP, BioCarta and Disease, we deduced COMP complete different activated and inhibited network in higher lung adenocarcinoma and lower human normal adjacent tissues. RESULTS: As visualized by GO, KEGG, GenMAPP, BioCarta and disease database integration, we proposed mainly that the mechanism and function of COMP complete different activated network in higher lung adenocarcinoma was involved in COMP activation with matrix-localized insulin-like factor coupling carboxypeptidase to metallopeptidase-induced proteolysis, whereas the corresponding inhibited network in lower human normal adjacent tissues participated in COMP inhibition with nucleus-localized vasculogenesis, B and T cell differentiation and neural endocrine factors coupling pyrophosphatase-mediated proteolysis. However, COMP complete different inhibited network in higher lung adenocarcinoma included COMP inhibition with nucleus-localized chromatin maintenance, licensing and assembly factors coupling phosphatase-inhibitor to cytokinesis regulators-mediated cell differentiation, whereas the corresponding activated network in lower human normal adjacent tissues contained COMP activation with cytoplasm-localized translation elongation factor coupling fucosyltransferase to ubiquitin-protein ligase-induced cell differentiation. CONCLUSION: COMP different
networks were verified not only by complete and uncomplete COMP activated or inhibited networks within human normal adjacent tissues or lung adenocarcinoma, but also by COMP activated and inhibited network between human normal adjacent tissues and lung adenocarcinoma.

[801]
**TÍTULO / TITLE:** - Bypass mechanisms of resistance to receptor tyrosine kinase inhibition in lung cancer.

**RESUMEN / SUMMARY:** - Receptor tyrosine kinases (RTKs) are activated by somatic genetic alterations in a subset of cancers, and such cancers are often sensitive to specific inhibitors of the activated kinase. Two well-established examples of this paradigm include lung cancers with either EGFR mutations or ALK translocations. In these cancers, inhibition of the corresponding RTK leads to suppression of key downstream signaling pathways, such as the PI3K (phosphatidylinositol 3-kinase)/AKT and MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal-regulated kinase) pathways, resulting in cell growth arrest and death. Despite the initial clinical efficacy of ALK (anaplastic lymphoma kinase) and EGFR (epidermal growth factor receptor) inhibitors in these cancers, resistance invariably develops, typically within 1 to 2 years. Over the past several years, multiple molecular mechanisms of resistance have been identified, and some common themes have emerged. One is the development of resistance mutations in the drug target that prevent the drug from effectively inhibiting the respective RTK. A second is activation of alternative RTKs that maintain the signaling of key downstream pathways despite sustained inhibition of the original drug target. Indeed, several different RTKs have been implicated in promoting resistance to EGFR and ALK inhibitors in both laboratory studies and patient samples. In this mini-review, we summarize the concepts underlying RTK-mediated resistance, the specific examples known to date, and the challenges of applying this knowledge to develop improved therapeutic strategies to prevent or overcome resistance.

[802]
**TÍTULO / TITLE:** - Small cell lung cancer-specific isoform of RE1-silencing transcription factor (REST) is regulated by neural-specific Ser/Arg repeat-related protein of 100 kDa (nSR100).
**RESUMEN / SUMMARY:** Small cell lung cancer (SCLC) is a highly malignant form of cancer, which originates from primitive neuroendocrine cells in the lung. SCLC cells express several autocrine neurotransmitters/neuropeptides and their respective receptors. Expression of these neuronal markers is frequently regulated by RE1-silencing transcription factor (REST). In SCLC cells, an SCLC-specific isoform of REST (sREST) is highly expressed while REST expression is undetectable, suggesting that the expression of sREST correlates with the pathogenesis of SCLC. Expression of sREST, which is derived through alternative splicing of REST, is abnormally regulated in SCLC cells, but the mechanism is unknown. Most recently, nSR100 (SRRM4) was described as an activator of REST alternative splicing. We now demonstrate that nSR100 is highly expressed in SCLC cells correlating with high sREST and low REST expression. Adhesion to the extracellular matrix (ECM) is thought to enhance tumorigenicity and confer resistance to apoptosis. Interestingly, nSR100 expression is enhanced in cells grown with ECM. Overexpression of REST caused repression of sREST and nSR100, the latter containing RE1-element controlled by REST. Culturing the SCLC cell line NCI-N417 cells with ECM also up-regulated RE1-containing gene, the voltage-gated calcium channel subunit. Inhibition of the PI3K/Akt/mTOR pathway by LY294002 induced nSR100 expression, while the specific MEK/ERK inhibitor U0126 inhibited nSR100 expression. Repressing nSR100 by siRNA effectively repressed sREST, and conversely increased REST in NCI-N417 cells. Taken together this report clarifies the ECM-dependent signaling pathway that impacts nSR100 expression and its regulation of alternative splicing in SCLC. Implications: The splicing factor nSR100 may be novel SCLC-specific biomarker as well as a therapeutic target.
Approximately 3-7% of non-small cell lung cancers harbor an anaplastic lymphoma kinase (ALK) gene fusion, constituting a new molecular subtype of lung cancer that responds to crizotinib, an ALK inhibitor. Although previous studies have evaluated ALK-rearranged lung cancers, the comprehensive analysis of lung cancer in Chinese has not well assessed. Herein, we identified 44 cases of ALK-rearranged samples by fluorescent in-situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription polymerase chain reaction (RT-PCR) in a large number of surgically resected lung cancers. All 44 ALK-rearranged lung cancers were adenocarcinomas, with 2 cases having additional focal squamous components. The goal was to analyse the clinicopathological features of ALK-rearranged lung adenocarcinomas. Our data showed that a cribriform structure, prominent extracellular mucus and any type of mucous cell pattern may be either sensitive or specific to predict an ALK rearrangement. We used FISH as the standard detection method. We compared the ALK rearrangement accuracy of FISH, RT-PCR and IHC. RT-PCR could define both the ALK fusion partner and the fusion variant, but seemed unable to detect all translocations involving the ALK gene. It is noteworthy that IHC using the D5F3 antibody (Cell Signaling Technology) showed higher sensitivity and specificity than the ALK1 antibody (Dako). Therefore, we conclude that IHC remains a cost-effective and efficient technique for diagnosing ALK rearrangements and that D5F3 can be the optimal screening antibody in clinical practice.

TÍTULO / TITLE: Serological investigation of the clinical significance of fascin in non-small-cell lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Teng Y; Xu S; Yue W; Ma L; Zhang L; Zhao X; Guo Y; Zhang C; Gu M; Wang Y

INSTITUCIÓN / INSTITUTION: Department of Cellular and Molecular Biology, Beijing TB and thoracic tumor research Institution/Beijing Chest Hospital, Capital Medical University, Beijing 101149, China.

RESUMEN / SUMMARY: OBJECTIVES: Fascin, a conserved actin bundling protein family member, is frequently up-regulated in various cancer types, including non-small-cell lung cancer (NSCLC), and it plays increasingly important roles in the progression of tumor invasion and metastasis. However, variations in the serum fascin level in tumor patients are usually neglected. MATERIALS AND METHODS: In the present study, serum samples from 501 stage I-IV NSCLC patients and 109 healthy volunteers were investigated by an enzyme-linked immunosorbent assay. RESULTS: The serum fascin level was markedly increased in the NSCLC patients (P<0.05), particularly in advanced
cases (P<0.01), compared with that in the healthy controls. We also found that the
serum fascin level was significantly correlated with female sex (P=0.02), non-smoking
status (P=0.044), and adenocarcinoma histology (P<0.001), with a higher positive rate
relative to each counterpart. Furthermore, our results suggested that the serum fascin
level reflects the aggressive progress of both lymphatic (P<0.001) and distant (P<0.001)
metastases in NSCLC. A survival analysis of 283 eligible patients who underwent a
follow-up examination after 3 years revealed that the patients in the serum fascin-
positive group had a significantly lower overall survival rate compared with those in
the negative group for 134 non-distant metastatic (stage M0) cases (P=0.044). A
subsequent Cox regression analysis revealed that the serum fascin level was an
independent prognostic factor for M0-stage NSCLC (univariate, P=0.001; multivariate,
P=0.038). CONCLUSION: Our study suggests that the serum fascin level is an
effective indicator of tumor aggressiveness, and that it plays an important role in the
prognosis of NSCLC, particularly for non-distant metastatic patients.

[805]
TÍTULO / TITLE: - Clinical development of S-1 for non-small cell lung cancer: a Japanese
perspective.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
10.1177/1758834013500702.
AUTORES / AUTHORS: - Takeda K
INSTITUCIÓN / INSTITUTION: - Department of Clinical Oncology, Osaka City General
Hospital, 2-13-22, Miyakoimahondori, Miyakojima-ku, Osaka, 534-0021, Japan.
RESUMEN / SUMMARY: - For more than a decade, S-1 has been investigated aggressively
against non-small cell lung cancer (NSCLC) in Japan. Recently, two randomized phase
III trials of S-1 combined with cisplatin (CDDP) or carboplatin (CBDCA) compared with
the standard platinum doublet chemotherapy were reported. S-1 and CDDP was
noninferior to CDDP and DTX in terms of overall survival (OS) (median survival time
[MST] 16.1 versus 17.1 months, respectively; hazard ratio [HR] 1.013; 96.4% confidence
interval [CI] 0.837-1.227). Noninferiority of S-1 and CBDCA compared with
CBDCA and paclitaxel was also confirmed for OS (MST 15.2 versus 13.3 months,
respectively; HR 0.928; 99.2% CI 0.671-1.283). The noninferiority design employed an
upper CI limit of HR<1.322 in the former trial and HR<1.33 in the latter. S-1 combined
with CDDP or CBDCA was thought to be one of the standard platinum doublet
regimens in the first-line setting for patients with advanced NSCLC in Japan. Some
additional interesting phase I and II studies have been published in Japan. They
include studies of S-1 as first-line chemotherapy when combined with nonplatinum
agents; as second-line chemotherapy; within chemoradiotherapy for locally advanced
This review will also describe the use of S-1 for the treatment of NSCLC in these settings.

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**TÍTULO / TITLE:** An unusual case of pleuropulmonary blastoma in a child with jejunal hamartomas.

**RESUMEN / SUMMARY:** We report a rare case of 9-month-old girl who presented with a choking episode and was found to have an incidental finding of a lung cyst and iron deficiency anemia leading to the diagnosis of pleuropulmonary blastoma (PPB) and a jejunal hamartoma. Our patient is the eighth that has been reported with the association of PPB with jejunal hamartoma and the first one in the radiological literature. PPB is the pulmonary analog of other dysontogenetic neoplasms in childhood. A biological sequence has been described with the three types of PPB to be interrelated as part of pathologic progression. PPB can be associated with other cysts and/or neoplasms in different organs. PPB is part of a hereditary neoplasia predisposition syndrome in up to 40% of cases. Mutations in DICER gene have been described with PPB. Hence, a pediatric patient diagnosed with PPB should be screened for associated conditions during childhood and adolescence including intestinal polyps. Obtaining family history for other neoplasms or cysts is important information that should raise the possibility of PPB in pediatric patients with cystic lung lesions. The presence of this syndrome should alert the clinician to screen and follow up patients and their relatives.

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**TÍTULO / TITLE:** Serum integrin-linked kinase (sILK) concentration and survival in non-small cell lung cancer: a pilot study.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Aug 27.

**AUTORES / AUTHORS:** - Posch F; Setinek U; Flores RM; Bernhard D; Hannigan GE; Mueller MR; Watzka SB

**INSTITUCIÓN / INSTITUTION:** - Division of Thoracic Surgery, Karl Landsteiner Institute for Thoracic Oncology, Otto Wagner Hospital, Sanatoriumstrasse 2, 1140, Vienna, Austria.
RESUMEN / SUMMARY: - BACKGROUND: Integrin-linked kinase (ILK) es un proteína de señalización intracelular críticamente involucrada en el crecimiento celular y la motilidad. En el cáncer de pulmón no de células pequeñas (NSCLC), la expresión aumentada de ILK se ha asociado con una supervivencia libre de recurrencias y en general disminuida. Recientemente, ILK ha sido detectado en el suero de pacientes con NSCLC. OBJETIVO: Evaluación del impacto pronóstico del concentrado sérico preoperatorio de ILK (sILK) sobre la supervivencia global en pacientes candidatos a cirugía. PATIENTS AND METHODS: El sILK se cuantificó por ELISA en 50 pacientes con NSCLC recién diagnosticados. Después de la cirugía, los pacientes fueron seguidos durante un intervalo medio de 2.5 años. RESULTOS: Los concentrados séricos de ILK variaron desde 0 a 2.44 ng/ml. La media del sILK fue alrededor de 2.3 veces más alta en los 16 pacientes que murieron en comparación con los 34 que sobrevivieron (1.04 vs. 0.45 ng/ml, p = 0.001). En el análisis de tiempo a evento univariado, la elevación del sILK se asoció con una supervivencia adversa [razón de riesgo (HR): 4.03, 95% IC: 2.00-8.13, p < 0.001]. Esta asociación prevaleció después del ajuste multivariado por varios parámetros clínicos, demográficos y laboratoriales (HR: 3.85, 95% IC: 1.53-9.72, p = 0.004). CONCLUSIONES: El suero ILK muestra potencial como un marcador pronóstico fuerte e independiente para la supervivencia postoperatoria en pacientes candidatos a cirugía.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Johnston B; Buchanan D; Papadopoulou C; Sandeman G; Lord H
INSTITUCIÓN / INSTITUTION: - Reader in Palliative Care, University of Dundee, School of Nursing and Midwifery, Dundee, Scotland, and Honorary Nurse Consultant (Palliative Care) NHS Tayside.
RESUMEN / SUMMARY: - Aim: The aim of this preliminary study was to evaluate the feasibility of conducting an effectiveness trial of early access to palliative care services for people with lung cancer through use of an integrated outpatient model. Methods: Newly diagnosed patients with lung cancer receiving palliative-intent treatment or best supportive care treatment were recruited over a 5-month period from one out-patient clinic in Scotland. Patients were offered a clinical review appointment with a palliative medicine consultant at two time points: baseline and 12 weeks later. Prior to each appointment patients completed three outcome measures addressing symptom severity, wellbeing, and health-care needs. One-to-one interviews were also conducted to explore patients’ experiences of being involved in the study. Results: Three patients participated in the study. The main reasons for low recruitment were patients’ deteriorating condition and unwillingness to undertake extra hospital visits. However, qualitative data indicated that the participants found this extra layer of supportive care useful in identifying and managing their needs, as well as enabling future planning. Conclusion: Further testing is needed to ascertain the feasibility of
conducting a trial of integrating early access to palliative care services into routine practice for people with lung cancer.

[809]

TÍTULO / TITLE: - Epidermal growth factor receptor mutation in lung adenocarcinoma in India: A single center study.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Doval DC; Azam S; Batra U; Choudhury KD; Talwar V; Gupta SK; Mehta A

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Research, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India ; Department of Research, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India.

RESUMEN / SUMMARY: - BACKGROUND: Adenocarcinoma, a subgroup of non-small cell lung cancer, is the most frequent form occurring in the non-smokers. Mutation in tyrosine kinase domain of epidermal growth factor receptor (EGFR) has been a common feature observed in lung adenocarcinoma. The study was carried out to detect the prevalence of EGFR mutation in lung adenocarcinoma. MATERIALS AND METHODS: EGFR mutation status in 166 lung adenocarcinoma patients was obtained retrospectively. Mutation tests were performed on paraffin embedded tissue blocks as a routine diagnostic procedure by polymerase chain reaction followed by direct nucleotide sequencing. Patient’s demographics and other clinical details were obtained from the medical records. RESULTS: EGFR mutation was detected in 43/166 (25.9%) patients. Gender wise mutation was observed as 18/55 (32.7%) in females and 25/111 (22.5%) in males. Overall, EGFR mutation was correlated with never smokers and distant metastasis (P < 0.05), but not associated with the gender, disease stage and pleural effusion. Exon 19 deletions were significantly correlated with females, never smokers, pleural effusion and distant metastasis (P < 0.05). However, point mutation on exon 21 did not show any statistical association with the above variables. Median overall survival was 22 months (95% confidence interval, 15.4-28.6). Female sex, EGFR mutation and absence of metastasis are associated with good prognosis.

CONCLUSION: EGFR mutation in lung adenocarcinoma was higher in never smokers, females and patients with distant metastasis. However, it was not linked with tobacco smoking. The prevalence of EGFR mutation observed is in range with the previously published reports from the Asian countries.

[810]

TÍTULO / TITLE: - Cardiac MRI Findings in a Dog with a Diffuse Pericardial Mesothelioma and Pericardial Effusion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gallach RG; Mai W
INSTITUCIÓN / INSTITUTION: - Radiology Section, School of Veterinary Medicine, Matthew J. Ryan Veterinary Hospital, University of Pennsylvania, Philadelphia, PA.
RESUMEN / SUMMARY: - Veterinary cardiac MRI (cMRI) is a relatively new technique. A dog with recurrent pericardial effusion and a questionable right atrial mass lesion on echocardiography underwent cMRI. cMRI provided excellent anatomic information about the heart and surrounding structures and helped to rule out the presence of a focal mass. A diffuse thickening and enhancement of the pericardium was detected. Pericardiectomy was performed and histopathology revealed a diffuse pericardial mesothelioma. This case illustrates the potential of cMRI in the management of patients with pericardial effusion when echocardiographic findings are equivocal and illustrates cMRI findings in a case of diffuse pericardial mesothelioma.

[811]

TÍTULO / TITLE: - Characterization of amplification patterns and target genes on the short arm of chromosome 7 in early-stage lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kang JU
INSTITUCIÓN / INSTITUTION: - Department of Biomedical Laboratory Science, Korea Nazarene University, Cheonan-si, Chungcheongnamdo 330-718, Republic of Korea.
RESUMEN / SUMMARY: - Chromosomal alterations are a predominant genomic force contributing to the development of lung adenocarcinoma (ADC). High density genomic arrays were conducted to identify critical genetic landmarks that may be important mediators in the formation or progression of early stage ADC. In this study, the most noteworthy and consistent observation was a copy number gain on the short arm of chromosome 7, which was detected in 85.7% (12/14) of cases. Notably, three distinct regions of amplification were identified between the 7p22.3 and q11.2 regions in 28.6% (4/14) of cases; at a size of 4.1 Mbp (7p22.3p21.1), 2.6 Mbp (7p15.2-p14.1) and 1.5 Mbp (7p12.3p11.2). Variations of the 7p11.2 locus that encodes EGFR are known to be oncogenic. Furthermore, potential target genes were identified that were previously not assumed to be involved in the pathogenesis of ADC, including CALM1P2 (7p11.2), HOXA4, HOXA5, HOXA6, HOXA7, HOXA9, HOXA10, HOXA11 and HOXA13 (7p15.2) and LOC442586, LOC442589, LOC442282, FAM20C and LOC442651 (7p22.3). The present study determined critical regions on the 7p arm of chromosome 7, which
were implicated in ADC. The pattern of rearrangements on the 7p arm may be a consequence of the high density of potential targets and the identified genes at the 7p regions may aid in the development of therapeutic targets for ADC.
BACKGROUND: The predictive value of thymidylate synthase (TYMS) to sensitivity to pemetrexed-based chemotherapy in advanced non-small cell lung cancer (NSCLC) patients is controversial. We conducted a meta-analysis of all relevant published data to assess the association of TYMS expression with the clinical outcomes of pemetrexed-based regimen in advanced NSCLC. PATIENTS AND METHODS: We conducted an electronic search using PubMed, Embase, OVID and Cochrane Library databases and manual search. Pooled odds ratio (OR) for the response rate and hazard ratio (HR) for the overall survival and progression free survival were calculated using the software Revman 5.0. RESULTS: There were 11 studies (n=798) met our criteria for evaluation. Response rate to pemetrexed-based regimen was significantly higher in patients with low/negative TYMS (OR=2.96, 95%CI [1.81, 4.86] P<0.0001). Patients with low/negative TYMS who were treated with pemetrexed-based regimen had longer progression free survival (HR 0.50, 95%CI [0.41, 0.61] P<0.00001) and overall survival (HR 0.41, 95%CI [0.22, 0.78] P=0.007) than those with high/positive TYMS. CONCLUSIONS: Low/negative TYMS expression was significantly associated with higher response rate, longer median survival and longer progression free survival for advanced NSCLC patients receiving pemetrexed-based chemotherapy. Hence, TYMS may be a potential predictor of sensitivity to pemetrexed-based chemotherapy in advanced NSCLC. Large scale prospective clinical trials are still warranted.

[814]

TÍTULO / TITLE: - Important recent insights into the genetics and biology of malignant pleural mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

REVISTA / JOURNAL: - Enlace al texto completo (gratuito o de pago) 3978/j.issn.2225-319X.2012.10.09

AUTORES / AUTHORS: - McMillan R; Zauderer M; Bott M; Ladanyi M

INSTIUTICIÓN / INSTITUTION: - Department of Pathology and Human Oncology & Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; -
Epigenetic aberrant methylation of tumor suppressor genes in small cell lung cancer.

Small cell lung cancer (SCLC), a special type of lung cancer, is reputed to carry a poor prognosis. The morbidity of SCLC is increasing in China and other countries. A variety of DNA alterations associated with non-small cell lung cancer (NSCLC) have been described. However, genetic and epigenetic changes of SCLC are not well established. Few studies have demonstrated that epigenetic silencing of key tumor suppressor genes (TSGs) is pivotal to initiation and development of SCLC.

Recently, promoter methylation of many TSGs have been identified in SCLC. These novel TSGs are potential tumor biomarkers for early diagnosis and prognostic prediction. Moreover, epigenetic promoter methylation of TSGs could be a target of intervention with a wide prospect of clinical application. This review summarizes recent studies on promoter methylation of TSGs in SCLC and aims to provide better understanding of the promoter methylation in tumorigenesis and progression of SCLC.

Combination of siRNA-directed Gene Silencing With Cisplatin Reverses Drug Resistance in Human Non-small Cell Lung Cancer.

One of the most challenging aspects of lung cancer therapy is the rapid acquisition of multidrug-resistant (MDR) phenotype. One effective approach would be to identify and downregulate resistance-causing genes in tumors using small interfering RNAs (siRNAs) to increase the sensitivity of tumor cells to chemotherapeutic challenge. After identifying the overexpressed resistance-related
antiapoptotic genes (survivin and bcl-2) in cisplatin-resistant cells, the siRNA sequences were designed and screened to select the most efficacious candidates. Modifications were introduced in them to minimize off-target effects. Subsequently, the combination of siRNA and cisplatin that gave the maximum synergy was identified in resistant cells. We then demonstrated that the combination treatment of the selected siRNAs and cisplatin encapsulated in CD44-targeting hyaluronic acid (HA)-based self-assembling nanosystems reversed the resistance to cisplatin and delayed the tumor growth significantly (growth inhibition increased from 30 to 60%) in cisplatin-resistant tumors. In addition, no abnormalities in body weights, liver enzyme levels or histopathology of liver/spleen tissues were observed in any of the treatment groups during the study period. Overall, we demonstrate that the combination of siRNA-mediated gene-silencing strategy with chemotherapeutic agents constitutes a valuable and safe approach for the treatment of MDR tumors.

Molecular Therapy-Nucleic Acids (2013) 2, e110; doi:10.1038/mtna.2013.29; published online 30 July 2013.

[817]

**TÍTULO / TITLE:** The Prognostic Value of SOX2 Expression in Non-Small Cell Lung Cancer: A Meta-Analysis.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Chen Y; Huang Y; Huang Y; Chen J; Wang S; Zhou J

**INSTITUCIÓN / INSTITUTION:** Department of Molecular Cell Biology and Toxicology, Jiangsu Key Lab of Cancer Biomarkers, Prevention & Treatment, Cancer Center; School of Public Health, Nanjing Medical University, Nanjing, Jiangsu Province, People’s Republic of China.

**RESUMEN / SUMMARY:** OBJECTIVE: To investigate the association of SOX2 expression in tumor with clinicopathological features and survival of non-small-cell lung carcinoma (NSCLC) patients. METHODS: Publications assessing the clinicopathological characteristics and prognostic significance of SOX2 in NSCLC were identified up to May 2013. A meta-analysis of eligible studies was performed using standard statistical methods to clarify the association between SOX2 expression and these clinical parameters. RESULTS: A total of eight studies met the inclusion criteria. Analysis of these data showed that SOX2 expression was positively associated with squamous histology, (pooled OR = 5.26, 95% CI: 1.08-25.6, P = 0.040). Simultaneously, we also found that SOX2 expression was positively associated with overall survival (pooled HR = 0.65, 95% CI: 0.47-0.89, P = 0.007, random-effect). CONCLUSIONS: SOX2 expression in tumor is a candidate positive prognostic biomarker for NSCLC patients.
- Diagnostic work-up and surgery in participants of the Gdansk lung cancer screening programme: the incidence of surgery for non-malignant conditions.

- OBJECTIVES: Low-dose computed tomography (LDCT) screening improves lung cancer prognosis but also results in diagnostic work-up and surgical treatment in many individuals without cancer. Therefore, we analysed the procedures that screening participants underwent to better understand the extent of overdiagnosis. METHODS: Between 2009 and 2011, 8649 healthy volunteers aged 50-75 years with a 20 pack-year smoking history underwent LDCT screening, of whom individuals with detected lung nodules had 2-years control. Participants with a nodule >10 mm in diameter or with suspected tumour morphology underwent diagnostic work-up: 283 (6%)/4694 (54%) screened participants had detected lung nodules. One hundred and four individuals underwent surgery, 27 underwent oncological treatment and 152 without a cancer diagnosis underwent further follow-up with LDCT. RESULTS: In 75% of participants accepted for diagnostic work-up and 25% of surgical patients, the procedures were unnecessary. In 70 (24.7%) participants, a specific diagnosis was obtained mainly due to the low efficacy of fine needle aspiration biopsy [sensitivity, 65.2%; negative predictive value (NPV), 95.9%] and bronchofiberoscopy (sensitivity, 71.4%; NPV, 50%) caused by overinterpretation of LDCT [positive predictive value (PPV), 2%]. Of 104 (36.7%) surgical patients, 43 (41.4%) had a preoperative cancer diagnosis, and 61 (58.6%) underwent surgery without pathological examination. In the latter group, intervention was justified in 35 (57.3%) patients. Complications occurred in 49 (17.3%) participants subjected to diagnostic work-up. In surgical patients, 67 (64.4%) malignant and 37 (35.6%) benign lesions were resected. In the latter group, intervention was justified in only 11 (29.7%) patients. No patient died because of diagnostic or treatment procedures during the study. The complication rate was 14.5% in the malignant and 10.8% in the benign groups. A neoplasm was found in 94 screening participants, of whom 67 (71.3%) underwent surgery; the remaining 27 (28.7%) patients were not surgical candidates. Adenocarcinoma accounted for 49/67 (73%) patients who underwent surgery for non-small-cell lung cancer (NSCLC); 56/67 (84%) patients had stage I NSCLC, and 26/67 (38%) underwent video-assisted thoracoscopic surgery lobectomy. CONCLUSIONS: Futile diagnostic work-ups and operations must be reduced before LDCT screening can be broadly used. Stage I adenocarcinoma dominated in the NSCLC patients who underwent surgery.
PURPOSE: The objective of this article was to estimate the social cost of respiratory cancer cases attributable to occupational risk factors in France in 2010. METHODS: According to the attributable fraction method and based on available epidemiological data from the literature, we estimated the number of respiratory cancer cases due to each identified risk factor. We used the cost-of-illness method with a prevalence-based approach. We took into account the direct and indirect costs. We estimated the cost of production losses due to morbidity (absenteeism and presenteeism) and mortality costs (years of production losses) in the market and nonmarket spheres. RESULTS: The social cost of lung, larynx, sinonasal and mesothelioma cancer caused by exposure to asbestos, chromium, diesel engine exhaust, paint, crystalline silica, wood and leather dust in France in 2010 were estimated at between 917 and 2,181 million euros. Between 795 and 2,011 million euros (87-92 %) of total costs were due to lung cancer alone. Asbestos was by far the risk factor representing the greatest cost to French society in 2010 at between 531 and 1,538 million euros (58-71 %), ahead of diesel engine exhaust, representing an estimated social cost of between 233 and 336 million euros, and crystalline silica (119-229 million euros). Indirect costs represented about 66 % of total costs. CONCLUSION: Our assessment shows the magnitude of the economic impact of occupational respiratory cancers. It allows comparisons between countries and provides valuable information for policy-makers responsible for defining public health priorities.
**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Institute of Jiangsu Province, Nanjing, China; The Fourth Clinical College of Nanjing Medical University, Nanjing, China.

**RESUMEN / SUMMARY:** - BACKGROUND: The correlation between xeroderma pigmentosum group D (XPD) polymorphisms (Lys751Gln and Asp312Asn) and clinical outcomes of non-small cell lung cancer (NSCLC) patients, who received platinum-based chemotherapy (Pt-chemotherapy), is still inconclusive. This meta-analysis was aimed to systematically review published evidence and ascertain the exact role of XPD polymorphisms. METHODS: Databases of MEDLINE and EMBASE were searched up to April 2013 to identify eligible studies. A rigorous quality assessment of eligible studies was conducted according the Newcastle-Ottawa Quality Assessment Scales. The relationship between XPD polymorphisms and response to Pt-chemotherapy and survival was analyzed. RESULTS: A total of 22 eligible studies were included and analyzed in this meta-analysis. The overall analysis suggested that the XPD Lys751Gln polymorphism was not associated with response to Pt-chemotherapy or survival. However, the XPD 312Asn allele was significantly associated with poor response to Pt-chemotherapy compared with the Asp312 allele (Asn vs. Asp: OR = 0.435, 95% CI: 0.261-0.726). Additionally, the variant genotype of XPD Asp312Asn polymorphism was associated with favorable survival in Caucasian (AspAsn vs. AspAsp: HR = 0.781, 95% CI: 0.619-0.986) but unfavorable survival in Asian (AspAsn+AsnAsn vs. AspAsp: HR = 1.550, 95% CI: 1.038-2.315). CONCLUSIONS: These results suggest that XPD Asp312Asn polymorphism may function as a predictive biomarker on platinum-based chemotherapy in NSCLC and further studies are warranted.

[821]

**TÍTULO / TITLE:** - Solitary fibrous tumor of the pleura: Ultrasonographic imaging findings of 3 cases.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Sekiya M; Yoshimi K; Muraki K; Suzuki K; Dambara T; Uekusa T; Takahashi K

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan. Electronic address: msekiya@juntendo.ac.jp.

**RESUMEN / SUMMARY:** - Solitary fibrous tumor (SFT) of the pleura is a rare tumor of mesenchymal origin. Although radiographic findings of thoracic computed tomography and magnetic resonance imaging in the evaluation of SFTs of the pleura have been documented, the value of ultrasonography is uncertain. We presented the ultrasonographic findings of 3 pathologically proven cases of SFTs arising from the
visceral pleura. In all the cases, thoracic ultrasonography demonstrated homogeneous, hypoechoic, hemicycle, extrapulmonary lesions, which showed respiratory movement with the adjacent lung, consistent with pedunculated tumors. Preoperative thoracic ultrasonography could be useful in the evaluation of patients with pleural tumors, especially SFTs.

[822]
TÍTULO / TITLE: - Fluorine-18 fluoro-2-deoxyglucose positron emission tomography/computed tomography in a case of suspected primary pericardial mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

[823]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

Nitric oxide (NO) found in the vicinity of lung cancer cells may play a role in the regulation of cancer cell behaviors. To explore the possible effects of NO on cell motility, human lung cancer cells were exposed to nontoxic concentrations of NO for 0-14 days, and the migratory characteristics of the cells were determined. The present study found that long-term treatment with NO significantly enhanced cell migration in a dose- and time-dependent manner. Furthermore, we found that the increased migratory action was associated with the increased expression of caveolin-1 (Cav-1), which in turn activated the focal adhesion kinase (FAK) and ATP-dependent tyrosine kinase (Akt) pathways. Notably, the NO-treated cells exhibited an increased number of filopodia per cell, as well as an increase in the levels of cell division cycle 42 (Cdc42) protein. Together, these results indicate that extended NO exposure has a novel effect on cell migration through a Cav-1-dependent mechanism, a finding that strengthens our understanding of cancer biology.
- Update on non-small cell lung cancer.

A study by Groth et al. (2013) identified the impact of insurance status on the delivery of definitive lobectomy for early-stage non-small cell lung cancer (NSCLC). One-fifth of an estimated 226,000 cases in 2012 presented with early-stage disease (Siegel, Naishadham, & Jemal, 2012). With appropriate therapy, five-year survival rates can exceed 65%, whereas, without prompt and aggressive intervention, five-year survival plummets to less than 5% (National Cancer Institute, 2010). Healthcare providers must offer access and optimal treatment to this patient population regardless of insurance status.

- Sleep, mood, and quality of life in patients receiving treatment for lung cancer.

Purpose/Objectives: To distinguish relationships among subjective and objective characteristics of sleep, mood, and quality of life (QOL) in patients receiving treatment for lung cancer. Design: Descriptive, correlational study. Setting: Two ambulatory oncology clinics. Sample: 35 patients with lung cancer. Methods: The following instruments were used to measure the variables of interest: Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Treatment-Lung (FACT-L), a sleep diary, and a motionlogger actigraph. Main Research Variables: Sleep, mood, and QOL. Findings: Significant differences were found between sleep diary and actigraph measures of
sleep efficiency (p = 0.002), sleep latency (p = 0.014), sleep duration (p < 0.001), and wake after sleep onset (p < 0.001). Poor sleepers (PSQI score greater than 5) were significantly different from good sleepers (PSQI score of 5 or lower) on sleep diary measures of sleep efficiency and sleep latency and the FACT-L lung cancer symptom subscale, but not on mood or actigraphy sleep measures. Conclusions: Although patients with lung cancer may report an overall acceptable sleep quality when assessed by a single question, those same patients may still have markedly increased sleep latencies or reduced total sleep time. The findings indicate the complexity of sleep disturbances in patients with lung cancer. Lung cancer symptoms had a stronger association with sleep than mood. Research using prospective methods will help to elucidate their clinical significance. Implications for Nursing: Patients receiving treatment for lung cancer are at an increased risk for sleep disturbances and would benefit from routine sleep assessment and management. In addition, assessment and management of common symptoms may improve sleep and, ultimately, QOL. Knowledge Translation: A high frequency of sleep disturbances in patients receiving treatment for lung cancer was evident, and poor sleepers had lower QOL. Sleep disturbances may be more related to lung cancer symptoms than anxiety or depression. Improving lung cancer symptoms such as dyspnea may improve sleep.
Affymetrix data from the JBR.1 adjuvant chemotherapy study were obtained from a public repository, normalised and mapped for CTAs. RESULTS: NY-ESO-1 was expressed in 50/199 (25%) samples. Expression of NY-ESO-1 in the NAC cohort was associated with significantly increased response rates (P = 0.03), but not overall survival. In the post-operative cohort, multivariate analyses identified NY-ESO-1 as an independent poor prognostic marker for those not treated with chemotherapy (HR 2.61, 95% CI 1.28-5.33; P = 0.008), whereas treatment with chemotherapy and expression of NY-ESO-1 was an independent predictor of improved survival (HR 0.267, 95% CI 0.07-0.980; P = 0.046). Similar findings for MAGE-A were seen, but did not meet statistical significance. Independent gene expression data from the JBR.10 dataset support these findings but were underpowered to demonstrate significant differences. There was no association between oncogenic mutations and CTA expression. CONCLUSIONS: NY-ESO-1 was predictive of increased response to neoadjuvant chemotherapy and benefit from adjuvant chemotherapy. Further studies investigating the relationship between these findings and immune mechanisms are warranted.

[827]

TÍTULO / TITLE: Suppression of respiratory papillomatosis with malignant transformation by erlotinib in a kidney transplant recipient.

RESUMEN / SUMMARY: A 52-year-old non-smoker and renal transplant recipient developed an incessant cough. A CT scan of the thorax revealed ill-defined hazy opacities in the right upper lung. He was diagnosed with non-tuberculosis Mycobacterium chelonae/abscessus infection based on sputum culture results. A trial of antibiotics initially resulted in some clinical improvement. A subsequent CT of the thorax documented worsening of the lesions in the right lung and new lesions on the left. An intratracheal growth was noted. Bronchoscopy with biopsy of the tracheal lesions documented respiratory papillomatosis with transformation to squamous cell cancer. Test for high-risk human papilloma virus was positive. Video-assisted thoracoscopic surgery biopsy with wedge resection of the left lower lobe revealed metastatic squamous cell lung cancer. He was treated with one ablation followed by four cycles of chemotherapy. He has been maintained on erlotinib ever since. There has been no recurrence of the cough or papillomas.
TÍTULO / TITLE: - Provider Continuity Prior to the Diagnosis of Advanced Lung Cancer and End-of-Life Care.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Sharma G; Wang Y; Graham JE; Kuo YF; Goodwin JS

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, United States of America.

RESUMEN / SUMMARY: - BACKGROUND: Little is known about the effect of provider continuity prior to the diagnosis of advanced lung cancer and end-of-life care.

METHODS: Retrospective analysis of 69,247 Medicare beneficiaries aged 67 years or older diagnosed with Stage IIIIB or IV lung cancer between January 1, 1993 and December 31, 2005 who died within two years of diagnosis. We examined visit patterns to a primary care physician (PCP) and/or any provider one year prior to the diagnosis of advanced lung cancer as measures of continuity of care. Outcome measures were hospitalization, ICU use and chemotherapy use during the last month of life, and hospice use during the last week of life. RESULTS: Seeing a PCP or any provider in the year prior to the diagnosis of advanced lung cancer increased the likelihood of hospitalization, ICU care, chemotherapy and hospice use during the end of life. Patients with 1-3, 4-7 or >7 visits to their PCP in the year prior to the diagnosis of lung cancer had 1.0 (reference), 1.08 (95% CI; 1.04-1.13), and 1.14 (95% CI; 1.08-1.19) odds of hospitalization during the last month of life, respectively. Odds of hospice use during the last week of life were higher in patients with visits to multiple PCPs (OR 1.10: 95% CI; 1.06-1.15) compared to those whose visits were all to the same PCP. CONCLUSION: Provider continuity in the year prior to the diagnosis of advanced lung cancer was not associated with lower use of aggressive care during end of life. Our study did not have information on patient preferences and result should be interpreted accordingly.

TÍTULO / TITLE: - Nicotinic acetylcholine receptors mediate lung cancer growth.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Improgo MR; Soll LG; Tapper AR; Gardner PD

INSTITUCIÓN / INSTITUTION: - Department of Psychiatry, Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School Worcester, MA, USA.
Ion channels modulate ion flux across cell membranes, activate signal transduction pathways, and influence cellular transport-vital biological functions that are inexorably linked to cellular processes that go awry during carcinogenesis. Indeed, deregulation of ion channel function has been implicated in cancer-related phenomena such as unrestrained cell proliferation and apoptotic evasion. As the prototype for ligand-gated ion channels, nicotinic acetylcholine receptors (nAChRs) have been extensively studied in the context of neuronal cells but accumulating evidence also indicate a role for nAChRs in carcinogenesis. Recently, variants in the nAChR genes CHRNA3, CHRNA5, and CHRNB4 have been implicated in nicotine dependence and lung cancer susceptibility. Here, we silenced the expression of these three genes to investigate their function in lung cancer. We show that these genes are necessary for the viability of small cell lung carcinomas (SCLC), the most aggressive type of lung cancer. Furthermore, we show that nicotine promotes SCLC cell viability whereas an alpha3beta4-selective antagonist, alpha-conotoxin AulB, inhibits it. Our findings posit a mechanism whereby signaling via alpha3/alpha5/beta4-containing nAChRs promotes lung carcinogenesis.

Atypical chemokine receptor D6 inhibits human non-small cell lung cancer growth by sequestration of chemokines.

Chemokines and their receptors have been shown to play a vital role in lung cancer progression. D6 is an atypical chemokine receptor which is able to internalize and degrade chemokines. To investigate the potential role of D6 in lung cancer, we established D6-overexpressing A549 lung cancer cell lines by the transfection of human D6 cDNA. Results showed that D6 inhibited the proliferation of cancer cells in vitro and tumorigenesis in vivo. We also determined chemokine levels in the supernatant and showed that a number of chemokines (CCL2/4/5) had significantly decreased protein levels in D6-overexpressing cells compared with the controls, whereas no significant changes in mRNA expression levels of these chemokines were detected. The cell cycle distribution and expression of certain growth factors and their receptors did not change in the D6-overexpressing cells compared with parental cells. Thus, our results suggest that D6 is a negative regulator of growth in lung cancer, mainly by the sequestration of specific chemokines.
TÍTULO / TITLE: miR-140 Suppresses Tumor Growth and Metastasis of Non-Small Cell Lung Cancer by Targeting Insulin-Like Growth Factor 1 Receptor.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Yuan Y; Shen Y; Xue L; Fan H

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: MicroRNAs (miRNAs) are a class of small noncoding RNA molecules that play important roles in carcinogenesis and tumor progression. In this study, we investigated the roles and mechanisms of miR-140 in human non-small cell lung cancer (NSCLC). We found that miR-140 is significantly downregulated in NSCLC tissues and cell lines. Both gain-of-function and loss-of-function studies demonstrated that miR-140 suppresses NSCLC cell proliferation, migration, and invasion in vitro. Importantly, overexpression of miR-140 effectively repressed tumor growth and metastasis in nude mouse models. Integrated analysis identified IGF1R as a direct and functional target of miR-140. Knockdown of IGF1R inhibited cell proliferation and invasion resembling that of miR-140 overexpression, while overexpression of IGF1R attenuated the function of miR-140 in NSCLC cells. Together, our results highlight the significance of miR-140 and IGF1R in the development and progression of NSCLC.

The expression of V-ATPase is associated with drug resistance and pathology of non-small-cell lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Lu Q; Lu S; Huang L; Wang T; Wan Y; Zhou CX; Zhang C; Zhang Z; Li X

RESUMEN / SUMMARY: OBJECTIVE: This article aims to investigate the expression of vacuolar-H + ATPase (V-ATPase) in non-small cell lung cancer (NSCLC) and its variations with pathological type and grade. Furthermore, to evaluate the chemotherapy drug sensitivity of different cancer tissues as well as its correlation with V-ATPase expression in NSCLC. METHODS: V-ATPase expression was examined in 92 NSCLC tissue samples using the immunohistochemical Envision method and immunofluorescence assay. The location of V-ATPase expression was observed by confocal laser scanning microscopy and the difference of its expression rate was evaluated. The sensitivity of cancer tissues to chemotherapy drug was examined using MTT assay and its correlation with the V-ATPase expression was tested in NSCLC by Spearman rank correlation analysis. RESULTS: V-ATPase expression was mainly localized in the cell
membrane and cytoplasm. The expression rate of V-ATPase was 71.43% in squamous cell lung cancer, significantly lower than that of the lung adenocarcinoma (83.72%, P = 0.000). In different pathological grades of squamous cell lung cancer, the expression rate of V-ATPase was 58.33% in grade II, significantly lower than that of the grade III (84.00%, P = 0.014). The expression rate of V-ATPase in grade II lung adenocarcinoma was 76.67%, significantly lower than that of the grade Iota adenocarcinoma (100.0%, P = 0.012). Correlation analysis showed that the sensitivity of NSCLC tissues to cyclophosphamide, gemcitabine, doxorubicin, paclitaxel and cisplatin was significantly correlated with the V-ATPase expression rate (P < 0.05). CONCLUSIONS: V-ATPase was overexpressed in NSCLC. The expression of V-ATPase was related to the pathological type and grade of cancer and was likely associated with chemotherapy drug resistance in NSCLC. Virtual slides: The virtual slide(s) for this article can be found here: diagnosticpathology.diagnomx.eu/vs/7515811511020000.

TÍTULO / TITLE: Can stereotactic ablative radiotherapy in early stage lung cancers produce comparable success as surgery?
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Shirvani SM; Chang JY; Roth JA
INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.

TÍTULO / TITLE: Spatiotemporal analysis of lung cancer incidence and case fatality in Villa Clara province, Cuba.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Batista NE; Anton OA
INSTITUCIÓN / INSTITUTION: Medical University of Villa Clara, Santa Clara, Cuba.
INTRODUCTION: Cancer has historically been a main cause of death in Cuba, with lung cancer the number one cause of cancer death in both sexes. Cancer morbidity and mortality rates are the basic measures of cancer impact in the community. Cancer mortality has been one of the major applications of geographic analysis and has made important progress in recent decades thanks to access to mortality statistics and to development and availability of geographic information systems. Cuba does not have a strong tradition of etiologic research using spatial analysis. High levels of lung cancer morbidity and mortality in Villa Clara and growing interest in spatial analysis as an epidemiologic tool motivated this study. OBJECTIVE: To identify spatial and/or spatiotemporal clusters of lung cancer morbidity and case fatality in the province of Villa Clara, and to demonstrate the value of cluster analysis as an epidemiologic tool. METHODS: Descriptive observational study based on administrative data, using the technique of space-time scan statistics. The study focused on new cases diagnosed in 2004 and case-fatality for those cases through 2009. Variables used were: cases diagnosed, deaths, date of diagnosis, date of death, municipality and Cartesian geocoding for each municipality. RESULTS: The study identified significant spatial and spatiotemporal clusters of greater than expected lung cancer incidence (municipalities of Encrucijada, Camajuani, Cifuentes, Sagua la Grande, Caibarien and Santa Clara) and case fatality (Encrucijada, Camajuani, Cifuentes, Sagua la Grande, Caibarien, Santa Clara, Placetas and Manicaragua). CONCLUSIONS: Although the results are not explanatory, the spatial and spatiotemporal patterns of excess lung cancer risk and case-fatality can support hypothesis generation for research and eventual interventions for targeted prevention and management.
mutation test was negative. After a multidisciplinary meeting, it was decided to start fetal lung maturation and cesarean section at 29 weeks gestation. The patient received two lines of chemotherapy and bone metastasis radiotherapy, but there was progression of the disease. An EML4-ALK translocation was identified in an additional genetic test. Crizotinib 250mg BID was started. The patient showed a progression-free survival of 9 months and died 19 months after lung adenocarcinoma was diagnosed.

[836]

**TÍTULO / TITLE**: Screening for EGFR and KRAS mutations in non-small cell lung carcinomas using DNA extraction by hydrothermal pressure coupled with PCR-based direct sequencing.

**RESUMEN / SUMMARY**: EGFR and KRAS mutations correlate with response to tyrosine kinase inhibitors in patients with non-small cell lung carcinoma (NSCLC). We reported a hydrothermal pressure method of simultaneous deparaffinization and lysis of formalin-fixed paraffin embedded (FFPE) tissue followed by conventional chaotropic salt column purification to obtain high quality DNA for mutation analysis using PCR-based direct sequencing. This study assessed the feasibility of using this method to screen for exons 18-21 of EGFR and exon 2 of KRAS gene mutations in surgical resection and core needle biopsy specimens from 251 NSCLC patients. EGFR mutations were identified in 140 (55.8%) NSCLC patients (118 in adenocarcinoma, 11 in squamous cell carcinoma, 7 in adenocarcinoma and 4 in NSCLC-not otherwise specified), including four novel substitutions (L718M, A743V, L815P, V819E). EGFR mutations were frequently present in female patients (72 of 113, 63.7%) and NSCLC with adenocarcinoma component (125/204, 61.3%) with statistical significance. Twenty-one patients had multiple mutations at different exons of EGFR, in which seventeen patients had deletions in exon 19. KRAS mutations were found in 18 (7.2%) patients (15 in adenocarcinoma, 2 in squamous cell carcinoma and one in NSCLC-not otherwise specified), including an uncommon substitution G13C. Deparaffinization and lysis by hydrothermal pressure, coupled with purification and PCR-based sequencing, provides a robust screening approach for EGFR and KRAS mutation analysis of FFPE tissues from either surgical resection or core needle biopsy in clinical personalized management of lung cancer.

[837]

**TÍTULO / TITLE**: Detecting the somatic mutations spectrum of Chinese lung cancer by analyzing the whole mitochondrial DNA genomes.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Fang Y; Huang J; Zhang J; Wang J; Qiao F; Chen HM; Hong ZP

INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology and.

RESUMEN / SUMMARY: - Abstract To detect the somatic mutations and character its spectrum in Chinese lung cancer patients. In this study, we sequenced the whole mitochondrial DNA (mtDNA) genomes for 10 lung cancer patients including the primary cancerous, matched paracancerous normal and distant normal tissues. By analyzing the 30 whole mtDNA genomes, eight somatic mutations were identified from five patients investigated, which were confirmed with the cloning and sequencing of the somatic mutations. Five of the somatic mutations were detected among control region and the rests were found at the coding region. Heterogeneity was the main character of the somatic mutations in Chinese lung cancer patients. Further potential disease-related screening showed that, except the C deletion at position 309 showed AD-weakly associated, most of them were not disease-related. Although the role of aforementioned somatic mutations was unknown, however, considering the relative higher frequency of somatic mutations among the whole mtDNA genomes, it hints that detecting the somatic mutation(s) from the whole mtDNA genomes can serve as a useful tool for the Chinese lung cancer diagnostic to some extent.

TÍTULO / TITLE: - The CD44(high) Tumorigenic Subsets in Lung Cancer Biospecimens Are Enriched for Low miR-34a Expression.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Basak SK; Veena MS; Oh S; Lai C; Vangala S; Elashoff D; Fishbein MC; Sharma S; Rao NP; Rao D; Phan R; Srivatsan ES; Batra RK

INSTITUCIÓN / INSTITUTION: - Wadsworth Stem Cell Institute, Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS), Los Angeles, California, United States of America; Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America.

RESUMEN / SUMMARY: - Cellular heterogeneity is an integral part of cancer development and progression. Progression can be associated with emergence of cells that exhibit high phenotypic plasticity (including “de-differentiation” to primitive developmental states), and aggressive behavioral properties (including high tumorigenic potentials). We observed that many biomarkers that are used to identify Cancer Stem Cells (CSC) can label cell subsets in an advanced clinical stage of lung cancer (malignant pleural effusions, or MPE). Thus, CSC-biomarkers may be useful for live sorting functionally
distinct cell subsets from individual tumors, which may enable investigators to hone in on the molecular basis for functional heterogeneity. We demonstrate that the CD44(hi) (CD44-high) cancer cell subsets display higher clonal, colony forming potential than CD44(lo) cells (n = 3) and are also tumorigenic (n = 2/2) when transplanted in mouse xenograft model. The CD44(hi) subsets express different levels of embryonal (de-differentiation) markers or chromatin regulators. In archived lung cancer tissues, ALDH markers co-localize more with CD44 in squamous cell carcinoma (n = 5/7) than Adeno Carcinoma (n = 1/12). MPE cancer cells and a lung cancer cell line (NCI-H-2122) exhibit chromosomal abnormalities and 1p36 deletion (n = 3). Since miR-34a maps to the 1p36 deletion site, low miR-34a expression levels were detected in these cells. The colony forming efficiency of CD44(hi) cells, characteristic property of CSC, can be inhibited by mir-34a replacement in these samples. In addition the highly tumorigenic CD44(hi) cells are enriched for cells in the G2 phase of cell cycle.

[839]

TÍTULO / TITLE: - The brain microenvironment negatively regulates miRNA-768-3p to promote K-ras expression and lung cancer metastasis.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Subramani A; Alsidawi S; Jagannathan S; Sumita K; Sasaki AT; Aronow B; Warnick RE; Lawler S; Driscoll JJ

INSTITUCIÓN / INSTITUTION: - 1] Division of Hematology and Oncology, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0508, USA [2] The Vontz Center for Molecular Studies, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0508, Cincinnati, OH 45267-0508, USA [3].

RESUMEN / SUMMARY: - The brain microenvironment promotes metastasis through mechanisms that remain elusive. Co-culture of lung cancer cells with astrocytes - the most abundant cell type within the metastatic brain niche - lead to downregulation of miRNA-768-3p which drives K-ras expression and key signaling pathways, enhances cell viability and promotes chemotherapeutic resistance. Vector-based forced expression of miRNA-768-3p complementary sequence or a chemically-engineered miRNA-768-3p inhibitor recapitulated the astrocyte effect to increase tumor cell viability. The miRNA-768-3p inhibitor targeted the K-ras 3’-UTR as demonstrated by increased luminescence from a luciferase reporter and strikingly increased the K-ras protein and the downstream effectors ERK1/2 and B-Raf. miRNA-768-3p was reduced in patient brain metastases compared to normal brain tissue and was lower in patient tissue from brain metastases compared to same-patient primary tumour tissue. The brain microenvironment negatively regulates miRNA-768-3p to enhance K-ras and promote metastasis. We propose that therapeutic replacement of the metastasis suppressor miRNA-768-3p holds clinical promise.
Histogenesis of pulmonary sclerosing hemangioma and significance of P63 expression.

**RESUMEN / SUMMARY:**

Objective: To investigate the histogenesis and the significance of expression of P63 in pulmonary sclerosing hemangioma (SH). Methods: Eighteen cases of SH were retrospectively studied and P63, SPB, TTF-1, EMA, CKpan, Vimentin, SMA, CgA, Syn and CD34 were immunohistochemically labeled with EnVision method. Results: There are mainly four types of structures in SH tissue: solid, papillary, angiomatous (hemorrhagic), and sclerotic pattern; the tumor cells are composed mainly of two types of cells: cuboidal tumor cells and polygonal cells. The immunohistochemistry showed that cuboidal tumor cells expressed P63 (+++) in 16 cases of SH (16/18 cases). Polygonal cells and cuboidal cells of all cases express both TTF-1 and EMA at the same time (18/18 cases); cuboidal tumor cells express SPB (18/18 cases); polygonal tumor cells express vimentin (18/18 cases). In one case, a polygonal tumor cell weakly expressed CgA and Syn. Conclusion: The P63 positive cuboidal tumor cells may be pluripotent original respiratory epithelial cells, with multidirectional differentiation capacity. Immunohistochemically labeling of P63 may have important value for SH diagnosis.
cancer cell lines. The treatment of low E-cadherin lung cancer cell lines with histone deacetylase inhibitor (HDACi, MS-275) resulted in the preferential expression of the correctly spliced transcripts in the low E-cadherin expressing cell lines only. Chromatin immunoprecipitation (ChIP) assays revealed that the histone hypoacetylation levels correlate with aberrant exon 11 splicing as there is more aberrant splicing in cell lines with E-cadherin promoter hypoacetylation. Inactivation of histone deacetylases (HDAC) 1, 2 and 3 resulted in an increase in E-cadherin expression and an increase in the ratio of the correctly spliced E-cadherin transcript. As transcription of the gene is closely linked to splicing, we considered the possibility that change in E-cadherin transcription correlates with splicing. The Zeb1 epithelial-mesenchymal transformation (EMT) inducer silences E-cadherin expression and could also alter the splicing of this exon. Inhibition of the E-cadherin promoter transcription with Zeb1 expression increases aberrant splicing and the reverse is observed when Zeb1 is knocked down. The role of HDAC inhibitors was also studied in vivo in a immunodecient mouse xenograft model. Exposure of mice to HDACi resulted in growth inhibition, increase in E-cadherin expression, alteration of aberrant splicing and the reversal of EMT in mouse tumors. The findings support the modulation of E-cadherin exon 11 inclusion or exclusion by histone epigenetic modifications as they change the overall chromatin structure. The results provide an interesting link between epigenetic alterations in cancer cells and gene splicing in addition to their effect on gene silencing.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Zheng L; Zhang W; Jiang M; Zhang H; Xiong F; Yu Y; Chen M; Zhou J; Dai X; Tang Y; Jiang M; Wang M; Cheng G; Yu W; Lin B; Fu H; Zhang X

INSTITUCIÓN / INSTITUTION: - College of Basic Medicine and School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210029, China.

RESUMEN / SUMMARY: - Many traditional Chinese medicine (TCM) formulae have been used in cancer therapy. The JIN formula is an ancient herbal formula recorded in the classic TCM book Jin Kui Yao Lue (Golden Chamber). The JIN formula significantly delayed the growth of subcutaneous human H460 xenografted tumors in vivo compared with the growth of mock controls. Gene array analysis of signal transduction in cancer showed that the JIN formula acted on multiple targets such as the mitogen-activated protein kinase, hedgehog, and Wnt signaling pathways. The coformula treatment of JIN and diamminedichloroplatinum (DDP) affected the stress/heat shock pathway. Proteomic analysis showed 36 and 84 differentially expressed proteins
between the mock and DDP groups and between the mock and JIN groups, respectively. GoMiner analysis revealed that the differentially expressed proteins between the JIN and mock groups were enriched during cellular metabolic processes, and so forth. The ones between the DDP and mock groups were enriched during protein-DNA complex assembly, and so forth. Most downregulated proteins in the JIN group were heat shock proteins (HSPs) such as HSP90AA1 and HSPA1B, which could be used as markers to monitor responses to the JIN formula therapy. The mechanism of action of the JIN formula on HSP proteins warrants further investigation.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Li X; Feng Y; Liu J; Feng X; Zhou K; Tang X
INSTITUCIÓN / INSTITUTION: Institute of Biochemistry and Molecular Biology, Guangdong Medical College, Zhanjiang, China.
RESUMEN / SUMMARY: Background/Aims: Numerous studies have shown that epigallocatechin-3-gallate (EGCG), a polyphenol component extracted from green tea, can inhibit the growth and induce apoptosis of various types of human tumor cells. In this study, we evaluated the inhibitory effects of EGCG on the proangiogenic capabilities of A549 cells. Methods: A549 cells starved in serum-free culture medium for 24 h were pretreated with EGCG at various concentrations (0, 10, 25, 50, and 100 mumol/l) for 1 h, followed by the addition of insulin-like growth factor-I (IGF-I) at the final concentration of 40 ng/ml and continued culturing for an additional 16 h. The in vitro angiogenesis analyzing test kit with ECMatrix gel was used to detect the formation of capillary tube-like structures. The mRNA expression of hypoxia-inducible factor-1alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) was determined by real-time PCR. The protein expression of HIF-1alpha and VEGF was detected by Western blotting and ELISA, respectively. Results: EGCG significantly inhibited the formation of capillary tube-like structures on the surface of ECMatrix induced by IGF-I both in vitro and in vivo and reduced the level of hemoglobin in Matrigel plugs. In addition, EGCG was shown to significantly inhibit the IGF-I-induced upregulation of HIF-1alpha protein expression. Meanwhile, EGCG at the concentration of 25 and 100 mumol/l exhibited obvious inhibitory effects on IGF-I-induced VEGF expression (p < 0.01). Conclusion: Our results suggest that EGCG has potent inhibitory effects on tumor angiogenesis induced by IGF-I in human non-small cell lung cancer cells, which may possibly contribute to the downregulation of HIF-1alpha and VEGF expression. © 2013 S. Karger AG, Basel.
High-dose accelerated hypofractionated three-dimensional conformal radiotherapy (at 3 Gy/fraction) with concurrent vinorelbine and carboplatin chemotherapy in locally advanced non-small-cell lung cancer: a feasibility study.

BACKGROUND: Increasing the radiotherapy dose can result in improved local control for non-small-cell lung cancer (NSCLC) and can thereby improve survival. Accelerated hypofractionated radiotherapy can expose tumors to a high dose of radiation in a short period of time, but the optimal treatment regimen remains unclear. The purpose of this study was to evaluate the feasibility of utilizing high-dose accelerated hypofractionated three-dimensional conformal radiotherapy (at 3 Gy/fraction) with concurrent vinorelbine (NVB) and carboplatin (CBP) chemotherapy for the treatment of local advanced NSCLC.

METHODS: Untreated patients with unresectable stage IIIA/IIIB NSCLC or patients with a recurrence of NSCLC received accelerated hypofractionated three-dimensional conformal radiotherapy. The total dose was greater than or equal to 60 Gy. The accelerated hypofractionated radiotherapy was conducted once daily at 3 Gy/fraction with 5 fractions per week, and the radiotherapy was completed in 5 weeks. In addition to radiotherapy, the patients also received at least 1 cycle of a concurrent two-drug chemotherapy regimen of NVB and CBP. RESULTS: A total of 26 patients (19 previously untreated cases and 7 cases of recurrent disease) received 60Gy-75Gy radiotherapy with concurrent chemotherapy. All of the patients underwent evaluations for toxicity and preliminary therapeutic efficacy. There were no treatment-related deaths within the entire patient group. The major acute adverse reactions were radiation esophagitis (88.5%) and radiation pneumonitis (42.3%). The percentages of grade III acute radiation esophagitis and grade III radiation pneumonitis were 15.4% and 7.7%, respectively. Hematological toxicities were common and did not significantly affect the implementation of chemoradiotherapy after supportive treatment. Two patients received high dose of 75 Gy had grade III late esophageal toxicity, and none had grade IV and above. Grade III and above late lung toxicity did not occur. CONCLUSION: High-dose accelerated hypofractionated three-dimensional conformal radiotherapy with a dose of 60 Gy or greater with concurrent NVB and CBP chemotherapy might be feasible. However esophagus toxicity needs special attention. A phase I trial is recommended to obtain
the maximum tolerated radiation dose of accelerated hypofractionated radiotherapy with concurrent chemotherapy.


RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

REVISTA / JOURNAL: - JAMA. %8?(3k+3s http://jama.ama-assn.org/search.dtl


AUTORES / AUTHORS: - Cornwell LD; Bakaeen FG; Lan CK; Omer S; Preventza O; Pickrell B; Nguyen A; Casal RF

INSTITUCIÓN / INSTITUTION: - Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas2Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas.

RESUMEN / SUMMARY: - IMPORTANCE Recently, preoperative lung cancer staging has evolved to include endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) biopsies of the hilar and mediastinal lymph nodes, but the feasibility and usefulness of the procedure have not been well studied in the veteran population. OBJECTIVE To determine the safety and effectiveness of EBUS-TBNA as a key component of a preoperative staging algorithm for lung cancer in veterans.

DESIGN, SETTING, AND PARTICIPANTS Review of a prospectively maintained thoracic surgery database that includes patients who underwent lung resection for lung cancer between January 1, 2009, and December 31, 2012, at a single Veterans Affairs medical center among a consecutive cohort of 166 patients with clinically early-stage (I or II) lung cancer who underwent lobectomy with nodal dissection. INTERVENTIONS Endobronchial ultrasonography-guided transbronchial needle aspiration mediastinal staging (EBUS group) in 62 patients (37.3%) was compared with noninvasive nodal staging plus integrated positron emission tomography-computed tomography only (PET/CT-only group) in 104 patients (62.7%). The accuracy of nodal staging was assessed by comparison with the final pathological staging after complete nodal dissection (the gold standard). MAIN OUTCOMES AND MEASURES Primary outcomes were feasibility, safety, accuracy, and negative predictive value of EBUS-TBNA for preoperative nodal staging. A secondary outcome was the rate of nontherapeutic lung resection for occult N2 disease, with comparison between the EBUS group and the PET/CT-only group. RESULTS No significant complications were attributable to the EBUS-TBNA procedure. In the EBUS group, 258 lymph node stations were sampled. N1 hilar metastases were diagnosed in 8 patients (12.9%) before surgery, and the remainder were staged N0. Accuracy and negative predictive value of EBUS-TBNA were 93.5% (58 of 62) and 92.6% (50 of 54), respectively. The overall rate of nontherapeutic
lungs resection performed in patients with occult N2 disease was 10.8% (18 of 166) (8.1% in the EBUS group and 12.5% in the PET/CT-only group) (P = .37). CONCLUSION AND RELEVANCE: A preoperative lung cancer staging strategy that includes EBUS-TBNA seems to be safe and effective in a veteran population, resulting in a low rate of nontherapeutic operations because of occult N2 nodal disease.

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TÍTULO / TITLE: A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Villanti AC; Jiang Y; Abrams DB; Pyenson BS


RESUMEN / SUMMARY: BACKGROUND: A 2011 report from the National Lung Screening Trial indicates that three annual low-dose computed tomography (LDCT) screenings for lung cancer reduced lung cancer mortality by 20% compared to chest X-ray among older individuals at high risk for lung cancer. Discussion has shifted from clinical proof to financial feasibility. The goal of this study was to determine whether LDCT screening for lung cancer in a commercially-insured population (aged 50-64) at high risk for lung cancer is cost-effective and to quantify the additional benefits of incorporating smoking cessation interventions in a lung cancer screening program. METHODS AND FINDINGS: The current study builds upon a previous simulation model to estimate the cost-utility of annual, repeated LDCT screenings over 15 years in a high risk hypothetical cohort of 18 million adults between age 50 and 64 with 30+ pack-years of smoking history. In the base case, the lung cancer screening intervention cost $27.8 billion over 15 years and yielded 985,284 quality-adjusted life years (QALYs) gained for a cost-utility ratio of $28,240 per QALY gained. Adding smoking cessation to these annual screenings resulted in increases in both the costs and QALYs saved, reflected in cost-utility ratios ranging from $16,198 per QALY gained to $23,185 per QALY gained. Annual LDCT lung cancer screening in this high risk population remained cost-effective across all sensitivity analyses. CONCLUSIONS: The findings of this study indicate that repeat annual lung cancer screening in a high risk cohort of adults aged 50-64 is highly cost-effective. Offering smoking cessation interventions with the annual screening program improved the cost-effectiveness of lung cancer screening between 20% and 45%. The cost-utility ratios estimated in this study were in line with other accepted
cancer screening interventions and support inclusion of annual LDCT screening for lung
cancer in a high risk population in clinical recommendations.
concentrations, the risks are unknown. We enrolled 196 lung cancer cases and 359 controls matched on age and gender from western Nevada and Kings County, California in 2002-2005. After adjusting for age, sex, education, smoking and occupational exposures, odds ratios for arsenic concentrations \( \geq 85 \) microg/L (median = 110 microg/L, mean = 173 microg/L, maximum = 1,460 microg/L) more than 40 years before enrollment were 1.39 (95% CI = 0.55-3.53) in all subjects and 1.61 (95% CI = 0.59-4.38) in smokers. Although odds ratios were greater than 1.0, these increases may have been due to chance given the small number of subjects exposed more than 40 years before enrollment. This study, designed before research in Chile suggested arsenic-related cancer latencies of 40 years or more, illustrates the enormous sample sizes needed to identify arsenic-related health effects in low-exposure countries with mobile populations like the U.S. Nonetheless, our findings suggest that concentrations near 100 microg/L are not associated with markedly high relative risks.

[TÍTULO / TITLE: - Lung Cancer with Gastrointestinal Metastasis - Review of Theories of Metastasis with Three Rare Case Descriptions.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Mehta RS; Liman AD; Passero VA; Liman AK

INSTITUCIÓN / INSTITUTION: - University of Pittsburgh Medical Center, Pittsburgh, USA, mehtars@upmc.edu.

RESUMEN / SUMMARY: - Approximately 1 in 14 men and women during their lifetime will be diagnosed with lung cancer, which is the leading cause of cancer-related mortality in the world. As of January 1, 2008, there were about 373,500 men and women living with lung cancer in the United States. Fewer than 60,000 of these are estimated to be alive by January 2013, reflecting a poor overall 5-year relative survival rate of under 16%. With metastatic cancer, the overall 5-year survival is meager 4%. On the other hand, the overall five-year survival is over 50% when the cancer is still in the localized stage. However, unfortunately, more than half of cases of lung cancer are diagnosed at an advanced stage Howlader et al. (2010). Cancer metastasis, the single most critical prognostic factor, is still poorly understood and a highly complex phenomenon. The most common sites of lung cancer metastasis are the lymph nodes, liver, adrenals, brain and bones. The gastrointestinal (GI) tract is an exceptionally rare site of metastasis; with only a handful of cases reported in the literature Centeno et al. (Lung Cancer, 18: 101-105, 1997); Hirasaki et al. (World J Gastroenterol, 14: 5481-5483, 2008); Carr and Boulos (Br J Surg, 83: 647, 1996); Otera et al. (Eur Respir Rev, 19: 248-252, 2010); Antler et al. (Cancer, 49: 170-172, 1982); Fujiwara et al. (Gen Thorac Cardiovasc Surg, 59: 748-752, 2011); Stinchcombe et al. (J Clin Oncol, 24: 4939-4940,
We report three cases of non-small cell (squamous cell) lung cancer with GI tract metastasis—two in the colon and one in the jejunum. Then we present a review of literature exploring various theories of metastasis, as an attempt to understand the reason of preferential tumor metastasis.

[851]

**TÍTULO / TITLE**: A rare case of primary malignant small cell carcinoma combined with urothelial cell carcinoma in the ureter.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1186/1477-7819-11-181

**AUTORES / AUTHORS**: Jang H; Yuk SM; Kim JO; Han DS

**INSTITUCIÓN / INSTITUTION**: Department of Urology, The Catholic University of Korea Daeyeon St, Mary’s Hospital, Daehueng-dong, Jung-gu, Daejeon, 301-723, Korea.

**RESUMEN / SUMMARY**: BACKGROUND: Extrapulmonary small cell carcinomas have been reported in a variety of organs, and their incidence in the genitourinary tract is second only to that in the gastrointestinal tract. To date, however, only a few cases of small cell carcinoma of the ureter have been reported. Because the extreme rarity of this type of carcinoma, its clinical behaviour, diagnostic methods, and effective treatment modalities have not yet been determined. CASE PRESENTATION: A 59-year-old man presented with a 1-month history of painless gross haematuria. Urine cytology revealed a urothelial carcinoma and computed tomography revealed left hydronephroureterosis with a distal ureteral stone and a mildly enhanced fungating mass just below the stone-impacted site. The preoperative TNM stage was T2N0M0. The patient underwent simultaneous diagnostic ureterorenoscopy and left laparoscopic nephroureterectomy with bladder cuff resection. Gross examination showed a 3.5 x 3.0 x 0.8 cm white, partly yellow mass in the left distal ureter. Light microscopy showed a small cell carcinoma, overlaid on a urothelial carcinoma in situ, invading the ureter and external lateral resection margins. The small cell carcinoma was diffusely positive for neuron-specific enolase, and exhibited focal positivity for CD56, synaptophysin, chromogranin and cytokeratin 20. The patient was treated with adjuvant chemotherapy, consisting of cisplatin and etoposide, and radiation therapy, and has been well, without evidence of tumour recurrence or metastasis in the 10 months after surgery. CONCLUSION: Small cell carcinoma of the ureter is rare. Although its clinical behaviour and diagnostic modalities have not been determined and it has yet to be diagnosed immunohistopathologically, multimodality treatment including surgery, chemotherapy and radiotherapy may improve patient survival.
Fibrous lung tumor: a peculiar case.

RESUMEN / SUMMARY: Solitary fibrous tumor (SFT) of the pleura and the lung is an uncommon spindle cell neoplasm arising from the visceral pleura in the majority of the cases. However there are some extrapleural sites including the lung. Current considerations were raised by a peculiar recent case: an 81-year-old female, non-smoker, presented with undefined left thoracic pain. Radiographic findings of a large solid lung mass (10 cm x 9 cm). Computed tomography (CT) confirmed the thoracic mass showing characteristics of a well defined mass with capsule, the position of the mass in proximity of the posterior-basal and lateral-basal wall. No secondary lesions were found. Through a left inferior lobectomy and ilo-mediastinal lymph nodes sampling, the entire mass was resected. Histopathological examination revealed a SFT. In conclusion STF is a rare lesion and this case showed a peculiar extremely large lesion never described before in literature.

The stability of osseous metastases of the spine in lung cancer - a retrospective analysis of 338 cases.

RESUMEN / SUMMARY: BACKGROUND: The objective of this retrospective analysis is to systematically assess osseous lesions on the basis of a validated scoring system in terms of stability and fractures prior to and following radiotherapy in 338 lung cancer patients with bone metastases in the vertebral column. METHODS: The stability of 338 patients with 981 osteolytic metastases in the thoracic and lumbar spine was evaluated retrospectively on the basis of the Taneichi-Score between January 2000
and January 2012. RESULTS: 64% (215 patients) were classified stable prior to radiotherapy. Of the stable osseous metastases, none were rated unstable in the further course (p < 0.001, McNemar test). Of the 123 patients in whom the metastases were classified unstable prior to radiotherapy, 21 patients (17%) were classified stable after three months, and 30 patients (24%) stable after six months. A pathological fracture was diagnosed in 62 patients (18%) prior to radiotherapy. Regarding cases of osteolytic metastases of the vertebral bodies in which no fractures could be detected prior to the start of therapy, fractures occurred in 2% of all patients (n = 7) within six months following radiotherapy. CONCLUSIONS: Our analysis demonstrated that pathological fractures following radiotherapy occur in the very minority of vertebral lesions for patients with a favorable outcome. The use of a systematic radiological scoring system to classify osteolytic metastases of the vertebral column has shown to be feasible in daily routine. Prospective clinical trials are warranted in order to analyse, to what extent patients with osseous metastases can be mobilized by physiotherapy for strengthening the paravertebral muscles before radiotherapy effects can be measured by means of radiological recalcification.

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TÍTULO / TITLE: Lung Carcinoma Presenting as an Obstructive Jaundice: Case Series with Literature Review.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: J Gastrointest Cancer. 2013 Sep 3.
AUTORES / AUTHORS: Chaudhari D; Khanna A; Goenka P; Young M
INSTITUCIÓN / INSTITUTION: Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, VA Building 1, PO Box 70622, Johnson City, TN, 37615, USA, chaudharidhara@yahoo.com.

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TÍTULO / TITLE: Giant malignant mesothelioma in the upper mediastinum: A case report.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Zhang S; Song P; Zhang B
INSTITUCIÓN / INSTITUTION: The Sixth Department of Surgery, Shangdong Tumor Hospital and Institute, Jinan, Shandong 250117, P.R. China.
RESUMEN / SUMMARY: Malignant mesothelioma in the mediastinum is rare and the majority of known cases have been reported as ‘localized mesothelioma’. The present study reports a case of an upper mediastinal tumor, which was diagnosed through thoracoscopic surgery and surgical biopsies of the mass. A computed tomography scan...
revealed a giant upper mediastinal tumor, adjacent to the aortic arch, trachea, superior vena cava and left pulmonary artery. The vessels in the mediastinum were compressed and were shifted to the lower right. The trachea became stenotic and a small amount of bilateral pleural effusion was observed. The mass was relatively well encapsulated. There was no pleural thickening or clearly swollen lymph nodes in the mediastinum. The histopathological and immunohistochemical examinations of the tumor verified the diagnosis of a malignant mesothelioma. The tumor was demonstrated to be derived from the mediastinal pleural mesothelium cells. The patient received pemetrexed disodium and cisplatin combination chemotherapy for four cycles. At present, the patient is undergoing follow-up.
The purpose of this study was to evaluate the stability of complex markers implanted into lung tumors throughout a course of stereotactic body radiotherapy (SBRT). Fifteen patients referred for lung SBRT were prospectively included. Radio-opaque markers were implanted percutaneously, guided by computed tomography (CT). Deep inspiration breath-hold CT scans (BHCT) were acquired at planning and on three treatment days. The treatment days’ BHCTs were registered to the planning BHCT. Intraobserver uncertainty in both tumor and marker registration was determined. Deviations in the difference between tumor and marker-based image registrations of the BHCT scans during treatment quantified the marker stability. Marker position deviation relative to tumor position of less than 2 mm in all three dimensions was considered acceptable for treatment delivery precision. Intra observer uncertainties for image registration in the left-right (LR), anterior-posterior (AP), craniocaudal (CC) directions and three-dimensional vector (3D) were 0.9 mm, 0.9 mm, 1.0 mm, and 1.1 mm (SD) for tumor registration and 0.3 mm, 0.5 mm, 0.7 mm, and 0.7 mm (SD) for marker registration. Mean 3D differences for tumor registrations on all days were significantly larger than for 3D marker registrations (p = 0.007). Overall median differences between tumor and marker position were 0.0 mm (range -2.9 to 2.6 mm) in LR, 0.0 mm (-1.8 to 1.5 mm) in AP, and -0.2 mm (-2.6 to 2.8 mm) in CC directions. Four patients had deviations exceeding 2 mm in one or more registrations throughout the SBRT course. This is the first study to evaluate stability of complex markers implanted percutaneously into lung tumors for image guidance in SBRT. We conclude that the observed stability of marker position within the tumor indicates that complex markers can be used as surrogates for tumor position during a short course of SBRT as long as the uncertainties related to their position within the tumor are incorporated into the planning target volume.
chest radiation (RT). Methods: Stage III NSCLC patients with Zubrod PS 2, or Zubrod PS 0-1 with poor pulmonary function and co-morbidities prohibiting chemoRT were eligible. A loading dose of cetuximab (400 mg/m(2)) was delivered week 1, followed by weekly cetuximab (250 mg/m(2))/RT to 64.8 Gy in 1.8 Gy daily fractions, and maintenance weekly cetuximab (250 mg/m(2)) for 2 years or until disease progression. H-score for EGFR protein expression was conducted in available tumors. Results: Twenty-four patients were enrolled. Twenty-two were assessed for outcome and toxicity. Median survival was 14 months and median progression-free survival was 8 months. The response rate was 47% and disease control rate was 74%. Toxicity assessment revealed 22.7% overall >/=Grade 3 non-hematologic toxicities. Grade 3 esophagitis was observed in one patient (5%). The skin reactions were mostly Grade 1 or 2 except two of 22 (9%) had Grade 3 acne and one of 22 (5%) had Grade 3 radiation skin burn. Grade 3-4 hypomagnesemia was seen in four (18%) patients. One patient (5%) had elevated cardiac troponin and pulmonary emboli. H-score did not reveal prognostic significance. An initially planned second cohort of the study did not commence due to slow accrual, which would have added weekly docetaxel to cetuximab/RT after completion of the first cohort of patients. Conclusion: Concurrent weekly cetuximab/chest RT followed by maintenance cetuximab for poor-risk stage III NSCLC was well tolerated. Further studies with larger sample sizes will be useful to establish the optimal therapeutic ratio of this regimen.

[859]

**TÍTULO / TITLE:** - Severe intraoperative complications during VATS Lobectomy compared with thoracotomy lobectomy for early stage non-small cell lung cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.08.13

**AUTORES / AUTHORS:** - Liang C; Wen H; Guo Y; Shi B; Tian Y; Song Z; Liu D

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, China-Japan Friendship Hospital, Beijing 100029, China.

**RESUMEN / SUMMARY:** - BACKGROUND: Video-assisted thoracic surgery (VATS) lobectomy has been proved to have shorter hospital stay, less perioperative complications and less pain compared with lobectomy by thoracotomy, but severe intraoperative complications during VATS lobectomy is rare reported. We compared intraoperative safety between VATS lobectomy and lobectomy by thoracotomy.

METHODS: 659 patients with postoperative stage I and IIa non-small cell lung cancer (NSCLC) who underwent lobectomy in China-Japan Friendship Hospital from February 2008 to June 2012 were analyzed retrospectively, in which 277 were performed by thoracotomy, 357 performed by VATS, and 25 performed by VATS converted to open.
Outcomes were analyzed to compare the incidence of significant bleeding, with conversion cases were included into VATS group. RESULTS: Ten severe intraoperative complications were identified in 10 patients (6 in VATS, 4 in open), with no intraoperative deaths. The incidence of severe intraoperative complications was similar between VATS group and thoracotomy group [1.57% (6/382) vs. 1.44% (4/277), P=1.0]. Most severe intraoperative complications were related to the injury of major pulmonary vessels (9/10), and most of these complications occurred during upper lobectomy (8/10). There was no statistically significant difference in blood loss (242.85+/-220.47 vs. 240.43+/-144.36, P=0.865), and operative time (198.00+/-75.24 vs. 208.05+/-61.97, P=0.061) between the open and VATS groups, respectively, but blood loss and operative time are significant different after elimination of conversion cases (214.34+/-151.85 vs. 240.43+/-144.36, P<0.01; 193.24+/-72.64 vs. 208.05+/-61.97, P<0.01). CONCLUSIONS: Our preliminary study demonstrated that the incidence of severe intraoperative complication during VATS lobectomy was low and similar to open lobectomy. The severe intraoperative complications during VATS lobectomy are manageable and the surgeons need to take proper caution in performing VATS lobectomy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yildirim M; Yildiz M; Duman E; Goktas S; Kaya V
INSTITUCIÓN / INSTITUTION: - Antalya Education and Research Hospital, Department of Medical Oncology, Antalya, Turkey.
RESUMEN / SUMMARY: - Purpose: Despite all primary prevention and therapeutic efforts around the world, non-small cell lung cancer (NSCLC) continues to be an important public health problem. In the treatment of patients, laboratory parameters can be used for the determination of treatment intensity. These laboratory parameters should be easily accessible, cheap and easy to use. For this purpose, the prognostic importance in NSCLC of serum albumin levels, neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) was investigated in the present study. Methods: Serum albumin levels and body mass index (BMI) were used to determine the nutritional status and NLR and TLR were used to determine the systemic inflammatory response (SIR). Results: While median survival was 9.1 months in hypoalbuminemic patients, it was 16.4 months in normoalbuminemic patients (p=0.002). The relationship of positive or negative NLR as an indicator of SIR with median survival was statistically significant (p=0.006). While median survival was 7.8 months for patients with NLR >/=5, it was 14.7 for the patients with NLR <5 (p=0.006). TLR as a SIR indicator was not connected with median survival (p=0.072). Conclusion: Serum albumin, indicating the
nutritional status and the NLR as an indicator of SIR, are significantly related with prognosis in locally advanced and metastatic NSCLC. Serum albumin measurement and calculation of NLR are easily accessible, cheap and easy to use laboratory methods. We consider that serum albumin levels and NLR can be utilized in the treatment planning of NSCLC patients.

[861]

TÍTULO / TITLE: - What is the most practical, optimal, and cost effective method for performing follow-up after lung cancer surgery, and by whom should it be done?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Tremblay L; Deslauriers J
INSTITUCIÓN / INSTITUTION: - Multidisciplinary Department of Pulmonology and Thoracic Surgery, Institut universitaire de cardiologie et de pneumologie de Quebec (IUCPQ), 2725 chemin Sainte-Foy, L-3540, Quebec City, Quebec G1V 4G5, Canada.
lise.tremblay@cricupq.ulaval.ca
RESUMEN / SUMMARY: - Surgery is the treatment of choice for early stage non-small cell lung cancer. In this context, postoperative follow-up is important to diagnose late postoperative complications, as well as to detect recurring cancer or new primaries as early as possible. There is, however, no high-quality evidence regarding the benefits of monitoring programs on survival and quality of life. Most studies recommend clinical and radiological follow-up (radiograph or chest computed tomography) performed more intensively during the first two years and annually thereafter. The physician doing the follow-up can be the thoracic surgeon, the diagnosing physician, or the family physician.

[862]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Paintal A; Raparia K; Zakowski MF; Nayar R
INSTITUCIÓN / INSTITUTION: - Northwestern University, Feinberg School of Medicine, Chicago, Illinois.
RESUMEN / SUMMARY: - BACKGROUND: The diagnosis of malignant mesothelioma (MM) in effusion specimens is controversial. At the study institution (Northwestern University), a primary diagnosis of MM is made on fluid cytology specimens. In an effort to estimate the practice at other institutions, a survey was disseminated
regarding cytologic diagnosis of MM. The authors also evaluated their own institution’s experience with primary cytologic diagnosis of MM. METHODS: Patients with MM at the study institution were identified from 1992 through 2011. Fluid cytology specimens preceding histologic diagnoses were reviewed. A survey was sent to a number of cytology laboratories to assess practice patterns regarding the diagnosis of MM. RESULTS: At the study institution, 20 cases of MM had effusion specimens preceding the diagnostic histologic material. In 6 cases (30%), a definitive diagnosis of MM was rendered via cytology alone. There were no false-positive diagnoses of MM. Of 55 laboratories that responded to the survey, 36 reported making a definitive diagnosis of MM after cytologic analysis. Almost all laboratories (35) willing to diagnose MM in effusions reported performing immunohistochemistry to distinguish adenocarcinoma from MM. A smaller proportion (18) of these laboratories reported doing additional immunohistochemistry or fluorescence in situ hybridization for p16 to help distinguish benign from malignant mesothelial proliferations. Those who do not definitively diagnose MM in fluid specimens state inability to identify invasion and overlap with reactive mesothelial proliferation as factors supporting their practice. Most respondents (32) felt that the clinicians at their institution would manage a patient based on a cytologic diagnosis of MM. CONCLUSIONS: The majority of respondents reported making a definitive diagnosis of MM in effusion cytology specimens. The diagnosis of MM in effusions, although not sensitive, is extremely specific. Cancer (Cancer Cytopathol) 2013. © 2013 American Cancer Society.
enabling differentiation between early and invasive lung cancer. The diagnostic yield of radial EBUS in the diagnostics of peripheral lung lesions is high, reducing the number of diagnostic thoracotomies. The application of miniature radial EBUS probes, together with guiding sheaths and other guiding accessories, allow the access to smaller and more peripheral lung lesions. In addition, EBUS bronchoscopy can be utilized for the placement of brachytherapy catheters, or evaluation of the distal bronchi in order to chose between different therapeutic bronchoscopic techniques for desobstruction. An experienced bronchoscopist, availability of ROSE and additional guiding devices might be necessary to accomplish the best possible results of EBUS bronchoscopy.

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**TÍTULO / TITLE:** - Malignant peritoneal mesothelioma with a sarcomatoid growth pattern and signet-ring-like structure in a female f344 rat.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** - Ohnuma-Koyama A; Yoshida T; Takahashi N; Akema S; Takeuchi-Kashimoto Y; Kuwahara M; Nagaie M; Inui K; Nakashima N; Harada T

**INSTITUCIÓN / INSTITUTION:** - Laboratory of Pathology, Toxicology Division, The Institute of Environmental Toxicology, 4321 Uchimoriya-machi, Joso, Ibaraki 303-0043, Japan.

**RESUMEN / SUMMARY:** - We report a biphasic malignant mesothelioma in an aged female F344/DuCrlCrlj rat. Macroscopically, multiple pale brown nodules were observed in the abdominal cavity with retention of bloody ascites. Histopathologically, the tumor cells spread over the peritoneum and formed masses on the surface and underlying adipose tissues. The tumor cells dominantly proliferated in a solid, nodular or nest-like pattern with modest amount of fibrillar connective tissues, which contained hyaluronan. The tumor consisted of ovoid, polygonal or spindle-shaped cells that possessed eosinophilic cytoplasms including glycogen; some tumor cells showed a signet-ring-like structure. Multinucleated cells and mitosis were found frequently, and direct invasion to intra-abdominal organs and intravascular metastasis to the liver were observed. Immunohistochemically, keratin and mesothelin were strongly positive in most of tumor cells, while vimentin was mainly positive in spindle-shaped cells. Podoplanin was also positive, particularly in the cell membrane of tumor cells. Electron microscopically, tumor cells showed an intercellular desmosome-like structure, basement membrane and microvillus. We diagnosed the case as a malignant peritoneal mesothelioma with a sarcomatoid growth pattern and signet-ring-like structure.

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**TÍTULO / TITLE:** - Biomarkers and prognostic factors for mesothelioma.
**TÍTULO / TITLE:** - Ki67-BCL2 index in prognosis of malignant peritoneal mesothelioma.

**RESUMEN / SUMMARY:** - Background: Malignant peritoneal mesothelioma (MPM) is a rare peritoneal mesothelial neoplasm. Ki67 and BCL2 are established prognostic markers in several cancers. High Ki67 expression indicates tumour progression, whilst similar expression of BCL2 retards tumour replication. Traditionally, prognosis in MPM is gauged with a single biomarker assessed separately in a dichotomous manner. Here, we examine prognosis with dual biomarkers incorporated in a model to predict survival. Materials and methods: Forty two MPM archival patient tumours were screened for Ki67 and BCL2 by immunohistochemistry and evaluated using standard methods. Ki67 and BCL2 expression was incorporated into a prognostic model to develop Ki67-BCL2 index. Using this index, three hazard groups were identified (high, medium and low risk). Kaplan-Meier survival analysis was performed to assess the significance of these hazard groups in the various clinicopathological categories. Results: In all clinicopathological categories, high risk group showed poor prognosis compared to low risk group (p = < 0.001). Compared to medium risk, high risk group carried poor prognosis in all tumours, females, epitheloid tumours, peritoneal cancer index (PCI) < 20, > = 20, age at diagnosis (AAD) < 60, and > = 60 years. Independent of the Ki67-BCL2 index, male, sarcomatoid, PCI > = 20 and AAD > = 60 were poor prognostic factors. High risk group was an independent poor prognostic factor in all tumours, males, females age < 60 years. The distribution of high risk: low risk group in male and female was 3: 2 and 2: 3, respectively, indicating a gender difference. Comparing hazard ratios generated by Ki67-BCL2 index to that of either Ki67 or BCL2, as a single prognostic biomarker, there was a reduction of HR values. Conclusion: Ki67-BCL2 index seems to suggest a more sensitive method of predicting...
prognosis. However, the current model needs further evaluation in an independent large cohort sample.

[867]
**TÍTULO / TITLE**: - Skeletal muscle metastases as the initial manifestation of an unknown primary lung cancer detected on F-18 fluorodeoxyglucose positron emission tomography/computed tomography.
**RESUMEN / SUMMARY**: - Enlace al Resumen / Link to its Summary
  ●● Enlace al texto completo (gratuito o de pago) 4103/0972-3919.116814
**AUTORES / AUTHORS**: - Agrawal K; Bhattacharya A; Singh N; Harisankar CN; Mittal BR
**INSTITUCIÓN / INSTITUTION**: - Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
**RESUMEN / SUMMARY**: - Skeletal muscle metastasis as the initial presentation of the unknown primary lung cancer is unusual. A 65-year-old male patient presented with pain and swelling of the right forearm. Fine needle aspiration of the swelling revealed metastatic squamous cell carcinoma. The patient underwent whole body F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) to identify the site of the primary malignancy. The authors present PET/CT images showing FDG-avid metastases to the skeletal muscles along with a previously unknown primary tumor in the right lung, in a patient presenting with initial muscular symptoms without any pulmonary manifestations.

[868]
**TÍTULO / TITLE**: - Highlights in management of early stage non-small cell lung cancer.
**RESUMEN / SUMMARY**: - Enlace al Resumen / Link to its Summary
  ●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.08.51
**AUTORES / AUTHORS**: - Li G
**INSTITUCIÓN / INSTITUTION**: - Editorial office, Journal of Thoracic Disease, Guangzhou 510120, China.

[869]
**TÍTULO / TITLE**: - Reversal of Lung Cancer Multidrug Resistance by pH-Responsive Micelleplexes Mediating Co-Delivery of siRNA and Paclitaxel.
**RESUMEN / SUMMARY**: - Enlace al Resumen / Link to its Summary
  ●● Enlace al texto completo (gratuito o de pago) 1002/mabi.201300282
RESUMEN / SUMMARY: The recent advances in RNA interference (RNAi) technology provided novel and promising solutions for human cancer treatment. In this study, the application of dual pH-responsive cationic micellar nanoparticles for small interfering RNA (siRNA) and paclitaxel (PTX) co-delivery to overcome cancer multidrug resistance (MDR) is reported. The in vitro siRNA transfection shows that siRNA-luciferase (Luc) loaded micelleplexes efficiently silences Luc expression in various carcinoma cell lines. The Luc knockdown ability of the micelleplexes can be enhanced by choloquine (CQ) co-incubation. However, is abolished by bafilomycin-A1 (Baf-A1) treatment. The micelleplexes are further exploited for co-delivery of siRNA-Bcl-2 and PTX to Bcl-2 overexpressing A549 lung cancer cells (A549-Bcl-2). The experimental results show that the micelleplexes could sensitize A549-Bcl-2 cells to PTX via down-regulation of anti-apoptosis gene of Bcl-2, suggesting that PDMA-b-PDPA micelleplexes are promising nanovectors for siRNA and anti-cancer drug co-delivery to overcome cancer MDR.
Video-assisted thoracoscopic surgery (VATS) represents a new trend in the development of minimally invasive thoracic surgery. When applied in lung cancer surgeries, VATS can be used for both pulmonary lobectomy and regional lymph node dissection. Currently the main concerns are focused on the completeness of lymph node dissection for lung cancer and the safety of surgery. The lymph node dissection includes two parts: (I) dissection of interlobar and hilar lymph nodes; and (II) dissection of mediastinal lymph nodes. The demonstrated surgical procedures are featured by: (I) the interlobar and hilar lymph nodes are not removed separately; rather, they are taken out en bloc with the pulmonary lobes during the surgery; and (II) systematic lymph node dissection, instead of systematic sampling, is applied for the removal of mediastinal lymph nodes. Also, during the fully anatomical resection, each blood vessel and bronchus underwent anatomical dissociation, indicating that this surgery is safe.


Small cell carcinoma of the bladder is a rare, aggressive, poorly differentiated neuroendocrine neoplasm accounting for only 0.3-0.7% of all bladder tumors. Since the tumor is very rare, pathogenesis is uncertain. Small cell carcinomas of the urinary bladder are mixed with classic urothelial carcinomas or adenocarcinomas of the bladder in 68% cases, making pure primary small cell carcinoma even a rarer entity. The unknown etiology and natural history of small cell carcinoma of the urinary bladder represent a challenge both to the pathologist and urologists for its diagnosis and treatment, respectively.
The Cell Block Method Increases the Diagnostic Yield in Exudative Pleural Effusions Accompanying Lung Cancer.

Objective: Thoracentesis is the first investigation to be performed in a patient with lung cancer and pleural effusion. The diagnostic yield of conventional smear studies varies in the first thoracentesis. In this study, we aimed to investigate if the cell block method increases the diagnostic yield in exudative pleural effusions accompanying lung cancer. Material and Method: Forty patients with lung cancer and exudative pleural effusions were included. Ten milliliters of fresh pleural fluid was obtained by thoracentesis from all patients in the initial evaluation. The pleural fluid sample was divided into two equal parts. One part was subjected to conventional smear and the other to the cell block method. Conventional smears were stained with May-Grunwald-Giemsa and Hematoxylin-Eosin. Cell block sections were stained with Hematoxylin-Eosin and mucicarmine. Conventional smear findings were grouped as “benign cytology” or “malignant cytology”. The cell block sections were evaluated for the presence of single tumor cells, acinar or papillary pattern, solid islands and staining with mucicarmine. Results: There were 20 patients each in the benign and malignant conventional smear group. In the benign group, adding the cell block method to conventional smear provided a diagnosis of malignancy in 4 more patients and the diagnosis of malignant effusion was increased by a ratio of 10% (4/40). In the malignant group, adding the cell block technique provided the subtyping of lung cancer as adenocarcinoma in 7 patients (7/20, 35%). Conclusion: Our study confirms that the cell block method combined with conventional smear increases the diagnostic yield in exudative pleural effusions accompanying lung cancer.
AUTORES / AUTHORS: - Suzuki A; Mimaki S; Yamane Y; Kawase A; Matsushima K; Suzuki M; Goto K; Sugano S; Esumi H; Suzuki Y; Tsuchihara K

INSTITUCIÓN / INSTITUTION: - Department of Medical Genome Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Chiba, Japan.

RESUMEN / SUMMARY: - We analyzed whole-exome sequencing data from 97 Japanese lung adenocarcinoma patients and identified several putative cancer-related genes and pathways. Particularly, we observed that cancer-related mutation patterns were significantly different between different ethnic groups. As previously reported, mutations in the EGFR gene were characteristic to Japanese, while those in the KRAS gene were more frequent in Caucasians. Furthermore, during the course of this analysis, we found that cancer-specific somatic mutations can be detected without sequencing normal tissue counterparts. 64% of the germline variants could be excluded using a total of 217 external Japanese exome datasets. We also show that a similar approach may be used for other three ethnic groups, although the discriminative power depends on the ethnic group. We demonstrate that the ATM gene and the PAPPA2 gene could be identified as cancer prognosis related genes. By bypassing the sequencing of normal tissue counterparts, this approach provides a useful means of not only reducing the time and cost of sequencing but also analyzing archive samples, for which normal tissue counterparts are not available.

ΤÍTULO / TITLE: - DNA microarray reveals different pathways responding to paclitaxel and docetaxel in non-small cell lung cancer cell line.


AUTORES / AUTHORS: - Che CL; Zhang YM; Zhang HH; Sang YL; Lu B; Dong FS; Zhang LJ; Lv FZ

INSTITUCIÓN / INSTITUTION: - Department of respiratory medicine, First Clinical Medical College affiliated to Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - The wide use of paclitaxel and docetaxel in NSCLC clinical treatment makes it necessary to find biomarkers for identifying patients who can benefit from paclitaxel or docetaxel. In present study, NCI-H460, a NSCLC cell line with different sensitivity to paclitaxel and docetaxel, was applied to DNA microarray expression profiling analysis at different time points of lower dose treatment with paclitaxel or docetaxel. And the complex signaling pathways regulating the drug response were identified, and several novel sensitivity-related markers were biocomputed. The dynamic changes of responding genes showed that paclitaxel effect is acute but that of docetaxel is durable at least for 48 hours in NCI-H460 cells. Functional annotation of the genes with altered expression showed that genes/pathways responding to these two drugs were dramatically different. Gene expression changes induced by paclitaxel treatment were mainly enriched in actin...
cytoskeleton (ACTC1, MYL2 and MYH2), tyrosine-protein kinases (ERRB4, KIT and TIE1) and focal adhesion pathway (MYL2, IGF1 and FLT1), while the expression alterations responding to docetaxel were highly co-related to cell surface receptor linked signal transduction (SHH, DRD5 and ADM2), cytokine-cytokine receptor interaction (IL1A and IL6) and cell cycle regulation (CCNB1, CCNE2 and PCNA). Moreover, we also confirmed some different expression patterns with real time PCR. Our study will provide the potential biomarkers for paclitaxel and docetaxel-selection therapy in clinical application.

[876]
**TÍTULO / TITLE**: Proteasome inhibitors block DNA repair and radiosensitize non-small cell lung cancer.
**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS**: Cron KR; Zhu K; Kushwaha DS; Hsieh G; Merzon D; Rameseder J; Chen CC; D'Andrea AD; Kozono D
**INSTITUCIÓN / INSTITUTION**: Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America.
**RESUMEN / SUMMARY**: Despite optimal radiation therapy (RT), chemotherapy and/or surgery, a majority of patients with locally advanced non-small cell lung cancer (NSCLC) fail treatment. To identify novel gene targets for improved tumor control, we performed whole genome RNAi screens to identify knockdowns that most reproducibly increase NSCLC cytotoxicity. These screens identified several proteasome subunits among top hits, including the topmost hit PSMA1, a component of the core 20 S proteasome. Radiation and proteasome inhibition showed synergistic effects. Proteasome inhibition resulted in an 80-90% decrease in homologous recombination (HR), a 50% decrease in expression of NF-kappaB-inducible HR genes BRCA1 and FANCD2, and a reduction of BRCA1, FANCD2 and RAD51 ionizing radiation-induced foci. IkappaBalpha RNAi knockdown rescued NSCLC radioresistance. Irradiation of mice with NCI-H460 xenografts after inducible PSMA1 shRNA knockdown markedly increased murine survival compared to either treatment alone. Proteasome inhibition is a promising strategy for NSCLC radiosensitization via inhibition of NF-kappaB-mediated expression of Fanconi Anemia/HR DNA repair genes.

[877]
**TÍTULO / TITLE**: Transcriptional blood signatures distinguish pulmonary tuberculosis, pulmonary sarcoidosis, pneumonias and lung cancers.
**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary
RATIONALE: New approaches to define factors underlying the immunopathogenesis of pulmonary diseases including sarcoidosis and tuberculosis are needed to develop new treatments and biomarkers. Comparing the blood transcriptional response of tuberculosis to other similar pulmonary diseases will advance knowledge of disease pathways and help distinguish diseases with similar clinical presentations. OBJECTIVES: To determine the factors underlying the immunopathogenesis of the granulomatous diseases, sarcoidosis and tuberculosis, by comparing the blood transcriptional responses in these and other pulmonary diseases. METHODS: We compared whole blood genome-wide transcriptional profiles in pulmonary sarcoidosis, pulmonary tuberculosis, to community acquired pneumonia and primary lung cancer and healthy controls, before and after treatment, and in purified leucocyte populations. MEASUREMENTS AND MAIN RESULTS: An Interferon-inducible neutrophil-driven blood transcriptional signature was present in both sarcoidosis and tuberculosis, with a higher abundance and expression in tuberculosis. Heterogeneity of the sarcoidosis signature correlated significantly with disease activity. Transcriptional profiles in pneumonia and lung cancer revealed an over-abundance of inflammatory transcripts. After successful treatment the transcriptional activity in tuberculosis and pneumonia patients was significantly reduced. However the glucocorticoid-responsive sarcoidosis patients showed a significant increase in transcriptional activity. 144-blood transcripts were able to distinguish tuberculosis from other lung diseases and controls. CONCLUSIONS: Tuberculosis and sarcoidosis revealed similar blood transcriptional profiles, dominated by interferon-inducible transcripts, while pneumonia and lung cancer showed distinct signatures, dominated by inflammatory genes. There were also significant differences between tuberculosis and sarcoidosis in the degree of their transcriptional activity, the heterogeneity of their profiles and their transcriptional response to treatment.

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TÍTULO / TITLE: - Amylase: sensitive tumor marker for amylase-producing lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Hyperamylasemia in patients with lung cancer is rarely, comprising 1% to 3% of all lung cancers. This report describes two cases of lung adenocarcinoma coexisting with hyperamylasemia in two women aged 77 and 57, respectively. In these two cases, CT revealed a normal pancreas. We monitored the serum and urine amylase levels during therapy and found it paralleled tumor response to chemotherapy and metastasis. We suggest that the amylase levels are related to the tumor size and might be a valuable factor in predicting chemotherapy and progression of disease for amylase-producing lung cancer.
genes (MCM4, - 5, - 6, - 7), most of which are associated with early lung development and poor prognosis. In addition, metabolic genes such as ALDH1A3 (a candidate marker for lung cancer cells with CSC-like properties) were identified. Thus, we measured the proportion of erlotinib-resistant cells expressing very high levels of aldehyde dehydrogenase (ALDH) activity attributed to ALDH1/3 isoforms. Using flow cytometry and the ALDEFLUOR® reagent, we confirmed that erlotinib-refractory cell populations contained drastically higher percentages (> 4500%) of ALDHbright cells than the parental erlotinib-responsive cells. Notably, strong decreases in the percentages of ALDHbright cells were observed following incubation with silibinin, a bioactive flavonolignan that can circumvent erlotinib resistance in vivo. The number of lung cancer spheres was drastically suppressed by silibinin in a dose-dependent manner, thus confirming the ability of this agent to inhibit the self-renewal of erlotinib-refractory CSC-like cells. This report is the first to show that: (1) loss of responsiveness to erlotinib in EGFR-mutant NSCLC can be explained in terms of erlotinib-refractory ALDHbright cells, which have been shown to exhibit stem cell-like properties; and (2) erlotinib-refractory ALDHbright cells are sensitive to the natural agent silibinin. Our findings highlight the benefit of administration of silibinin in combination with EGFR TKIs to target CSCs and minimize the ability of tumor cells to escape cell death in EGFR-mutant NSCLC patients.

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**TÍTULO / TITLE**: Anti-Lung Cancer Activity through Enhancement of Immunomodulation and Induction of Cell Apoptosis of Total Triterpenes Extracted from Ganoderma luncidum (Leyss. ex Fr.) Karst.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS**: Feng L; Yuan L; Du M; Chen Y; Zhang MH; Gu JF; He JJ; Wang Y; Cao W

**INSTITUCIÓN / INSTITUTION**: Key Laboratory of New Drug Delivery Systems of Chinese Materia Medica, Jiangsu Provincial Academy of Chinese Medicine, Nanjing 210028, Jiangsu, China. ychen202@hotmail.com.

**RESUMEN / SUMMARY**: Ganoderma luncidum (Leyss. ex Fr.) Karst. (GLK) has been used traditionally for the prevention and treatment of cancers or tumors for a long time in Traditional Chinese Medicine. The triterpenes as main effective components of GLK have been found to be beneficial for the efficacy. The purpose of this study was to examine the anti-lung cancer activity of triterpenes of GLK in vitro and in vivo and to explore their anti-lung cancer effects and potential mechanisms. A549 cells and Lewis tumor-bearing mice were used to evaluate the inhibition effects of triterpenes on cell proliferation and tumor growth. The IC50 of triterpenes of GLK on A549 cells was 24.63
mug/mL. Triterpenes of GLK could significantly inhibit tumor growth in mice (30, 60 and 120 mg/kg). The immune organs indexes including spleen and thymus were increased remarkably by the treatment with triterpenes. Moreover, they were able to stimulate the immune response by increasing the expressions of IL-6 and TNF-alpha. Flow cytometric analysis revealed that cell arrest caused by triterpenes treatment (7.5, 15 and 30 mug/mL) was in the G2/M phase in A549 cells. Triterpenes induced apoptosis by decreasing the expression of the antiapoptotic protein Bcl-2 and procaspase 9 and increasing the levels of cleaved-caspase 9. Our findings suggested that the triterpenes of GLK have anti-lung cancer activity in vitro and in vivo via enhancement of immunomodulation and induction of cell apoptosis. The study provides insights into the mechanism of GLK in the prevention and treatment of lung cancer.

[881]

Título / Title: 5-Demethyltangeretin inhibits human nonsmall cell lung cancer cell growth by inducing G2/M cell cycle arrest and apoptosis.

Resumen / Summary: Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1002/mnfr.201300136

Autores / Authors: Charoensinphon N; Qiu P; Dong P; Zheng J; Ngauv P; Cao Y; Li S; Ho CT; Xiao H

Institución / Institution: Department of Food Science, University of Massachusetts, Amherst, MA, USA.

Resumen / Summary: Scope: Tangeretin (TAN) and 5-demethyltangeretin (5DT) are two closely related polymethoxyflavones found in citrus fruits. We investigated growth inhibitory effects on three human nonsmall cell lung cancer (NSCLC) cells. Methods and Results: Cell viability assay demonstrated that 5DT inhibited NSCLC cell growth in a time- and dose-dependent manner, and IC50s of 5DT were 79-fold, 57-fold, and 56-fold lower than those of TAN in A549, H460, and H1299 cells, respectively. Flow cytometry analysis showed that 5DT induced extensive G2/M cell cycle arrest and apoptosis in NSCLC cells, while TAN at tenfold higher concentrations did not. The apoptosis induced by 5DT was further confirmed by activation of caspase-3 and cleavage of PARP. Moreover, 5DT dose-dependently upregulated p53 and p21Cip1/Waf1, and downregulated Cdc-2 (Cdk-1) and cyclin B1. HPLC analysis revealed that the intracellular levels of 5DT in NSCLC cells were 2.7-4.9 fold higher than those of TAN after the cells were treated with 5DT or TAN at the same concentration. Conclusion: Our results demonstrated that 5DT inhibited NSCLC cell growth by inducing G2/M cell cycle arrest and apoptosis. These effects were much stronger than those produced by TAN, which is partially due to the higher intracellular uptake of 5DT than TAN.

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[882] **TÍTULO / TITLE:** Association of non-traumatic complex regional pain syndrome with adenocarcinoma lung on 99mTc-MDP bone scan.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Damle NA; Tripathi M; Singhal A; Bal C; Kumar P; Kandasamy D; Jana M

**INSTITUCIÓN / INSTITUTION:** Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India.

**RESUMEN / SUMMARY:** Complex regional pain syndrome (CRPS) is usually associated with trauma. Rarely, it may be seen in association with malignancies. We present here the bone scan and X-ray findings in the case of a 56-year-male-patient with adenocarcinoma lung who also had non-traumatic CRPS without involvement of the stellate ganglion. The case highlights the fact that spontaneous development of reflex sympathetic dystrophy may be associated with a neoplastic etiology.


**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Colombi D; Di Lauro E; Silva M; Manna C; Rossi C; De Filippo M; Zompatori M; Ruffini L; Sverzellati N

**INSTITUCIÓN / INSTITUTION:** Department of Surgical Sciences, Section of Diagnostic Imaging, University Hospital of Parma, Parma, Italy.

**RESUMEN / SUMMARY:** The imaging techniques in patients treated for lung cancer may be challenging to interpret. Radiologists are often asked to evaluate computed tomography (CT) scans after surgery, and this interpretation requires an understanding of both the timing and type of the surgical procedure. However, follow-up strategies are still not well defined. The assessment of tumor response to chemoradiotherapy relies on a tight integration of CT and clinical findings. Positron emission tomography-computed tomography (PET-CT) with fluorodeoxyglucose may help to exclude tumor recurrence when the sole CT scan is equivocal. More efforts are needed to validate the tools for volumetric tumor measurement in routine practice and to demonstrate their superiority compared to the Response Evaluation Criteria in Solid Tumors (RECIST). Familiarity with the assessment of lung cancer perfusion is also important because of the increasing use of cytostatic therapy. In this review, we outlined the imaging assessment of tumor recurrence after surgery and the role of CT, magnetic resonance...
imaging, and PET-CT in the follow-up after chemotherapy, radiotherapy, and radiofrequency ablation.

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[884]

TÍTULO / TITLE - Which type of surgery should become the preferred procedure for malignant pleural mesothelioma: extrapleural pneumonectomy or extended pleurectomy?

RESUMEN / SUMMARY - Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.07.40

AUTORES / AUTHORS - Bedirhan MA; Cansever L; Demir A; Ceyhan S; Akin H; Urer HN; Olcmen A; Kocaturk C; Dincer I

INSTITUCIÓN / INSTITUTION - Department of Surgery, Yedikule Hospital for Chest Disease, Istanbul, Turkey;

RESUMEN / SUMMARY - PURPOSES: Since radiation and chemotherapy have limitations as therapies for malignant pleural mesothelioma (MPM). The type of surgery [extrapleural pneumonectomy (EPP), extended pleurectomy (E/P), and pleurectomy/decortication (P/D)] remains controversial. METHODS: This study involves 76 consecutive patients. 58 of the cases were males (76%) with a median age of 53.17+/-10.93 years. EPP, E/P, and P/D were performed in 31, 20, and 25 cases, respectively. RESULTS: The median survival time was 20 months in all patients. Overall, five-year survival rate was 14.3%. The survival rate was significantly better in epithelioid mesothelioma (P=0.049). For EPP cases, the median survival rate was 17 months, and the three-to-five year survival rates were 21% and 17%, respectively. For E/P cases, the median survival rate was 27 months and the three-year and four-year survival rates were 34% and 30%, respectively. For P/D cases, the median survival rate was 15 months and the three-to-five year survival rate was 13% and 0%. There were no statistically significant differences between the three surgical techniques (P=0.088). A comparative analysis indicates only a statistically significant difference in the E/P and P/D comparison (P=0.032). Hospital mortality showed a higher trend in EPP group (EPP: 12.9%, E/P: 0% and P/D: 4%, P=0.145). N2 cases, there were no cases of two-year survival. The survival rate in N2 was comparatively much lower, which was statistically significant (P=0.005). In multivariate analysis, only P/D (OR 0.3, 95% CI: 0.1-0.9, P=0.049) and N2 (OR 1.6, 95% CI: 0.9-2.6, P=0.090) were found to be poor prognostic factors. CONCLUSIONS: E/P could be encouraged to EPP with lower mortality rate and better survival trend in MPM. N2 diseases were negative prognostic factors in MPM.

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[885]

RESUMEN / SUMMARY: Video-assisted thoracic surgery (VATS) is a minimally invasive technique that has many advantages in postoperative pain and recovery time. Because of its advantages, VATS is one of the surgical techniques widely used in patients with lung cancer. Most surgeons perform VATS for lung cancer with three or more incisions. As the technique of VATS has evolved, single-port VATS for lung cancer has been attempted and its advantages have been reported. We describe our experiences of VATS for lung cancer with a single incision in this report.

TÍTULO / TITLE: Radical surgery for malignant pleural mesothelioma: have we identified the appropriate selection tools?

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - van Zandwijk N; Reid G; Linton A; Kao S

INSTITUCIÓN / INSTITUTION: - Asbestos Diseases Research Institute, University of Sydney, PO Box 3628, Rhodes NSW 2138, Australia.

RESUMEN / SUMMARY: Surgery for nonsmall cell lung cancer.

TÍTULO / TITLE: - Surgery for nonsmall cell lung cancer.


AUTORES / AUTHORS: - Lang-Lazdunski L

INSTITUCIÓN / INSTITUTION: - Dept of Thoracic Surgery, Guy’s Hospital, London, and Division of Cancer Studies, King’s College London, London, UK.

RESUMEN / SUMMARY: Surgery remains the best curative option in patients with early stage lung cancer (stage I and II). Developments in minimally invasive techniques now allow surgeons to perform lung resections on elderly patients, patients with poor pulmonary function or significant cardiopulmonary comorbidities. New techniques, such as stereotactic radiotherapy and ablative procedures, are being evaluated in
early-stage lung cancer and may represent an alternative to surgery in patients unfit for lung resection. Perioperative mortality rates have dropped significantly at most institutions in the past two decades and complications are managed more efficiently. Progress in imaging and staging techniques have helped cut futile thoracotomy rates and offer patients the most adequate treatment options. Large randomised trials have helped clarify the role of neoadjuvant, induction and adjuvant chemotherapy, as well as radiotherapy. Surgery remains an essential step in the multimodality therapy of selected patients with advanced-stage lung cancer (stage III and IV). Interventional and endoscopic techniques have reduced the role of surgery in the diagnosis and staging of nonsmall cell lung cancer, but surgery remains an important tool in the palliation of advanced-stage lung cancer. Large national/international surgical databases have been developed and predictive risk-models for surgical mortality/morbidity published by learned surgical societies. Nonetheless, lung cancer overall survival rates remain deceptively low and it is hoped that early detection/screening, better understanding of tumour biology and development of biomarkers, and development of efficient targeted therapies will help improve the prognosis of lung cancer patients in the next decade.

[888]

**TÍTULO / TITLE:** Evaluation of lung flute in sputum samples for molecular analysis of lung cancer.

**RESUMEN / SUMMARY:** BACKGROUND: Molecular analysis of sputum provides a promising approach for lung cancer diagnosis, yet is limited by the difficulty in collecting the specimens from individuals who can’t spontaneously expectorate sputum. Lung Flute is a small self-powered audio device that can induce sputum by generating sound waves and vibrating in the airways of the lungs. Here we propose to evaluate the usefulness of Lung Flute for sputum sampling to assist diagnosis of lung cancer. METHODS: Forty-three stage I lung cancer patients and 47 cancer-free individuals who couldn’t spontaneously cough sputum were instructed to use Lung Flute for sputum sampling. Expressions of two microRNAs, miRs-31 and 210, were determined in the specimens by qRT-PCR. The results were compared with sputum cytology. RESULTS: Sputum was easily collected from 39 of 43 (90.7%) lung cancer patients and 42 of 47 (89.4%) controls with volume ranges from 1 to 5 ml (median, 2.6 ml). The specimens had less than 4% oral squamous cells, indicating that sputum was obtained from low respiratory tract. Expressions of miRs-31 and 210 in sputum were considerably higher in cancer patients than cancer-free individuals (8.990 vs. 4.514; 0.6847 vs. 0.3317; all P <0.001). Combined use of the two miRNAs produced a
significantly higher sensitivity (61.5% vs. 35.9%, P = 0.002) and a slightly lower specificity (90.5% vs. 95.2%, p = 0.03) compared with cytology for lung cancer diagnosis. CONCLUSION: Lung Flute could potentially be useful in convenient and efficient collection of sputum for molecular diagnosis of lung cancer.

[889]
**TITULO / TITLE:** FGF10 Signaling differences between type I pleuropulmonary blastoma and congenital cystic adenomatoid malformation.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** Orphanet J Rare Dis. 2013 Sep 3;8(1):130.

**AUTORES / AUTHORS:** Lezmi G; Verkarre V; Khen-Dunlop N; Vibhushan S; Hadchouel A; Rambaud C; Copin MC; Rittie JL; Benachi A; Fournet JC; Delacourt C

**RESUMEN / SUMMARY:** BACKGROUND: Type I pleuropulmonary blastoma (PPB) and congenital cystic adenomatoid malformation of the lung (CCAM) are cystic lung diseases of childhood. Their clinical and radiological presentations are often similar, and pathologic discrimination remains difficult in many cases. As a consequence, type I PPB and CCAM are frequently confused, leading to delayed adequate management for type I PPB. Recent studies have suggested a role for fibroblast growth factor (FGF) 10 signal pathway in CCAM pathogenesis. The objective of our study was to determine whether FGF10 signaling differs between CCAM and type I PPB. METHODS: Immunohistochemical studies were performed for expression of FGF10, its receptor FGFR2b, and its inhibitor sonic hedgehog (SHH) in focal type I PPB (n=6), CCAM type I (n=7), CCAM type II (n=7), and control lungs (n=5). RESULTS: FGF10, FGFR2b, and SHH expressions differed markedly between type I PPB and both types of CCAM. Type I and type II CCAM cystic walls expressed FGF10, FGFR2b, and SHH, whereas staining was absent or poor in type I PPB cystic walls. Expression of FGF10, FGFR2b, and SHH did not differ between CCAM cystic walls and control airway walls. CONCLUSIONS: These findings show that immunohistochemistry with FGF10, FGFR2b, or SHH could be useful in differentiating CCAM from type I PPB, when a child presents with a focal cystic lung lesion. The absence of strong expression of FGF10, FGFR2b, and/or SHH makes the diagnosis of CCAM very doubtful.

[890]
**TITULO / TITLE:** Metastasis to the male breast from squamous cell lung carcinoma.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS:** Genc B; Solak A; Sahin N; Gulsen A
RESUMEN / SUMMARY: Metastasis to breast from extra mammarian organs is quite rare with an incidence of 0.5-3%. Malignancies that most commonly metastasize to breast are lymphomas, leukemias, and malignant melanoma. Metastasis of lung cancer to breast is a very rare condition. We present here a case with squamous cell lung cancer that metastasized to breast. A 65-year-old man presented with cough in addition to a mass in the left breast, which had been noted 3 weeks ago and grown gradually since then. A histopathological diagnosis of metastasis of squamous lung cancer was made for the mass in the left breast. PET/CT scan showed no distant metastasis. Chemoradiation therapy was applied for lung cancer. As the prognosis of such patients is extremely poor, it is of a great importance to distinguish a primary breast cancer from a metastatic breast lesion in order to determine the appropriate treatment modality.


RESUMEN / SUMMARY: Reactive oxygen or nitrogen species (ROS, RNS) and oxidative stress in the respiratory system increase the production of mediators of pulmonary inflammation and initiate or promote mechanisms of carcinogenesis. The lungs are exposed daily to oxidants generated either endogenously or exogenously (air pollutants, cigarette smoke, etc.). Cells in aerobic organisms are protected against oxidative damage by enzymatic and non-enzymatic antioxidant systems. Recent epidemiologic investigations have shown associations between increased incidence of respiratory diseases and lung cancer from exposure to low levels of various forms of respirable fibers and particulate matter (PM), at occupational or urban air polluting environments. Lung cancer increases substantially for tobacco smokers due to the synergistic effects in the generation of ROS, leading to oxidative stress and inflammation with high DNA damage potential. Physical and chemical characteristics of particles (size, transition metal content, speciation, stable free radicals, etc.) play an important role in oxidative stress. In turn, oxidative stress initiates the synthesis of mediators of pulmonary inflammation in lung epithelial cells and initiation of
carcinogenic mechanisms. Inhalable quartz, metal powders, mineral asbestos fibers, ozone, soot from gasoline and diesel engines, tobacco smoke and PM from ambient air pollution (PM10 and PM2.5) are involved in various oxidative stress mechanisms. Pulmonary cancer initiation and promotion has been linked to a series of biochemical pathways of oxidative stress, DNA oxidative damage, macrophage stimulation, telomere shortening, modulation of gene expression and activation of transcription factors with important role in carcinogenesis. In this review we are presenting the role of ROS and oxidative stress in the production of mediators of pulmonary inflammation and mechanisms of carcinogenesis.

[892]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ma Q; Jiang Q; Pu Q; Zhang X; Yang W; Wang Y; Ye S; Zhong G; Ren J; Zhang Y; Liu L; Zhu W
INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, 610041, China.
RESUMEN / SUMMARY: - Background: MicroRNAs (miRNAs) play important roles in many biological processes, including cancer development. Among those miRNAs, miR-143 shows tumor-suppressive activity in some human cancers. However, the function and mechanism of miR-143 in lung cancer cells remains unknown. Here we explored the role of miR-143 in lung cancer. Results: According to qRT-PCR, we found that miR-143 was notably down-regulated in 19 NSCLC tissues and 5 cell lines. In vitro experiments showed us that miR-143 could significantly suppress the migration and invasion of NSCLC cell lines while it had no effects on the growth of NSCLC cell lines, and in vivo metastasis assay showed the same results. Finally, we found that the mechanism of miR-143 inhibiting the migration and invasion of NSCLC might be through targeting CD44v3. Conclusions: The up-regulated miR-143 in lung cancer could significantly inhibit cell migration and invasion, and this might work through targeting CD44v3, which was newly identified by us.

[893]
TÍTULO / TITLE: - Peritoneal mesothelioma in a jaguar (Panthera onca).
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Souza Fd e A; de Carvalho CJ; de Almeida HM; Pires LV; Silva Ldos S; Costa FA; Silva SM
A 21-yr-old female jaguar (Panthera onca) died in a zoo in Teresina, Piaui, Brazil, following a history of abdominal distension, ascites, anorexia, and dyspnea. At necropsy, a dark red, watery, blood-tinged serous fluid was present in the abdominal cavity. The peritoneum was thick with firm, yellow, villous projections. Histologically, the tumors were composed of a biphasic population of cells, which reacted to anti-cytokeratin and anti-vimentin antibodies, consistent with a biphasic benign mesothelioma of peritoneal origin. This is the first reported case of mesothelioma in a captive jaguar.

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TÍTULO / TITLE: A practical approach to radiological evaluation of CT lung cancer screening examinations.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Xie X; Heuvelmans MA; van Ooijen PM; Oudkerk M; Vliegenthart R
INSTITUCIÓN / INSTITUTION: Center for Medical Imaging - North East Netherlands, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; Department of Radiology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
RESUMEN / SUMMARY: Lung cancer is the most common cause of cancer-related death in the world. The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) was launched to investigate whether screening for lung cancer by low-dose multidetector computed tomography (CT) in high-risk patients will lead to a decrease in lung cancer mortality. The NELSON lung nodule management is based on nodule volumetry and volume doubling time assessment. Evaluation of CT examinations in lung cancer screening can also include assessment of coronary calcification, emphysema and airway wall thickness, biomarkers for major diseases that share risk factors with lung cancer. In this review, a practical approach to the radiological evaluation of CT lung cancer screening examinations is described.

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RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Furrukh M

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman, E-mail: furrukh_1@yahoo.com.

RESUMEN / SUMMARY: - Tobacco smoking remains the most established cause of lung carcinogenesis and other disease processes. Over the last 50 years, tobacco refinement and the introduction of filters have brought a change in histology, and now adenocarcinoma has become the most prevalent subtype. Over the last decade, smoking also has emerged as a strong prognostic and predictive patient characteristic along with other variables. This article briefly reviews scientific facts about tobacco, and the process and molecular pathways involved in lung carcinogenesis in smokers and never-smokers. The evidence from randomised trials about tobacco smoking’s impact on lung cancer outcomes is also reviewed.

[896]

TÍTULO / TITLE: - Microenvironment-Dependent Phenotypic Changes in a SCID Mouse Model for Malignant Mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Darai-Ramqvist E; Nilsonne G; Flores-Staino C; Hjerpe A; Dobra K

INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm, Sweden; Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden.

RESUMEN / SUMMARY: - Background and Aims: Malignant mesothelioma is an aggressive, therapy-resistant tumor. Mesothelioma cells may assume an epithelioid or a sarcomatoid phenotype, and presence of sarcomatoid cells predicts poor prognosis. In this study, we investigated differentiation of mesothelioma cells in a xenograft model, where mesothelioma cells of both phenotypes were induced to form tumors in severe combined immunodeficiency mice. Methods: Xenografts were established and thoroughly characterized using a comprehensive immunohistochemical panel, array comparative genomic hybridization (aCGH) of chromosome 3, fluorescent in situ hybridization, and electron microscopy. Results: Epithelioid and sarcomatoid cells gave rise to xenografts of similar epithelioid morphology. While sarcomatoid-derived xenografts had higher growth rates, the morphology and expression of differentiation-related markers was similar between xenografts derived from both phenotypes. aCGH showed a convergent genotype for both xenografts, resembling the original aggressive sarcomatoid cell sub-line. Conclusion: Human mesothelioma xenografts from sarcomatoid and epithelioid phenotypes converged to a similar differentiation state, and genetic analyses suggested that clonal selection in the mouse microenvironment...
was a major contributing factor. This thoroughly characterized animal model can be
used for further studies of molecular events underlying tumor cell differentiation.

[897]

TÍTULO / TITLE: - Antitumor effect of para-toluenesulfonamide against lung cancer
xenograft in a mouse model.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Gao Y; Gao Y; Guan W; Huang L; Xu X; Zhang C; Chen X; Wu Y; Zeng G; Zhong N

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Respiratory Disease, First Affiliated
Hospital of Guangzhou Medical University, Guangzhou 510120, China;

RESUMEN / SUMMARY: - BACKGROUND: Conventional chemotherapy and radiation
therapy against non-small cell lung cancer (NSCLC) are relatively insensitive and
unsatisfactory. Para-toluenesulfonamide (PTS), a unique antitumor drug for local
intratumoral injection, shows an efficacy of severely suppressing solid tumor growth
with mild side effects in clinical trials. The aim of this study was to investigate the
effect of PTS on lung cancer H460 cells in vivo in nude mice and its underlying
mechanisms in vitro. METHODS: A lung cancer model for in vivo experiment was
established in BALB/c nude mice using H460 cells to examine the effect of local
injection of PTS on tumor suppression. We also assessed the injury to the normal
tissue by subcutaneous injection of PTS. In vitro, PTS was diluted into different doses
for study on its antitumor mechanisms. We evaluated the necrotic effect of PTS on
H460 cells by PI and Hoechst 33342 staining. Cell viability and membrane permeability
were also determined by using CCK-8 and LDH assays respectively. All these tests were
conducted in comparison with traditional local injection of anhydrous ethanol.

RESULTS: PTS was shown to significantly inhibit the growth of H460 tumor xenografts
in nude mice by inducing necrosis of the tumor histologically. Its effect on tumor
growth was significantly stronger than that of anhydrous ethanol. By contrast, the
injured normal tissue by PTS injection was less than that by ethanol. In vitro, PTS still
demonstrated excellent necrotizing effect on H460 cells when diluted to a lower
concentration. Detailed analysis of PTS on H460 cells indicated that PTS had a better
effect on attenuating the cell viability and increasing the cell membrane permeability
than ethanol at the same level. CONCLUSIONS: PTS exhibits excellent inhibition effect
on the growth of lung cancer by necrotizing tumor in vivo and in vitro, reducing tumor
cell viability and augmenting the membrane permeability in vitro, with only mild injury
to normal tissue. The antitumor effect of PTS on lung cancer in vivo and in vitro is
stronger than that of ethanol.
Long Non Coding RNAs (lncRNAs) Are Dysregulated in Malignant Pleural Mesothelioma (MPM).

Malignant Pleural Mesothelioma (MPM) is an aggressive cancer that is often diagnosed at an advanced stage and is characterized by a long latency period (20-40 years between initial exposure and diagnosis) and prior exposure to asbestos. Currently accurate diagnosis of MPM is difficult due to the lack of sensitive biomarkers and despite minor improvements in treatment, median survival rates do not exceed 12 months. Accumulating evidence suggests that aberrant expression of long non-coding RNAs (lncRNAs) play an important functional role in cancer biology. LncRNAs are a class of recently discovered non-protein coding RNAs >200 nucleotides in length with a role in regulating transcription. Here we used NCode long noncoding microarrays to identify differentially expressed lncRNAs potentially involved in MPM pathogenesis. High priority candidate lncRNAs were selected on the basis of statistical (P<0.05) and biological significance (>3-fold difference). Expression levels of 9 candidate lncRNAs were technically validated using RT-qPCR, and biologically validated in three independent test sets: (1) 57 archived MPM tissues obtained from extrapleural pneumonectomy patients, (2) 15 cryopreserved MPM and 3 benign pleura, and (3) an extended panel of 10 MPM cell lines. RT-qPCR analysis demonstrated consistent up-regulation of these lncRNAs in independent datasets. ROC curve analysis showed that two candidates were able to separate benign pleura and MPM with high sensitivity and specificity, and were associated with nodal metastases and survival following induction chemotherapy. These results suggest that lncRNAs have potential to serve as biomarkers in MPM.


This review summarizes current preclinical and clinical evidence in support of the hypothesis that smoking and psychological stress have significant cancer promoting effects on non small cell lung cancer and pancreatic cancer via direct and indirect effects on nicotinic receptor-regulated beta-adrenergic signaling. Evidence is provided that targeted pharmacological interference with the resulting hyperactive cAMP-dependent signaling by beta-blockers or by gamma-aminobutyric acid as well as positive psychological influences may be highly effective in preventing and improving clinical outcomes of these cancers, provided that appropriate diagnostic protocols are followed to monitor systemic levels of stress neurotransmitters and cAMP.
cancer metastasis in vivo, including bone and liver metastasis. Taken together, our results demonstrate that miR-29c serves as a tumor metastasis suppressor, which suppresses lung cancer cell adhesion to ECM and metastasis by directly inhibiting integrin beta1 and MMP2 expression and by further reducing MMP2 enzyme activity. The results show that miR-29c may be a novel therapeutic candidate target to slow lung cancer metastasis.

[901]

TÍTULO / TITLE: - Synthesis and Biological Evaluation of O-[3-(18)F-fluoropropyl]- alpha -methyl Tyrosine in Mesothelioma-Bearing Rodents.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Shih IH; Kong FL; Ali MS; Zhang Y; Yu DF; Duan X; Yang DJ
INSTITUCIÓN / INSTITUTION: - Department of Experimental Diagnosis Imaging, Unit 59, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
RESUMEN / SUMMARY: - Radiolabeled tyrosine analogs enter cancer cells via upregulated amino acid transporter system and have been shown to be superior to (18)F-fluoro-2-deoxy-D-glucose ((18)F-FDG) in differential diagnosis in cancers. In this study, we synthesized O-[3-(19)F-fluoropropyl]- alpha -methyl tyrosine ((19)F-FPAMT) and used manual and automated methods to synthesize O-[3-(18)F-fluoropropyl]- alpha -methyl tyrosine ((18)F-FPAMT) in three steps: nucleophilic substitution, deprotection of butoxycarbonyl, and deesterification. Manual and automated synthesis methods produced (18)F-FPAMT with a radiochemical purity >96%. The decay-corrected yield of (18)F-FPAMT by manual synthesis was 34% at end-of-synthesis (88 min). The decay-corrected yield of (18)F-FPAMT by automated synthesis was 15% at end-of-synthesis (110 min). (18)F-FDG and (18)F-FPAMT were used for in vitro and in vivo studies to evaluate the feasibility of (18)F-FPAMT for imaging rat mesothelioma (IL-45). In vitro studies comparing (18)F-FPAMT with (18)F-FDG revealed that (18)F-FDG had higher uptake than that of (18)F-FPAMT, and the uptake ratio of (18)F-FPAMT re

[902]
**TÍTULO / TITLE:** Quantifying variability of intrafractional target motion in stereotactic body radiotherapy for lung cancers.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** Chan MK; Kwong DL; Tam E; Tong A; Ng SC

**INSTITUCIÓN / INSTITUTION:** The University of Hong Kong; Tuen Mun Hospital. markkhchan@yahoo.com

**RESUMEN / SUMMARY:** In lung stereotactic body radiotherapy (SBRT), variability of intrafractional target motion can negate the potential benefits of four-dimensional (4D) treatment planning that aims to account for the dosimetric impacts of organ motion. This study used tumor motion data obtained from CyberKnife SBRT treatments to quantify the reproducibility of probability motion function (pmf) of 37 lung tumors. The reproducibility of pmf was analyzed with and without subtracting the intrafractional baseline drift from the original motion data. Statistics of intrafractional tumor motion including baseline drift, target motion amplitude and period, were also calculated. The target motion amplitude significantly correlates with variations (1SD) of motion amplitude and baseline drift. Significant correlation between treatment time and variations (1 SD) of motion amplitude was observed in anterior-posterior (AP) motion, but not in craniocaudal (CC) and left-right (LR) motion. The magnitude of AP and LR baseline drifts significantly depend on the treatment time, while the CC baseline drift does not. The reproducibility of pmf as a function of time can be well described by a two-exponential function with a fast and slow component. The reproducibility of pmf is over 60% for the CC motion and over 50% for the AP and LR motions when baseline variations were subtracted from the original motion data. It decreases to just over 30% for the CC motion and about 20% for the AP and LR motion, otherwise. 4D planning has obvious limitations due to variability of intrafractional target motion. To account for potential risks of overdosing critical organs, it is important to simulate the dosimetric impacts of intra- and interfractional baseline drift using population statistics obtained from SBRT treatments.

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**TÍTULO / TITLE:** Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC.

**RESUMEN / SUMMARY:** [Enlace al Resumen / Link to its Summary](#)

**REVISTA / JOURNAL:** Cancer Discov. 2013 Sep 25.

**AUTORES / AUTHORS:** Walter AO; Tjin Tham Sjin R; Haringsma HJ; Ohashi K; Sun J; Lee K; Dubrovskiy A; Labenski M; Zhu Z; Wang Z; Sheets M; St Martin T; Karp R; van Kalken D; Chaturvedi P; Niu D; Nacht M; Petter RC; Westlin W; Lin K; Jaw-Tsai S; Raponi M; Van Dyke T; Etter J; Weaver Z; Pao W; Singh J; Simmons AD; Harding TC; Allen A

[903] Enlace al texto completo (gratuito o de pago) 1158/2159-8290.CD-13-0314
INSTITUCIÓN / INSTITUTION: - 1Translational Medicine, Clovis Oncology, Inc.
RESUMEN / SUMMARY: - Non-small cell lung cancer (NSCLC) patients with activating epidermal growth factor receptor (EGFR) mutations initially respond to first generation reversible EGFR tyrosine kinase inhibitors. However, clinical efficacy is limited by acquired resistance, frequently driven by the EGFR T790M mutation. CO-1686 is a novel, irreversible and orally delivered kinase inhibitor that specifically targets the mutant forms of EGFR including T790M while exhibiting minimal activity towards the wild-type (WT) receptor. Oral administration of CO-1686 as single agent induces tumor regression in EGFR mutated NSCLC tumor xenograft and transgenic models. Minimal activity of CO-1686 against the WT EGFR receptor was observed. In NSCLC cells with acquired resistance to CO-1686 in vitro, there was no evidence of additional mutations or amplification of the EGFR gene, but resistant cells exhibited signs of epithelial-mesenchymal transition (EMT) and demonstrated increased sensitivity to AKT inhibitors. These results suggest CO-1686 may offer a novel therapeutic option for patients with mutant EGFR NSCLC.

[904]
TÍTULO / TITLE: - Malignant pleural mesothelioma: an epidemiological perspective.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2225-319X.2012.11.04
AUTORES / AUTHORS: - Robinson BM
INSTITUCIÓN / INSTITUTION: - The Baird Institute for Applied Heart and Lung Surgical Research, Sydney, Australia.
RESUMEN / SUMMARY: - This paper reviews the aetiology, distribution and projected future incidence of malignant mesothelioma. Asbestos exposure is the most thoroughly established risk factor. Debate continues regarding the relative importance of the different asbestos fibre types and the contribution of Simian virus 40 (SV40). Disease incidence varies markedly within and between countries. The highest annual rates of disease, approximately 30 case per million, are reported in Australia and Great Britain. The risk of disease increases with age and is higher in men. Time from asbestos exposure to disease diagnosis is on average greater than 40 years. Non-occupational asbestos exposures contribute an increasing proportion of disease. With the exception of the United States, incidence continues to increase. In developed countries peak incidence is expected to occur before 2030.

[905]
TÍTULO / TITLE: - Orai3 constitutes a native store-operated calcium entry that regulates non small cell lung adenocarcinoma cell proliferation.
Orai channels have been associated with cell proliferation, survival and metastasis in several cancers. The present study investigates the expression and the role of Orai3 in cell proliferation in non-small cell lung cancer (NSCLC). We show that Orai3 is over-expressed in cancer tissues as compared to the non-tumoral ones. Furthermore, Orai3 staining is stronger in high grade tumors. Pharmacological inhibition or knockdown of Orai3 significantly reduced store operated calcium entry (SOCE), inhibited cell proliferation and arrested cells of two NSCLC cell lines in G0/G1 phase. These effects were concomitant with a down-regulation of cyclin D1, cyclin E, CDK4 and CDK2 expression. Moreover, Orai3 silencing decreased Akt phosphorylation levels. In conclusion, Orai3 constitutes a native SOCE pathway in NSCLC that controls cell proliferation and cell cycle progression likely via Akt pathway.

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**TÍTULO / TITLE:** Structural Basis for Hyperpermeability of Tumor Vessels in Advanced Lung Adenocarcinoma Complicated by Pleural Effusion.

**RESUMEN / SUMMARY:** BACKGROUND: Malignant pleural effusion (MPE) has a profound impact on quality of life and survival in patients with lung cancer. Identification of the factors within the tumor and its environment that mediate MPE is still lacking. PATIENTS AND METHODS: Intratumoral microvessel density (MVD), endothelial cell and pericyte (PC) capillary coverage, endothelial cell (EC)-PC relationship, lymphatic endothelium integrity, and the expression of receptor tyrosine kinases were all assessed immunohistochemically in pleural tumor biopsy specimens from 24 patients with lung adenocarcinoma (ADC) with and without pleural disease, with the aim to evaluate the involvement with MPE. RESULTS: In the effusion-positive (+) specimens, MVD values were found to be significantly higher, and a number of vessels were noted...
to lack immunoreactivity for ECs (CD31). Likewise, PC alpha-smooth muscle actin (alphaSMA) expression was also less extensive in the MPE+ cases. The observation of only sporadic staining of PCs can also explain the findings regarding platelet-derived growth factor receptors (PDGFRs), the expression of which, although more prominent in MPE+ samples, were almost exclusively detected on tumor stromal cells and not on vascular PCs. Conversely, vascular endothelial growth factor receptors (VEGFRs) appeared on both kinds of cells. With respect to lymphatic vessels, lymphatic intraluminal tumor cells were occasionally found in MPE+ specimens. CONCLUSION: Our study suggests that disturbed vessel wall integrity, as well as abnormalities of fluid clearance by the lymphatic system, together with overexpression of growth factors, may take part in the pleural fluid accumulation in lung ADCs. Results of the decreased PC capillary coverage and PDGFR expression in MPE are discussed.

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[907]

**TÍTULO / TITLE:** - Overcoming chemoresistance of small-cell lung cancer through stepwise HER2-targeted antibody-dependent cell-mediated cytotoxicity and VEGF-targeted antiangiogenesis.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Minami T; Kijima T; Kohmo S; Arase H; Otani Y; Nagatomo I; Takahashi R; Miyake K; Higashiguchi M; Morimura O; Ihara S; Tsujino K; Hirata H; Inoue K; Takeda Y; Kida H; Tachibana I; Kumanogoh A

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka, Japan.

**RESUMEN / SUMMARY:** - Small-cell lung cancer (SCLC) easily recurs with a multidrug resistant phenotype. However, standard therapeutic strategies for relapsed SCLC remain unestablished. We found that human epidermal growth factor receptor 2 (HER2) is not only expressed in pretreated human SCLC specimens, but is also upregulated when HER2-positive SCLC cells acquire chemoresistance. Trastuzumab induced differential levels of antibody-dependent cell-mediated cytotoxicity (ADCC) to HER2-positive SCLC cells. Furthermore, as a mechanism of the differential levels of ADCC, we have revealed that coexpression of intracellular adhesion molecule (ICAM)-1 on SCLC cells is essential to facilitate and accelerate the trastuzumab-mediated ADCC. Although SN-38-resistant SCLC cells lacking ICAM-1 expression were still refractory to trastuzumab, their in vivo growth was significantly suppressed by bevacizumab treatment due to dependence on their distinctive and abundant production of vascular endothelial growth factor. Collectively, stepwise treatment with trastuzumab and bevacizumab is promising for the treatment of chemoresistant SCLC.

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[908]
**TÍTULO / TITLE:** Microspheres targeted with a mesothelin antibody and loaded with doxorubicin reduce tumor volume of human mesotheliomas in xenografts.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**REVISTA / JOURNAL:** BMC Cancer. 2013 Sep 11;13(1):400.

●● Enlace al texto completo (gratuito o de pago) 1186/1471-2407-13-400

**AUTORES / AUTHORS:** Macura SL; Steinbacher JL; Macpherson MB; Lathrop MJ; Sayan M; Hillegass JM; Beuschel SL; Perkins TN; Spiess PC; van der Vliet A; Butnor KJ; Shukla A; Wadsworth M; Landry CC; Mossman BT

**RESUMEN / SUMMARY:** BACKGROUND: Malignant mesotheliomas (MMs) are chemoresistant tumors related to exposure to asbestos fibers. The long latency period of MM (30-40 yrs) and heterogeneity of tumor presentation make MM difficult to diagnose and treat at early stages. Currently approved second-line treatments following surgical resection of MMs include a combination of cisplatin or carboplatin (delivered systemically) and pemetrexed, a folate inhibitor, with or without subsequent radiation. The systemic toxicities of these treatments emphasize the need for more effective, localized treatment regimens. METHODS: Acid-prepared mesoporous silica (APMS) microparticles were loaded with doxorubicin (DOX) and modified externally with a mesothelin (MB) specific antibody before repeated intraperitoneal (IP) injections into a mouse xenograft model of human peritoneal MM. The health/weight of mice, tumor volume/weight, tumor necrosis and cell proliferation were evaluated in tumor-bearing mice receiving saline, DOX high (0.2 mg/kg), DOX low (0.05 mg/kg), APMS-MB, or APMS-MB-DOX (0.05 mg/kg) in saline. RESULTS: Targeted therapy (APMS-MB-DOX at 0.05 mg/kg) was more effective than DOX low (0.05 mg/kg) and less toxic than treatment with DOX high (0.2 mg/kg). It also resulted in the reduction of tumor volume without loss of animal health and weight, and significantly decreased tumor cell proliferation. High pressure liquid chromatography (HPLC) of tumor tissue confirmed that APMS-MB-DOX particles delivered DOX to target tissue. CONCLUSIONS: Data suggest that targeted therapy results in greater chemotherapeutic efficacy with fewer adverse side effects than administration of DOX alone. Targeted microparticles are an attractive option for localized drug delivery.

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**TÍTULO / TITLE:** Quantitative proteomics profiling of primary lung adenocarcinoma tumors reveals functional perturbations in tumor metabolism.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary


●● Enlace al texto completo (gratuito o de pago) 1021/pr4002096

**AUTORES / AUTHORS:** Pernemalm M; De Petris L; Branca RM; Forshed J; Kanter L; Soria JC; Girard P; Validire P; Pawitan Y; van den Oord J; Lazar V; Pahlman S; Lewensohn R; Lehtio J
INSTITUCIÓN / INSTITUTION: - Cancer Proteomics Mass Spectrometry, Department of Oncology-Pathology, Science for Life Laboratory, Karolinska Institutet, Stockholm, Sweden.

RESUMEN / SUMMARY: - In this study, we have analyzed human primary lung adenocarcinoma tumors using global mass spectrometry to elucidate the biological mechanisms behind relapse post surgery. In total, we identified over 3000 proteins with high confidence. Supervised multivariate analysis was used to select 132 proteins separating the prognostic groups. Based on in-depth bioinformatics analysis, we hypothesized that the tumors with poor prognosis had a higher glycolytic activity and HIF activation. By measuring the bioenergetic cellular index of the tumors, we could detect a higher dependency of glycolysis among the tumors with poor prognosis. Further, we could also detect an up-regulation of HIF1alpha mRNA expression in tumors with early relapse. Finally, we selected three proteins that were upregulated in the poor prognosis group (cathepsin D, ENO1, and VDAC1) to confirm that the proteins indeed originated from the tumor and not from a stromal or inflammatory component. Overall, these findings show how in-depth analysis of clinical material can lead to an increased understanding of the molecular mechanisms behind tumor progression.

[910]

TÍTULO / TITLE: - Autophagy is required for mitochondrial function, lipid metabolism, growth and fate of KRAS (G12D) -driven lung tumors.

RESUMEN / SUMMARY: - Evidence suggests that the role of autophagy in tumorigenesis is context dependent. Using genetically engineered mouse models (GEMMs) for human non-small-cell lung cancer (NSCLC), we found that deletion of the essential autophagy gene, Atg7, in KRAS (G12D) -driven NSCLC inhibits tumor growth and converts adenomas and adenocarcinomas to benign oncocytomas characterized by the accumulation of respiration-defective mitochondria. Atg7 is required to preserve mitochondrial fatty acid oxidation (FAO) to maintain lipid homeostasis upon additional loss of Trp53 in NSCLC. Furthermore, cell lines derived from autophagy-deficient tumors depend on glutamine to survive starvation. This suggests that autophagy is essential for the metabolism, growth and fate of NSCLC.

[911]

TÍTULO / TITLE: - Radical sublobar resection for small-diameter lung cancers.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 1016/j.thorsurg.2013.04.003

Enlace al Resumen / Link to its Summary

Enlace al texto completo (gratuito o de pago) 1016/j.clclc.2013.06.001

Enlace al texto completo (gratuito o de pago) 1016/j.clclc.2013.06.001
collates data from January 2000 through August 2012 on the use of pemetrexed-platinum regimens in the adjuvant setting either alone or in combination with targeted agents. To date, more than 1000 patients with early stage NSCLC have been enrolled in adjuvant therapy studies evaluating various pemetrexed-containing treatment regimens, and additional patients are being enrolled in ongoing studies. Current evidence appears to favor the combination with cisplatin over that with carboplatin. We await more robust safety and efficacy data from these ongoing adjuvant trials to define with clarity the role of pemetrexed-containing regimens in this setting.

[913]
TÍTULO / TITLE: Surgeon’s view: is palliative resection of lung cancer ever justified?
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Shamji FM; Deslauriers J
INSTITUCIÓN / INSTITUTION: Division of Thoracic Surgery, Ottawa Hospital - General Campus, University of Ottawa, 501 Smyth Road, Room 6362, Box 708, Ottawa, Ontario K1H 8L6, Canada. fshamji@ottawahospital.on.ca
RESUMEN / SUMMARY: Thoracic surgeons are often asked to see patients with locally advanced primary lung cancer in whom the goal of treatment is palliation for relief of disabling symptoms. The last four decades have brought great changes in the care of patients with primary lung cancer. The goals of the treatment must be well-defined by the interdisciplinary team. The thoracic surgeon has to make the final decision on whether to consider an operation for palliation and what is the expectation of the recommended treatment.

[914]
TÍTULO / TITLE: Unidirectionally progressive resection of lower right lung cancer under video-assisted thoracoscopy.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Cai K; Wu H; Ren P; Cai R; Xiong G; Wang H
INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
RESUMEN / SUMMARY: The surgery is performed under general anesthesia with double-lumen endotracheal intubation. The patient is placed in a 90-degree position lying on the unaffected side. An approximately 1.5-cm observation port is created in the 7th
intercostal space between the middle and anterior axillary lines, an approximately 4-cm working port in the 4th intercostal space between the anterior axillary line and the midclavicular line, and an approximately 1.5-cm auxiliary port in the 9th intercostal space between the posterior axillary line and the subscapular line. The operator stands in front of the patient, manipulating the endoscopic instruments while watching the monitor. SURGICAL PROCEDURE: since the patient has right lower lung cancer, a unidirectional procedure is adopted for the surgery, in which the layers of structure are treated one after another until the fissure from a single direction through the working port. Hence, the pulmonary vein, bronchi, pulmonary artery and the poorly developed fissure of the right lower lobe are treated successively during lobectomy. The vessels, bronchi and fissures are cut using an endoscopic linear stapler or the Hemolock clips. The resected lobe is placed into a size 8 sterile glove and retrieved through the working port to prevent contamination of the chest incision by any tumor tissue. Mediastinal lymph node dissection is performed at the end.

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TÍTULO / TITLE: Indication for VATS sublobar resections in early lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Martin-Ucar AE; Delgado Roel M
INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Nottingham University Hospitals NHS Trust, Nottingham, UK;
RESUMEN / SUMMARY: When dealing with early non-small cell lung cancer (NSCLC) sublobar resections still remain part of the surgical armamentarium. In selected patients with lung cancer, the combination of the potential benefits of parenchyma sparing procedures to the limited trauma provided by Video Assisted Thoracic Surgery (VATS) techniques can become very appealing. Two main groups are included: non-anatomical (wedges) and anatomical (segmentectomies) excisions. We describe the techniques, results and potential indications of both of these techniques.

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TÍTULO / TITLE: Inflammation in malignant mesothelioma - friend or foe?
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Linton A; van Zandwijk N; Reid G; Clarke S; Cao C; Kao S
Unilateral pulmonary hilar tumor mass: is it always lung cancer?

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by noncaseating epithelioid cell granulomas. In sarcoidosis, the most common radiological findings are mediastinal and bilateral hilar lymph node enlargement. We present a case of sarcoidosis with a rare radiological aspect of pulmonary hilar tumor mass. A 54-year-old female patient, active smoker (40 packs/year), with a history of cutaneous lupus, was admitted in our institute for progressive dyspnea and dry cough. At admission physical examination and laboratory tests were normal. Pulmonary function tests diagnosed an obstructive syndrome. Chest X-ray showed a tumor mass of the right pulmonary hilum. Transbronchial biopsy was nondiagnostic. HRCT-scan showed a tumor mass in the right hilum, which raised the suspicion of a lung cancer. PET-CT scan revealed a high metabolic activity of the tumor mass and of a paratracheal right lymphadenopathy. Lymph node biopsy by mediastinoscopy showed noncaseating epithelioid-cell granulomas, sustaining the diagnosis of sarcoidosis. The outcome was favorable, with spontaneous remission without treatment, but with a relapse that responded after systemic corticotherapy. In conclusion, even if a tumor mass in the pulmonary hilum is highly suggestive of lung cancer, a positive diagnosis should be made only after histological examination, because other benign conditions, like sarcoidosis, could have such an aspect.

Hyaluronan and N-ERC/Mesothelin as Key Biomarkers in a Specific Two-Step Model to Predict Pleural Malignant Mesothelioma.

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by noncaseating epithelioid cell granulomas. In sarcoidosis, the most common radiological findings are mediastinal and bilateral hilar lymph node enlargement. We present a case of sarcoidosis with a rare radiological aspect of pulmonary hilar tumor mass. A 54-year-old female patient, active smoker (40 packs/year), with a history of cutaneous lupus, was admitted in our institute for progressive dyspnea and dry cough. At admission physical examination and laboratory tests were normal. Pulmonary function tests diagnosed an obstructive syndrome. Chest X-ray showed a tumor mass of the right pulmonary hilum. Transbronchial biopsy was nondiagnostic. HRCT-scan showed a tumor mass in the right hilum, which raised the suspicion of a lung cancer. PET-CT scan revealed a high metabolic activity of the tumor mass and of a paratracheal right lymphadenopathy. Lymph node biopsy by mediastinoscopy showed noncaseating epithelioid-cell granulomas, sustaining the diagnosis of sarcoidosis. The outcome was favorable, with spontaneous remission without treatment, but with a relapse that responded after systemic corticotherapy. In conclusion, even if a tumor mass in the pulmonary hilum is highly suggestive of lung cancer, a positive diagnosis should be made only after histological examination, because other benign conditions, like sarcoidosis, could have such an aspect.
PURPOSE: Diagnosis of malignant mesothelioma is challenging. The first available diagnostic material is often an effusion and biochemical analysis of soluble markers may provide additional diagnostic information. This study aimed to establish a predictive model using biomarkers from pleural effusions, to allow early and accurate diagnosis.

PATIENTS AND METHODS: Effusions were collected prospectively from 190 consecutive patients at a regional referral centre. Hyaluronan, N-ERC/mesothelin, C-ERC/mesothelin, osteopontin, syndecan-1, syndecan-2, and thioredoxin were measured using ELISA and HPLC. A predictive model was generated and validated using a second prospective set of 375 effusions collected consecutively at a different referral centre.

RESULTS: Biochemical markers significantly associated with mesothelioma were hyaluronan (odds ratio, 95% CI: 8.82, 4.82-20.39), N-ERC/mesothelin (4.81, 3.19-7.93), CERC/mesothelin (3.58, 2.43-5.59) and syndecan-1 (1.34, 1.03-1.77). A two-step model using hyaluronan and N-ERC/mesothelin, and combining a threshold decision rule with logistic regression, yielded good discrimination with an area under the ROC curve of 0.99 (95% CI: 0.97-1.00) in the model generation dataset and 0.83 (0.74-0.91) in the validation dataset, respectively.

CONCLUSIONS: A two-step model using hyaluronan and N-ERC/mesothelin predicts mesothelioma with high specificity. This method can be performed on the first available effusion and could be a useful adjunct to the morphological diagnosis of mesothelioma.

Squamous cell lung cancer causes approximately 400,000 deaths worldwide per year. Identification of specific molecular alterations, such as activating mutations in the epidermal growth factor receptor kinase and echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase fusions have led to significant therapeutic gains in patients with adenocarcinoma. However, meaningful therapeutic gains based on the molecular pathobiology of squamous cell lung cancer have not yet been realized. A comprehensive genomic characterization of 178 cases of squamous cell lung cancer has recently been reported. Squamous cell lung cancer appears to be characterized by a broader and more complex group of genomic alterations than adenocarcinoma. In this review, potentially targetable genes or pathways in squamous cell lung cancer are emphasized in relation to available treatment options.
therapeutic agents in development or active clinical trials. This organization of data will provide a framework for development for clinical investigation. Squamous cell lung cancer appears to be characterized by not only driver mutations in candidate genes but also gene copy number alterations resulting in tumor proliferation and survival. Better understanding of these genetic alterations and their use as therapeutic targets will require broad collaboration between industry, government, the cooperative groups, and academic institutions with the ultimate goal of rapid translation of scientific advancement to patient benefit.

[920]

TÍTULO / TITLE: - Role of E3 ubiquitin ligases in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Snoek BC; de Wilt LH; Jansen G; Peters GJ
INSTITUCIÓN / INSTITUTION: - Barbara C Snoek, Leonie HAM de Wilt, Godefridus J Peters, Department of Medical Oncology, VU University Medical Center, 1081 HV Amsterdam, The Netherlands.
RESUMEN / SUMMARY: - E3 ubiquitin ligases are a large family of proteins that catalyze the ubiquitination of many protein substrates for targeted degradation by the 26S proteasome. Therefore, E3 ubiquitin ligases play an essential role in a variety of biological processes including cell cycle regulation, proliferation and apoptosis. E3 ubiquitin ligases are often found overexpressed in human cancers, including lung cancer, and their deregulation has been shown to contribute to cancer development. However, the lack of specific inhibitors in clinical trials is a major issue in targeting E3 ubiquitin ligases with currently only one E3 ubiquitin ligase inhibitor being tested in the clinical setting. In this review, we focus on E3 ubiquitin ligases that have been found deregulated in lung cancer. Furthermore, we discuss the processes in which they are involved and evaluate them as potential anti-cancer targets. By better understanding the mechanisms by which E3 ubiquitin ligases regulate biological processes and their exact role in carcinogenesis, we can improve the development of specific E3 ubiquitin ligase inhibitors and pave the way for novel treatment strategies for cancer patients.

[921]

TÍTULO / TITLE: - Elevated prx1 provides resistance to docetaxel, but is not associated with predictive significance in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

Epub 2013 Aug 30.
RESUMEN / SUMMARY: BACKGROUND: This study was conducted in order to elucidate the effects of docetaxel on the growth of peroxiredoxin 1 (Prx1) knockdown A549 xenograft tumors and further tested the role of Prx1 as a predictor for how a patient would respond to docetaxel treatment. METHODS: Effects of docetaxel on the growth of scrambled- and shPrx1-infected A549 xenograft tumors in nude mice were measured. Moreover, immunohistochemical expression of Prx1 was evaluated in paraffin-embedded tissues from 24 non-small cell lung cancer patients who had received docetaxel-cisplatin regimens as a first-line treatment. RESULTS: Docetaxel treatment in Prx1 knockdown xenograft tumor resulted in reduced tumors growth compared with other groups. Prx1 knockdown increased the production of cleaved caspases-8 and -9 in the control itself compared to scramble tumors. Moreover, docetaxel treatment in Prx1 knockdown tissue led to an increased protein band. Phosphorylated Akt was found in Prx1 scramble tissues. Phosphorylated FOXO1 was detected in the docetaxel treatment group. On the other hand, Prx1 knockdown completely suppressed the Akt-FOXO1 axis. The median progression-free survival (PFS) of patients with low Prx1 expression was 7 months (95% confidence interval [CI], 6.0-7.7), whereas the median progression-free survival of patients with high Prx1 expression was 4 months (95% CI, 4.0-5.0). However, high Prx1 expression was not associated with decreased PFS (p=0.114). CONCLUSION: Our findings suggest that elevated Prx1 provides resistance to docetaxel treatment through suppression of FOXO1-induced apoptosis in A549 xenograft tumors, but may not be related with the predictive significance for response to docetaxel treatment.
RESUMEN / SUMMARY: Lung cancer is biologically aggressive and is the leading cause of cancer-related deaths. The development of lung cancer is unique in each patient according to clinical characterizations, prognosis, response and tolerance to treatment. Traditional capillary-based single-gene sequencing by a first-generation technique (known as Sanger sequencing) has been replaced by next-generation sequencing (NGS) since it allows massive parallel sequencing with lower cost and higher throughput. The NGS approach has made remarkable advances compared with traditional methods. We expect these methodologies to comprehensively interpret the global landscape of cancer and provide more information to fulfill the needs of personalized medicine. This review covers a brief introduction and summary on various NGS technologies, applications and important findings by NGS in lung cancer advances, including further discoveries in previously known target genes (EGFR, ALK and KRAS), the identification of additional lung cancer mutations and the global coordination of cancer genome studies.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Schuerle T; Aoun E; Farah K
INSTITUCIÓN / INSTITUTION: West Penn Allegheny Health System, Pittsburgh, Pennsylvania, USA.
RESUMEN / SUMMARY: Primary small cell carcinoma of the oesophagus is a rare, highly aggressive malignancy with diagnosis usually occurring at the most advanced stages. We report a case of small cell carcinoma of the oesophagus presenting with dysphagia and melena. A 79-year-old Caucasian man presented to an outside hospital with dizziness, light-headedness, chest pain and melena for 3 days. He had a history of intermittent dysphagia for solids and a 25-pound weight loss in the past 2 months. He underwent an esophagogastrroduodenoscopy that revealed a large polypoid, well-circumscribed friable oesophageal mass causing near complete obstruction of the lumen. This mass extended into the gastric cardia. Oesophageal biopsies were consistent with small cell neuroendocrine carcinoma. He underwent chemotherapy with subsequent remission and developed recurrence of disease in the oesophagus 2 years later. Overall, the patient has had two recurrences of his disease but has survived for more than 2 years with chemotherapy alone.
Combination of carbonic anhydrase inhibitor, acetazolamide, and sulforaphane, reduces the viability and growth of bronchial carcinoid cell lines.

BACKGROUND: Bronchial carcinoids are pulmonary neuroendocrine cell-derived tumors comprising typical (TC) and atypical (AC) malignant phenotypes. The 5-year survival rate in metastatic carcinoid, despite multiple current therapies, is 14-25%. Hence, we are testing novel therapies that can affect the proliferation and survival of bronchial carcinoids.

METHODS: In vitro studies were used for the dose-response (AlamarBlue) effects of acetazolamide (AZ) and sulforaphane (SFN) on clonogenicity, serotonin-induced growth effect and serotonin content (LC-MS) on H-727 (TC) and H-720 (AC) bronchial carcinoid cell lines and their derived NOD/SCID mice subcutaneous xenografts. Tumor ultrastructure was studied by electron microscopy. Invasive fraction of the tumors was determined by matrigel invasion assay. Immunohistochemistry was conducted to study the effect of treatment(s) on proliferation (Ki67, phospho histone-H3) and neuroendocrine phenotype (chromogranin-A, tryptophan hydroxylase).

RESULTS: Both compounds significantly reduced cell viability and colony formation in a dose-dependent manner (0-80 mM, 48 hours and 7 days) in H-727 and H-720 cell lines. Treatment of H-727 and H-720 subcutaneous xenografts in NOD/SCID mice with the combination of AZ + SFN for two weeks demonstrated highly significant growth inhibition and reduction of 5-HT content and reduced the invasive capacity of H-727 tumor cells. In terms of the tumor ultrastructure, a marked reduction in secretory vesicles correlated with the decrease in 5-HT content.

CONCLUSIONS: The combination of AZ and SFN was more effective than either single agent. Since the effective doses are well within clinical range and bioavailability, our results suggest a potential new therapeutic strategy for the treatment of bronchial carcinoids.


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CONCLUSIONS: The combination of AZ and SFN was more effective than either single agent. Since the effective doses are well within clinical range and bioavailability, our results suggest a potential new therapeutic strategy for the treatment of bronchial carcinoids.
INSTITUCIÓN / INSTITUTION: Hugo W. Moser Research Institute at Kennedy Krieger, Baltimore, Maryland, United States of America.

RESUMEN / SUMMARY: Lung cancer is the leading cause of cancer deaths worldwide. In the United States, only one in six lung cancer patients survives five years after diagnosis. These statistics may improve if new therapeutic targets are identified. We previously reported that an enzyme of fatty acid metabolism, very long-chain acyl-CoA synthetase 3 (ACSVL3), is overexpressed in malignant glioma, and that depleting glioblastoma cells of ACSVL3 diminishes their malignant properties. To determine whether ACSVL3 expression was also increased in lung cancer, we studied tumor histologic sections and lung cancer cell lines. Immunohistochemical analysis of normal human lung showed moderate ACSVL3 expression only in bronchial epithelial cells. In contrast, all of 69 different lung tumors tested, including adenocarcinoma, squamous cell, large cell, and small cell carcinomas, had robustly elevated ACSVL3 levels. Western blot analysis of lung cancer cell lines derived from these tumor types also had significantly increased ACSVL3 protein compared to normal bronchial epithelial cells. Decreasing the growth rate of lung cancer cell lines did not change ACSVL3 expression. However, knocking down ACSVL3 expression by RNA interference reduced cell growth rates in culture by 65-76%, and the ability of tumor cells to form colonies in soft agar suspension by 65-80%. We also conducted studies to gain a better understanding of the biochemical properties of human ACSVL3. ACSVL3 mRNA was detected in many human tissues, but the expression pattern differed somewhat from that of the mouse. The enzyme activated long- and very long-chain saturated fatty acid substrates, as well as long-chain mono- and polyunsaturated fatty acids to their respective coenzyme A derivatives. Endogenous human ACSVL3 protein was found in a punctate subcellular compartment that partially colocalized with mitochondria as determined by immunofluorescence microscopy and subcellular fractionation. From these studies, we conclude that ACSVL3 is a promising new therapeutic target in lung cancer.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Sarkar A; Das A; Basuthakur S; Pandit S; Das SK; Choudhury S
INSTITUCIÓN / INSTITUTION: Department of Pulmonary Medicine, Midnapore Medical College, Paschim Midnapore, West Bengal, India.
RESUMEN / SUMMARY: Pancoast syndrome is a common presentation of bronchogenic carcinoma, but other malignancies are rarely cited as its cause. Pancoast syndrome due to non-Hodgkin’s lymphoma is rarely described in the literature. Here, we report a case of Pancoast syndrome due to non-Hodgkin’s lymphoma to increase the awareness
of the clinicians regarding essentiality of tissue diagnosis of Pancoast tumor before starting the treatment.

[928]
TÍTULO / TITLE: - The role of afatinib in the management of non-small cell lung carcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1517/1742525.2013.832755
AUTORES / AUTHORS: - Yap TA; Popat S
INSTITUCIÓN / INSTITUTION: - Royal Marsden NHS Foundation Trust , London , UK +44 20 7352 8171 ; sanjay.popat@rmh.nhs.uk.
RESUMEN / SUMMARY: - Introduction: Despite initial patient benefit, drug resistance to first-generation EGFR tyrosine kinase inhibitors (TKIs) is inevitable. One of the key mechanisms responsible for the development of acquired drug resistance is the secondary T790M missense mutation in exon 20 of the EGFR kinase domain. Afatinib is an ATP-competitive small molecule inhibitor that potently and irreversibly inhibits EGFR and mutated EGFR including the T790M variant, as well as other members of the ErbB family in preclinical studies. Areas covered: The authors describe the rationale and provide the preclinical background to afatinib and its potential as a NSCLC therapy. Specifically, the authors detail the drug’s pharmaco-kinetic profile and review its clinical efficacy and toxicity profile. Expert opinion: Afatinib is an effective treatment option for therapy-naive advanced NSCLC harboring an activating EGFR mutation. Furthermore, it is also of potential benefit to patients with acquired resistance to EGFR kinase inhibitors. In the future, the authors envision the clinical development of third-generation EGFR mutation-specific inhibitors in NSCLC, which may potentially spare normal tissue toxicity. Nevertheless, afatinib currently represents a bona fide treatment option in the NSCLC therapeutic armamentarium.

[929]
TÍTULO / TITLE: - Mesothelin-targeted immunotherapies for malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 3978/j.issn.2225-319X.2012.10.03
AUTORES / AUTHORS: - Villena-Vargas J; Adusumilli PS
INSTITUCIÓN / INSTITUTION: - Center for Cell Engineering and Department of Surgery, Thoracic Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA.
Pulmonary tuberculosis and lung cancer: simultaneous and sequential occurrence.

Objective: Lung cancer (LC) is the leading cause of cancer-related death and represents a major public health problem worldwide. Another major cause of morbidity and mortality, especially in developing countries, is tuberculosis. The simultaneous or sequential occurrence of pulmonary tuberculosis and LC in the same patient has been reported in various case series and case-control studies. The objective of this study was to describe the characteristics of patients developing tuberculosis and LC, either simultaneously or sequentially. Methods: This was a cross-sectional study based on the review of medical charts. Results: The study involved 24 patients diagnosed with tuberculosis and LC between 2009 and 2012. The diagnoses of tuberculosis and LC occurred simultaneously in 10 patients, whereas tuberculosis was diagnosed prior to LC in 14. The median time between the two diagnoses was 5 years (interquartile range: 1-30 years). Fourteen patients (58.3%) were male, 20 (83.3%) were White, and 22 (91.7%) were smokers or former smokers. The most common histological type was adenocarcinoma, identified in 14 cases (58.3%), followed by epidermoid carcinoma, identified in 6 (25.0%). Seven patients (29.2%) presented with distant metastases at diagnosis; of those 7 patients, 5 (71%) were diagnosed with LC and tuberculosis simultaneously. Conclusions: In the present study, most of the patients with tuberculosis and LC were smokers or former smokers, and tuberculosis was diagnosed either before or simultaneously with LC. Non-small cell lung cancer, especially adenocarcinoma, was the most common histological type.

Optimizing the management of lung cancer: Role of the pulmonologist in India.

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EGFR Exon-Level Biomarkers of the Response to Bevacizumab/Erlotinib in Non-Small Cell Lung Cancer.

RESUMEN / SUMMARY: - Activating epidermal growth factor receptor (EGFR) mutations are recognized biomarkers for patients with metastatic non-small cell lung cancer (NSCLC) treated with EGFR tyrosine kinase inhibitors (TKIs). EGFR TKIs can also have activity against NSCLC without EGFR mutations, requiring the identification of additional relevant biomarkers. Previous studies on tumor EGFR protein levels and EGFR gene copy number revealed inconsistent results. The aim of the study was to identify novel biomarkers of the response to TKIs in NSCLC by investigating whole genome expression at the exon-level. We used exon arrays and clinical samples from a previous trial (SAKK19/05) to investigate the expression variations at the exon-level of 3 genes potentially playing a key role in modulating treatment response: EGFR, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and vascular endothelial growth factor (VEGFA). We identified the expression of EGFR exon 18 as a new predictive marker for patients with untreated metastatic NSCLC treated with bevacizumab and erlotinib in the first line setting. The overexpression of EGFR exon 18 in tumor was significantly associated with tumor shrinkage, independently of EGFR mutation status. A similar significant association could be found in blood samples. In conclusion, exonic EGFR expression particularly in exon 18 was found to be a relevant predictive biomarker for response to bevacizumab and erlotinib. Based on these results, we propose a new model of EGFR testing in tumor and blood.

Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database.

RESUMEN / SUMMARY: - Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database.

AUTORES / AUTHORS: - Rusch VW; Giroux D
INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, New York, NY, USA;

RESUMEN / SUMMARY: - INTRODUCTION: A number of staging systems have been proposed for malignant pleural mesothelioma (MPM) in the past, but few have utilized a TNM (tumor, node, metastasis) system. The International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG) previously developed a TNM-staging system which has been accepted by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). The present study examines this staging system by analysing the updated IASLC database for patients with MPM. METHODS: De-identified data from participating centres dated from 1995 to 2009 were submitted to the IASLC Statistical Center. Surgical procedures included those with a curative or palliative intent. Survival was measured from the date of pathologic diagnosis to the most recent contact or death. Endpoints included overall survival and analysis of potential prognostic factors. RESULTS: Data was available for 3,101 patients from 15 centers, mostly from North America and Europe. After a median follow-up of 15 months, a number of clinicopathological and treatment-related prognostic factors were found to significantly influence overall survival. These included overall tumor stage based on the proposed TNM staging system, T category, N category, tumor histology, gender, age, and type of operation. CONCLUSIONS: The IASLC database represents the largest, multicenter and international database on MPM to date. Analyses demonstrate that the proposed TNM staging system effectively distinguishes the T and N categories, but also highlight areas for potential revision in the future.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Dhodapkar KM; Gettinger SN; Das R; Zebroski H; Dhodapkar MV

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics; Yale University; New Haven, CT USA; Yale Cancer Center; Yale University; New Haven, CT USA.

RESUMEN / SUMMARY: - Immunotherapeutic strategies including the blockade of programmed death 1 (PD-1) receptors hold promise for the treatment of various cancers including non-small cell lung carcinoma (NSCLC). Preclinical data suggest that pre-existing tumor immunity is important for disease regression upon checkpoint blockade-based therapies. However, the nature of antigen-specific T-cell responses that correlate with the clinical response to immunotherapy in NSCLC patients is not known. The embryonic stem cell gene SRY (sex determining region Y)-box 2 (SOX2) has recently emerged as a major oncogenic driver in NSCLC. Here, we show that nearly
50% of a cohort of NSCLC patients mounted both CD4+ and CD8+ T-cell responses against SOX2, which could be readily detected among peripheral blood mononuclear cells. T-cell responses against SOX2 were associated with NSCLC regression upon immunotherapy with anti-PD-1 monoclonal antibodies, whereas none of the patients lacking SOX2-specific T cells experienced disease regression following immune checkpoint blockade. Conversely, cellular and humoral responses against viral antigens or another tumor-associated antigen (NY-ESO-1) failed to correlate with the clinical response of NSCLC patients to immunotherapy. Of note, the administration of PD-1-blocking antibodies was associated with intramolecular epitope spread as well as with the amplification of SOX2-specific immune responses in vivo. These findings identify SOX2 as an important tumor-associated antigen in NSCLC and link the presence of SOX2-specific T cells with the clinical response of lung cancer patients to immunotherapy.

[TÍTULO / TITLE:] - Obstructive Jaundice due to Pancreatic Metastasis from Non-small Cell Lung Cancer.
[RESUMEN / SUMMARY:] - Enlace al Resumen / Link to its Summary
[AUTORES / AUTHORS:] - Bestari MB; Agustanti N
[INSTITUCIÓN / INSTITUTION:] - Department of Internal Medicine, Faculty of Medicine, Padjadjaran University - Hasan Sadikin Hospital, Bandung, Indonesia.
[RESUMEN / SUMMARY:] - We report a 67-year-old female patient, recently diagnosed to have non-small cell lung cancer (NSCLC). On first PET (positron emission tomography) examination in October 2009, no distant metastasis. Four months later, second PET examination was done, detecting pancreatic foci in the uncinate process and in the tail of the pancreas measuring 22 mm which were more likely to be metastatic rather than primary origin. The patient underwent chemotherapy and radiotherapy. After 1 month of follow up, jaundice was noticed. Laboratory exams and MRCP showed obstructive jaundice. ERCP was performed with biliary stenting for palliative treatment. Symptomatic metastatic lesions of the pancreas from carcinoma of the lung are extremely rare. Typically, the patients remain asymptomatic until their disease reaches a fairly advanced stage, and therapeutic options are then limited to palliative measures.

[936]
[RESUMEN / SUMMARY:] - Enlace al Resumen / Link to its Summary
[AUTORES / AUTHORS:] - Scher KS; Saldivar JS; Fishbein M; Marchevsky A; Reckamp KL
INSTITUCIÓN / INSTITUTION: - From City of Hope Comprehensive Cancer Center, Duarte, California; bDavid Geffen School of Medicine at UCLA, Los Angeles, California; and cCedars Sinai Medical Center, Hollywood, California.

RESUMEN / SUMMARY: - This case report describes the rare occurrence of a T790M resistance mutation found in a central nervous system (CNS) parenchymal metastasis. A concomitant squamous histology transformation in a lung non-T790M-resistant metastasis is also described. The authors hypothesize that this CNS resistance and histology transformation may have resulted from intermittent use of erlotinib treatment. This case report emphasizes the complexities of using erlotinib in the induction setting.

TÍTULO / TITLE: - Cytologic subtyping of lung adenocarcinoma by using the proposed International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) adenocarcinoma classification.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Rodriguez EF; Monaco SE; Dacic S

INSTITUCIÓN / INSTITUTION: - Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

RESUMEN / SUMMARY: - BACKGROUND: The significance of histologic subtyping of surgically resected lung adenocarcinoma (ADC) was recently proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification. Approximately 70% of lung cancer patients present with advanced disease, and small biopsies or cytology specimens are frequently the only available diagnostic material. It is uncertain whether proposed morphologic subtyping of ADC can be applied to small specimens. The objective of this study was to assess the applicability of morphologic subtyping of ADC on cytologic specimens. METHODS: Consecutive, newly diagnosed primary lung ADC specimens from patients with matched surgical resection and cytology specimens (n = 66) were selected for the study. The dominant morphologic pattern was determined according to the IASLC/ATS/ERS classification. The number and percentage of malignant cells in cytology specimens were also evaluated. RESULTS: Concordant subtyping of ADC between the dominant pattern on resection and cytology specimens was observed in 26 cases (40%), and was discordant in 32 cases (48%). Concordance increased in specimens that had >200 cells and when correlating with the primary or secondary histologic pattern. The acinar pattern was the most common in concordant cases, whereas discordant cases had a predominantly solid pattern. CONCLUSIONS: Application of the IASLC/ATS/ERS ADC classification to cytologic specimens is challenging and depends on the sufficient cellularity of cytologic preparations. The
identification of solid and micropapillary patterns is prognostically important but may be unreliable and difficult on cytology specimens. Future studies are needed to establish reproducible cytologic criteria for the precise subtyping of lung ADC on small specimens. Cancer (Cancer Cytopathol) 2013. © 2013 American Cancer Society.

[TÍTULO / TITLE] - Malignant peritoneal mesothelioma presenting umbilical hernia and Sister Mary Joseph’s nodule.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary]


AUTORES / AUTHORS: - Tsuuya K; Matsushima M; Nakajima T; Fujisawa M; Shirakura K; Igarashi M; Koike J; Suzuki T; Mine T

INSTITUCIÓN / INSTITUTION: - Kota Tsuuya, Masashi Matsushima, Takayuki Nakajima, Mia Fujisawa, Katsuya Shirakura, Muneki Igarashi, Jun Koike, Takayoshi Suzuki, Tetsuya Mine, Division of Gastroenterology, Department of Internal Medicine, Tokai University School of Medicine, Isehara 259-1193, Japan.

RESUMEN / SUMMARY: - Malignant peritoneal mesothelioma is a rare aggressive tumor of the peritoneum. An increasing number of malignant mesothelioma cases have been reported in recent years. We report here a very rare case of malignant peritoneal mesothelioma with both umbilical hernia and umbilical metastasis which is also called Sister Mary Joseph’s nodule. We performed laparoscopy which showed specific laparoscopic findings, and the pathological findings of the biopsy specimen led to the diagnosis. This case was associated with umbilical hernia which could be induced by massive ascites. A newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma, as shown in the present case.


RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary]


AUTORES / AUTHORS: - Krysan K; Cui X; Gardner BK; Reckamp KL; Wang X; Hong L; Walser TC; Rodriguez NL; Pagano PC; Garon EB; Brothers JF 2nd; Elashoff D; Lee JM; Spira AE; Sharma S; Fishbein MC; Dubinett SM

INSTITUCIÓN / INSTITUTION: - Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA Los Angeles, CA.

RESUMEN / SUMMARY: - PURPOSE: The EGFR tyrosine kinase inhibitors (TKIs) demonstrate efficacy in NSCLC patients whose tumors harbor activating EGFR mutations. However, patients who initially respond to EGFR TKI treatment invariably
develop resistance to the drugs. Known mechanisms account for approximately 70% of native and acquired EGFR TKI resistance. In the current study we investigated a novel mechanism of NSCLC resistance to erlotinib. Experimental Design: The mechanisms of acquired erlotinib resistance were evaluated by microarray analysis in thirteen NSCLC cell lines and in vivo in mice. Correlations between plasma neutrophil gelatinase associated lipocalin (NGAL) levels, erlotinib response and the EGFR mutational status were assessed in advanced stage NSCLC patients treated with erlotinib. RESULTS: In 5 of 13 NSCLC cell lines NGAL was significantly upregulated. NGAL knockdown in erlotinib-resistant cells increased erlotinib sensitivity in vitro and in vivo. NGAL overexpression in erlotinib-sensitive cells augmented apoptosis resistance. This was mediated by NGAL-dependent modulation of the pro-apoptotic protein Bim levels. Evaluation of the plasma NGAL levels in NSCLC patients that received erlotinib revealed that patients with lower baseline NGAL demonstrated a better erlotinib response. Compared to patients with wild type EGFR, patients with activating EGFR mutations had lower plasma NGAL at baseline and weeks 4 and 8. CONCLUSIONS: Our studies uncover a novel mechanism of NGAL-mediated modulation of Bim levels in NSCLC that might contribute to TKI resistance in lung cancer patients. These findings provide the rationale for the further investigations of the utility of NGAL as a potential therapeutic target or diagnostic biomarker.

[940]

TÍTULO / TITLE: - Development of a virtual multidisciplinary lung cancer tumor board in a community setting.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Stevenson MM; Irwin T; Lowry T; Ahmed MZ; Walden TL; Watson M; Sutton L
INSTITUCIÓN / INSTITUTION: - Duke University Health System, Durham, NC, USA.
steve041@mc.duke.edu
RESUMEN / SUMMARY: - PURPOSE: Creating an effective platform for multidisciplinary tumor conferences can be challenging in the rural community setting. The Duke Cancer Network created an Internet-based platform for a multidisciplinary conference to enhance the care of patients with lung cancer. This conference incorporates providers from different physical locations within a rural community and affiliated providers from a university-based cancer center 2 hours away. An electronic Web conferencing tool connects providers aurally and visually. METHODS: Conferences were set up using a commercially available Web conferencing platform. The video platform provides a secure Web site coupled with a secure teleconference platform to ensure patient confidentiality. Multiple disciplines are invited to participate, including radiology,
radiation oncology, thoracic surgery, pathology, and medical oncology. Participants only need telephone access and Internet connection to participate. RESULTS: Patient histories and physicals are presented, and the Web conferencing platform allows radiologic and histologic images to be reviewed. Treatment plans for patients are discussed, allowing providers to coordinate care among the different subspecialties. Patients who need referral to the affiliated university-based cancer center for specialized services are identified. Pertinent treatment guidelines and journal articles are reviewed. On average, there are 10 participants with one to two cases presented per session. CONCLUSION: The use of a Web conferencing platform allows subspecialty providers throughout the community and hours away to discuss lung cancer patient cases. This platform increases convenience for providers, eliminating travel to a central location. Coordination of care for patients requiring multidisciplinary care is facilitated, shortening evaluation time before definitive treatment plan.

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TÍTULO / TITLE: Primary small cell carcinoma of the esophagus: patient data metaanalysis and review of the literature.

RESUMEN / SUMMARY: We analysed the typical features of primary small cell carcinoma of the esophagus (SCCE) with emphasis on occurrence, behaviour, outcome and treatment options. This metaanalysis was aimed at collecting and analyzing information from international studies about handling this disease. This seems necessary due to the rarity of this disease. Studies were acquired from electronic databases and reference lists. We finally analysed 313 patient cases from the literature with oesophageal SCC. A data extraction was accomplished referring to 13 evaluable features that are described in the “methods”, whereof 7 were analyzed with univariate and multivariate tests. Three hundred thirteen cases were analyzed, 109 patients (35%) had limited stage (LS), whereas 167 (54%) had extensive stage (ES). There is no information about the remaining 35 patients concerning the stage. Univariate and multivariate analysis showed only age (<50 years vs. >50 years, HR 1.024; 95% CI 1.000-1.041, P<0.0001) and disease stage (LS vs. ES, HR 4.884; 95% CI 2.572-9.27, P<0.0001) as significant prognostic factors. There also was a statistically significant difference in survival between those patients who received therapy compared to those who only received best supportive care (11.6 months vs. 0.8 months, HR 0.093, CI 95% 0.053-0.16, P<0.001). In this first multivariate analysis for SCCE we show that SCCE is an aggressive type of tumour with a shorter survival rate compared to its counterpart.
from the lung. It is demonstrated that only disease stage (limited vs. extensive stage), age (<50 years vs. >50 years) and therapy are independent significant predictors of prognosis.

[942]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang X; Shen W; Dong X; Fan J; Liu L; Gao X; Kernstine KH; Zhong L
INSTITUCIÓN / INSTITUTION: - Department of Cell Biology, Hebei University College of Life Sciences, Baoding, Hebei, P.R.China.
RESUMEN / SUMMARY: - BACKGROUND: The malignant mesothelioma (MM) survival rate has been hampered by the lack of efficient and accurate early detection methods. The immune system may detect the early changes of tumor progression by responding with tumor-associated autoantibody production. Hence, in this study, we translated the humoral immune response to cancer proteins into a potential blood test for MM.
METHODOLOGY/PRINCIPAL FINDINGS: A T7 phage MM cDNA library was constructed using MM tumor tissues and biopanned for tumor-associated antigens (TAAs) using pooled MM patient and normal serum samples. About 1008 individual phage TAA clones from the biopanned library were subjected to protein microarray construction and tested with 53 MM and 52 control serum samples as a training group. Nine candidate autoantibody markers were selected from the training group using Tclass system and logistic regression statistical analysis, which achieved 94.3% sensitivity and 90.4% specificity with an AUC value of 0.89 in receiver operating characteristic analysis. The classifier was further evaluated with 50 patient and 50 normal serum samples as an independent blind validation, and the sensitivity of 86.0% and the specificity of 86.0% were obtained with an AUC of 0.82. Sequencing and BLASTN analysis of the classifier revealed that five of these nine candidate markers were found to have strong homology to cancer related proteins (PDIA6, MEG3, SDCCAG3, IGHG3, IGHG1). CONCLUSIONS/SIGNIFICANCE: Our results indicated that using a panel of 9 autoantibody markers presented a promising accuracy for MM detection. Although the results need further validation in high-risk groups, they provided the potentials in developing a serum-based assay for MM diagnosis.

[943]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
TÍTULO / TITLE: - About a submucosal tracheal tumor.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1186/1477-7819-11-229
AUTORES / AUTHORS: - Serraj M; Lakranbi M; Ghalimi J; Ouadnouni Y; Tiznit1 S; Smahi M
RESUMEN / SUMMARY: - The authors report the case of a 46-year-old man with recurrent hemoptysis. Bronchoscopy revealed a submucosal tumor protruding into the tracheal lumen. Transbrachial biopsy failed to obtain a conclusive diagnosis; only surgery allowed complete resection of the tumor and confirmed the diagnosis of tracheal mucoepidermoid carcinoma. We discuss the unusual submucosal presentation of this tumor, and the contribution of surgery for diagnosis and therapy.

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TÍTULO / TITLE: - Proteomic analysis of non-small cell lung cancer tissue interstitial fluids.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●● Enlace al texto completo (gratuito o de pago) 1186/1477-7819-11-173
AUTORES / AUTHORS: - Li S; Wang R; Zhang M; Wang L; Cheng S
RESUMEN / SUMMARY: - BACKGROUND: Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers, and reliable biomarkers are desirable. The present investigation assesses our ability to identify tumor relevant proteins from NSCLC tissue interstitial fluid (TIF). METHODS: Paired TIF was collected from three NSCLC patients at the time of surgery, and resolved by two-dimensional gel electrophoresis and in-gel digestion for proteomic analysis. Differentially expressed spots were extracted from the two-dimensional gel and characterized by high-performance liquid chromatography-tandem mass spectrometry. Then, ELISA was used to verify the expression of peroxiredoxin 1 (PRDX1) in TIF of patients with NSCLC and benign lung disease. Finally, the relationship between expression of PRDX1 and clinicopathological features was determined. RESULTS: Comparative proteomic analysis showed 24 protein spots were differentially expressed with significant changes, including 11 upregulated proteins and 13 downregulated proteins. Of these, PRDX1 was selected for validation in TIF by Western blot and expression of PRDX1 was confirmed to be upregulated in tumor TIF. It was also demonstrated that PRDX1 was significantly
elevated in 40 NSCLC patients with a mean level of 36.0 ng/mL compared to 6.26 ng/mL from 20 patients with benign lung disease. A significant correlation was found between the high level of PRDX1 expression and lymph node metastasis and tumor differentiation. CONCLUSIONS: PRDX1 might be correlated with lymph node metastasis and differentiation, and its elevated expression in TIF may be an adverse biomarker for patients with NSCLC. PRDX1 may be attributed to the malignant transformation of NSCLC, and attention should be paid to a possible target for therapy.

[946]
TÍTULO / TITLE: Malignant mesothelioma of the pericardium: a report of two different presentations.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Makarawate P; Chaosuwannakit N; Chindaprasirt J; Ungarreevittaya P; Chaiwiriyakul S; Wirasorn K; Kuptarnond C; Sawanyawisuth K
INSTITUCIÓN / INSTITUTION: Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
RESUMEN / SUMMARY: Malignant mesothelioma of the pericardium is a rare and fatal condition that clinicians should be aware of due to its variability of clinical manifestation. The diagnosis may be delayed as a result of delayed treatment. Here, we report two cases of malignant pericardial mesothelioma with two different clinical aspects: cardiac tamponade and mimic tuberculous pericarditis. Both patients: may have indirect exposure to asbestos. Despite chemotherapy, both patients died at 2 weeks and 3 months after the diagnosis. Malignant mesothelioma of the pericardium is fatal, has a variety of presentation, and may not be related to asbestosis exposure.

[947]
TÍTULO / TITLE: Beneficial role of overexpression of TFPI-2 on tumour progression in human small cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Lavergne M; Jourdan ML; Blechet C; Guyetant S; Pape AL; Heuze-Vourch N; Courty Y; Lerondel S; Sobilo J; Iochmann S; Reverdiau P
INSTITUCIÓN / INSTITUTION: EA 6305, Universite Francoise Rabelais de Tours, Tours F-37032, France; Centre d'Etude des Pathologies Respiratoires, UMR 1100/EA6305, Tours F-37032, France.
RESUMEN / SUMMARY: - Tissue factor pathway inhibitor-2 (TFPI-2) is a potent inhibitor of plasmin, a protease which is involved in tumour progression by activating (MMPs). This therefore makes TFPI-2 a potential inhibitor of invasiveness and the development of metastases. In this study, low levels of TFPI-2 expression were found in 65% of patients with small cell lung cancer (SCLC), the most aggressive type of lung cancer. To study the impact of TFPI-2 in tumour progression, TFPI-2 was overexpressed in NCI-H209 SCLC cells which were orthotopically implanted in nude mice. Investigations showed that TFPI-2 inhibited lung tumour growth. Such inhibition could be explained in vitro by a decrease in tumour cell viability, blockade of G1/S phase cell cycle transition and an increase in apoptosis shown in NCI-H209 cells expressing TFPI-2. We also demonstrated that TFPI-2 upregulation in NCI-H209 cells decreased MMP expression, particularly by downregulating MMP-1 and MMP-3. Moreover, TFPI-2 inhibited phosphorylation of the MAPK signalling pathway proteins involved in the induction of MMP transcripts, among which MMP-1 was predominant in SCLC tissues and was inversely expressed with TFPI-2 in 35% of cases. These results suggest that downregulation of TFPI-2 expression could favour the development of SCLC.

[948]

TÍTULO / TITLE: - RAF1-MEK1-ERK/AKT axis may confer NSCLC cell lines resistance to erlotinib.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Xu ZH; Hang JB; Hu JA; Gao BL

INSTITUCIÓN / INSTITUTION: - Department of Geriatrics, Ruijin Hospital affiliated to Shanghai JiaoTong University, Shanghai, China.

RESUMEN / SUMMARY: - The fact that advanced NSCLC patients with wild type (wt) EGFR can benefit from erlotinib therapy makes it critical to find out biomarkers for effective selection of patients and improving the therapy effects. In present study, 3 NSCLC cell lines (U1752, Calu-6 and NCI-H292) with wt EGFR and different sensitivities to erlotinib were used for microarray analysis. The differential basal gene expression between 2 NSCLC cell lines was analyzed, about 353 genes were expression-altered with higher than 2-fold changes between Calu-6 and U1752. And Ingenuity Pathway Analysis (IPA) showed that these genes were mainly enriched in regulation of epithelial-mesenchymal transition (EMT) pathway, Wnt-beta catenin signaling, Tec kinase signaling and some types of cancer-related signaling. More interestingly, RAF1 (c-raf), MAP2K1 (MEK1), SNAI and downstream signaling molecules ERK and AKT were predicted to be activated in erlotinib-resistant cell line by IPA. Subsequent immunoblotting experiments showed that the phosphorylation of ERK and AKT were exactly increased stepwise from erlotinib sensitive cell line to erlotinib resistant cell lines. Collectively, activation of RAF1-MEK1-ERK/AKT axis may determine the
resistance of NSCLC cell lines bearing wt EGFR to erlotinib. Our work provides potential biomarkers and therapeutic targets for NSCLC patients harboring wt EGFR.

[949]

**TÍTULO / TITLE:** - BetaHCG secretion by a pulmonary adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Vicier C; Tabouret E; Tallet A; Goncalves A; Chetaille B; Viens P; Madroszyk A

**RESUMEN / SUMMARY:** - We report a rare case of metastatic non-small-cell lung cancer in a 43-year-old woman with a history of smoking. The tumor secreted human chorionic gonadotropin and its beta subunit (BetaHCG). The patient presented with amenorrhea, a positive pregnancy test and chest pain. A physical examination and investigations revealed no pregnancy, and it was determined that a paraneoplastic syndrome stemming from a pulmonary tumor was responsible for the secretion of BetaHCG. This secretion decreased with tumor response to chemotherapy. Only a few reports of paraneoplastic BetaHCG secretion can be found in the literature for several different cancers.

[950]

**TÍTULO / TITLE:** - Array analysis for potential biomarker of gemcitabine identification in non-small cell lung cancer cell lines.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Zhang HH; Zhang ZY; Che CL; Mei YF; Shi YZ

**INSTITUCIÓN / INSTITUTION:** - Department of rheumatism and immunology, First Clinical Medical College affiliated to Harbin Medical University Harbin, China.

**RESUMEN / SUMMARY:** - Gemcitabine is one of the most widely used drugs for the treatment of advanced Non-small cell lung cancer (NSCLC), but modest objective response rate of patients to gemcitabine makes it necessary to identify novel biomarkers for patients who can benefit from gemcitabine-based therapy and to improve the effect of clinical therapy. In this work, 3 NSCLC cell lines displaying different sensivities to gemcitabine were applied for mRNA and microRNA (miR) expression chips to figure out the biomarkers for gemcitabine sensitivity. Genes whose expression increased dramatically in sensitive cell lines were mainly enriched in cell adhesion (NRP2, CXCR3, CDK5R1, IL32 and CDH2) and secretory granule (SLC11A1, GP5, CD36 and IGF1), while genes with significantly upregulated expression in resistant cell line were mainly clustered in methylation modification (HIST1H2BF, RAB23 and TP53) and oxidoreductase (TP53I3, CYP27B1 and SOD3). The most intriguing is the activation of Wnt/beta-catenin signaling in gemcitabine resistant NSCLC cell lines.
miR-155, miR-10a, miR-30b, miR-24-2* and miR-30c-2* were upregulated in sensitive cell lines, while expression of miR-200c, miR-203, miR-885-5p, miR-195 and miR-25* was increased in resistant cell line. Genes with significantly altered expression and putatively mediated by the expression-changed miRs were mainly enriched in chromatin assembly (MAF, HLF, BCL2, and IGSF3), anti-apoptosis (BCL2, IGF1 and IKKβ), protein kinase (NRP2, PAK7 and CDK5R1) (all the above genes were upregulated in sensitive cells) and small GTPase mediated signal transduction (GNA13, RAP2A, ARHGAP5 and RAB23, down-regulated in sensitive cells). Our results might provide potential biomarkers for gemcitabine sensitivity prediction and putative targets to overcome gemcitabine resistance in NSCLC patients.
Chemoresistance is a major cause of treatment failure in patients with lung cancer. Although the extensive efforts have been made in overcoming chemoresistance, the underlying mechanisms are still elusive. Cancer cells reprogram cellular metabolism to satisfy the demands of malignant phenotype. To reveal roles of cancer metabolism in regulating chemoresistance, we profiled the metabolic characteristics in paclitaxel-resistant lung cancer cells by flux assay. Glucose and oleate metabolism were significantly different between resistant and non-resistant cells. In addition, targeting metabolism as a strategy to overcome drug resistance was investigated using specific metabolic inhibitors. Inhibition of glycolysis and oxidative phosphorylation by 2-deoxyglucose and malonate, respectively, potentiated the effects of paclitaxel on nonresistant lung adenocarcinoma cells but not paclitaxel-resistant cells. By contrast, inhibition of lipolysis by mercaptoacetate or etomoxir synergistically inhibited drug-resistant lung adenocarcinoma cell proliferation. We conclude that lipolysis inhibition potentially be a therapeutic strategy to overcome drug resistance in lung cancer.

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TÍTULO / TITLE: - Primary intrapulmonary malignant peripheral nerve sheath tumor mimicking lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - La Mantia E; Franco R; Cantile M; Rocco R; De Chiara A; Martucci N; Rocco G

INSTITUCIÓN / INSTITUTION: - Pathology Unit, National Cancer Institute, Pascale Foundation, Naples, Italy;

RESUMEN / SUMMARY: - Malignant peripheral nerve sheath tumors (MPNSTs) are sarcomas originating from the cells constituting the nerve sheaths such as Schwann cells, perineural cells or fibroblasts. They represent approximately 5-10% of all soft tissue sarcomas. They have been rarely observed in the lung. We describe a rare case of primary lung MPNST in an elderly male patient, in which surgical approach has obtained a good control of the disease. Immuno-histochemical and molecular analyses...
have been required on the surgical specimen due to inadequate possibility of recognition through morphology alone.

[954]

**TÍTULO / TITLE**: Genomic Deregulation of the E2F/Rb Pathway Leads to Activation of the Oncogene EZH2 in Small Cell Lung Cancer.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS**: Coe BP; Thu KL; Aviel-Ronen S; Vucic EA; Gazdar AF; Lam S; Tsao MS; Lam WL

**INSTITUCIÓN / INSTITUTION**: Integrative Oncology Department, BC Cancer Research Centre, Vancouver, Canada.

**RESUMEN / SUMMARY**: Small cell lung cancer (SCLC) is a highly aggressive lung neoplasm with extremely poor clinical outcomes and no approved targeted treatments. To elucidate the mechanisms responsible for driving the SCLC phenotype in hopes of revealing novel therapeutic targets, we studied copy number and methylation profiles of SCLC. We found disruption of the E2F/Rb pathway was a prominent feature deregulated in 96% of the SCLC samples investigated and was strongly associated with increased expression of EZH2, an oncogene and core member of the polycomb repressive complex 2 (PRC2). Through its catalytic role in the PRC2 complex, EZH2 normally functions to epigenetically silence genes during development, however, it aberrantly silences genes in human cancers. We provide evidence to support that EZH2 is functionally active in SCLC tumours, exerts pro-tumourigenic functions in vitro, and is associated with aberrant methylation profiles of PRC2 target genes indicative of a “stem-cell like” hypermethylator profile in SCLC tumours.

Furthermore, lentiviral-mediated knockdown of EZH2 demonstrated a significant reduction in the growth of SCLC cell lines, suggesting EZH2 has a key role in driving SCLC biology. In conclusion, our data confirm the role of EZH2 as a critical oncogene in SCLC, and lend support to the prioritization of EZH2 as a potential therapeutic target in clinical disease.

[955]

**TÍTULO / TITLE**: Hypothermia activates adipose tissue to promote malignant lung cancer progression.

**RESUMEN / SUMMARY**: Enlace al Resumen / Link to its Summary


**AUTORES / AUTHORS**: Du G; Zhao B; Zhang Y; Sun T; Liu W; Li J; Liu Y; Wang Y; Li H; Hou X
INSTITUCIÓN / INSTITUTION: - Institute of Pharmacy, Pharmaceutical College of Henan University, Jinming District, Kaifeng, Henan, China.

RESUMEN / SUMMARY: - Microenvironment has been increasingly recognized as a critical regulator of cancer progression. In this study, we identified early changes in the microenvironment that contribute to malignant progression. Exposure of human bronchial epithelial cells (BEAS-2B) to methylnitrosourea (MNU) caused a reduction in cell toxicity and an increase in clonogenic capacity when the temperature was lowered from 37 degrees C to 28 degrees C. Hypothermia-incubated adipocyte media promoted proliferation in A549 cells. Although a hypothermic environment could increase urethane-induced tumor counts and Lewis lung cancer (LLC) metastasis in lungs of three breeds of mice, an increase in tumor size could be discerned only in obese mice housed in hypothermia. Similarly, coinjections using differentiated adipocytes and A549 cells promoted tumor development in athymic nude mice when adipocytes were cultured at 28 degrees C. Conversely, fat removal suppressed tumor growth in obese C57BL/6 mice inoculated with LLC cells. Further studies show hypothermia promotes a MNU-induced epithelial-mesenchymal transition (EMT) and protects the tumor cell against immune control by TGF-beta1 upregulation. We also found that activated adipocytes trigger tumor cell proliferation by increasing either TNF-alpha or VEGF levels. These results suggest that hypothermia activates adipocytes to stimulate tumor boost and play critical determinant roles in malignant progression.

[956]

TÍTULO / TITLE: - Beneficial Impact of CCL2 and CCL12 Neutralization on Experimental Malignant Pleural Effusion.

RESUMEN / SUMMARY: - Enlace al texto completo (gratis o de pago) 1371/journal.pone.0071207

AUTORES / AUTHORS: - Marazioti A; Kairi CA; Spella M; Giannou AD; Magkouta S; Giopanou I; Papaleonidopoulos V; Kalomenidis I; Snyder LA; Kardamakis D; Stathopoulos GT

INSTITUCIÓN / INSTITUTION: - Laboratory for Molecular Respiratory Carcinogenesis, Department of Physiology, Faculty of Medicine, University of Patras, Rio, Achaia, Greece.

RESUMEN / SUMMARY: - Using genetic interventions, we previously determined that C-C motif chemokine ligand 2 (CCL2) promotes malignant pleural effusion (MPE) formation in mice. Here we conducted preclinical studies aimed at assessing the specific therapeutic potential of antibody-mediated CCL2 blockade against MPE. For this, murine MPEs or skin tumors were generated in C57BL/6 mice by intrapleural or subcutaneous delivery of lung (LLC) or colon (MC38) adenocarcinoma cells. Human lung adenocarcinoma cells (A549) were used to induce MPEs in severe combined immunodeficient mice. Intraperitoneal antibodies neutralizing mouse CCL2 and/or
CCL12, a murine CCL2 ortholog, were administered at 10 or 50 mg/kg every three days. We found that high doses of CCL2/12 neutralizing antibody treatment (50 mg/kg) were required to limit MPE formation by LLC cells. CCL2 and CCL12 blockade were equally potent inhibitors of MPE development by LLC cells. Combined CCL2 and CCL12 neutralization was also effective against MC38-induced MPE and prolonged the survival of mice in both syngeneic models. Mouse-specific CCL2-blockade limited A549-caused xenogeneic MPE, indicating that host-derived CCL2 also contributes to MPE precipitation in mice. The impact of CCL2/12 antagonism was associated with inhibition of immune and vascular MPE-related phenomena, such as inflammation, new blood vessel assembly and plasma extravasation into the pleural space. We conclude that CCL2 and CCL12 blockade are effective against experimental MPE induced by murine and human adenocarcinoma in mice. These results suggest that CCL2-targeted therapies may hold promise for future use against human MPE.
Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Within the molecular scope of NSCLC, a complex landscape of dysregulated cellular signaling has emerged, defined largely by mutations in select mediators of signal transduction, including the epidermal growth factor receptor (EGFR) and anaplastic lymphoma (ALK) kinases. Consequently, these mutant kinases become constitutively activated and targets for chemotherapeutic intervention. Encouragingly, small molecule inhibitors of these pathways have shown promise in clinical trials or are approved for clinical use. However, many protein kinases are dysregulated in NSCLC without genetic mutations. To quantify differences in tumor cell signaling that are transparent to genomic methods, we established a super-SILAC internal standard derived from NSCLC cell lines grown in vitro and labeled with heavy lysine and arginine, and deployed them in a phosphoproteomic workflow. We identified 9019 and 8753 phosphorylation sites in two separate tumors. Relative quantification of phosphopeptide abundance between tumor samples allowed for the determination of specific hubs and pathways differing between each tumor. Sites downstream of Ras showed decreased inhibitory phosphorylation (Raf/Mek) and increased activating phosphorylation (Erk1/2) in one tumor versus another. In this way, we were able to quantitatively access oncogenic kinase signaling in primary human tumors. BIOLOGICAL SIGNIFICANCE: Through the use of quantitative proteomics, we demonstrated the feasibility and coverage that large scale mass spectrometry can leverage for understanding kinase networks in cancer. By incorporating Super-SILAC based quantitation into a typical pathology workflow, we were able to access and compare tumors from multiple patients in this analysis with high accuracy and dynamic range. We analyzed tumors from patients diagnosed with non-small cell lung cancer and were able to detect comprehensive phosphorylation networks relaying through known hubs of oncogenesis in lung cancer. We hereby show that it is possible to track changes to phosphorylation networks across multiple tumors, opening up the possibility that drug susceptibility and patient-specific stratification can be implemented downstream of classical pathology.
Small cell lung cancer (SCLC) is a rapidly progressing, incurable cancer that frequently spreads to bone. New insights are needed to identify therapeutic targets to prevent or retard SCLC metastatic progression. Human SCLC SBC-5 cells in mouse xenograft models home to skeletal and non-skeletal sites while human SCLC SBC-3 cells only pervade non-skeletal sites. Because microRNAs (miRNAs) often act as tumor-regulators, we investigated their role in preclinical models of SCLC. miRNA expression profiling revealed selective and reduced expression of miR-335 and miR-29a in SBC-5 cells, compared to SBC-3 cells. In SBC-5 cells, miR-335 expression correlated with bone osteolytic lesions while miR-29a expression did not. Over-expression of miR-335 in SBC-5 cells significantly reduced cell migration, invasion, proliferation, colony formation, and osteoclast induction in vitro. Importantly, in miR-335 over-expressing SBC-5 cell xenografts (n=10), there were minimal osteolytic lesions in the majority of mice and none in three mice. Expression of RANKL and IGF-1R, key mediators of bone metastases, were elevated in SBC-5 as compared to SBC-3 cells. Mechanistically, over-expression of miR-335 in SBC-5 cells reduced RANKL and IGF-1R expression. In conclusion, loss of miR-335 promoted SCLC metastatic skeletal lesions via de-regulation of IGF-1R and RANKL pathways and was associated with metastatic osteolytic skeletal lesions. IMPLICATION STATEMENT: These preclinical findings establish a need to pursue the role of miR-335 in human SCLC with metastatic skeletal disease.
Pulmonary mucinous cystadenocarcinoma presenting as a pleural mesothelioma.

INTRODUCTION: Primary Pulmonary Mucinous Cystadenocarcinoma (PPMC) is an extremely rare subtype of pulmonary adenocarcinoma, with only a few dozen cases reported in the literature to date.

PRESENTATION OF CASE: We report a extremely rare case of pulmonary mucinous cystadenocarcinoma presenting as a pleural mesothelioma. A 53-year-old man exposed to asbestos was admitted to hospital with a 5cm mass in the right pleura. He was treated by wedge resection. Sparse groups of malignant cells were microscopically observed in pools of mucin. The postoperative histopathological findings were in accordance with the diagnosis of pulmonary mucinous cystadenocarcinoma on cystic adenoid malformation of the lung. 5 years later, the patient has no recurrence.

DISCUSSION: PPMC is usually asymptomatic; hemoptysis is seen occasionally. Preoperative diagnosis is very difficult to establish. Both FNA cytology and transbronchial lung biopsy seem inadequate. Our patient went on to undergo open lung biopsy and histopathological testing that confirmed the diagnosis of PPMC.

CONCLUSION: It is important to differentiate this rare pathological feature of the lung from other lung tumors as the treatment is surgical rather than medical. Thoracic surgeons should bear in mind this rare tumor for the differential diagnosis of a pleural mesothelioma because this tumor has a favorable prognosis.

Jugular foramen syndrome as initial presentation of metastatic lung cancer.

Metastatic involvement of the cranial base and jugular foramen generally presents with headache and lower cranial neuropathy but may escape early diagnosis. In this report, a patient developed a jugular foramen syndrome as the initial...
presentation of metastatic lung cancer soon after being diagnosed and treated surgically for extracranial atherosclerotic internal carotid artery disease. With the appropriate diagnosis established, he underwent local fractionated radiation therapy and systemic chemotherapy but succumbed to the disease. This report analyses metastatic disease affecting the cranial base and in particular, the jugular foramen, with a discussion of the clinical syndromes that accompany this rare condition.

[964]

TÍTULO / TITLE: - Small-cell lung cancer: where are we now and what can we expect for the future?
RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)
AUTORES / AUTHORS: - Karachaliou N; Rosell R
INSTITUCIÓN / INSTITUTION: - Pangaea Biotech S.L, Sabino Arana 5-19, 08023, Barcelona, España. nkarachaliou@pangaeabiotech.com

[965]

TÍTULO / TITLE: - Roles of Mir-144-ZFX Pathway in Growth Regulation of Non-Small-Cell Lung Cancer.
RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)
AUTORES / AUTHORS: - Zha W; Cao L; Shen Y; Huang M
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The First Affiliated Hospital, Nanjing Medical University, Nanjing, China.
RESUMEN / SUMMARY: - BACKGROUND: Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung carcinoma (NSCLC) accounts for most of the lung cancer cases and the prognosis of this disease remains poor despite decades of intensive investigation. Thus new insights into underlying mechanisms by which NSCLC develops are avidly needed as the basis for development of new lines of therapeutic strategies. The past decade has witnessed a growing interest on the regulatory roles of micro RNAs on various categories of malignancies. Related data has been well documented in carcinogenesis and pathophysiology of a variety of malignancies. Even so, there is a relative lack of data on roles of mir-144 in tumor biology and there has been no report showing the involvement of mir-144 in NSCLC development. METHODS/PRINCIPAL FINDING: From human NSCLC tumor tissue samples and cell culture samples, we found that the expression of mir-144 is associated with malignant phenotype of NSCLC. Further investigations showed that ectopic mir-144 expression dramatically inhibits NSCLC tumor cell growth and induces
apoptosis as manifested by elevated apoptotic protein markers and flow cytometry change. Moreover, we also found that ZFX protein expression is also associated with malignant phenotype of NSCLC and knockdown of ZFX protein results in a similar effect as of ectopic mir-144 expression. Finally, we found that ZFX expression is highly adjustable upon presence of mir-144 and ectopic expression of ZFX dramatically dampens mir-144 action of tumor inhibition. CONCLUSIONS: Our results for the first time showed mir-144-ZFX pathway is involved in the development of NSCLC, which sheds a light for further investigations on underlying mechanisms toward better understanding and management of NSCLC.

[966]
TÍTULO / TITLE: Management of tumors involving the chest wall including pancoast tumors and tumors invading the spine.
RESUMEN / SUMMARY: Bronchogenic carcinomas involving the chest wall include tumors invading the ribs and spine, as well as Pancoast tumors. In the past, such neoplasms were considered to be incurable, but with new multimodality regimens, including induction chemoradiation followed by surgery, they can now be completely resected and patients can benefit from prolonged survival. The most important prognostic factors are the completeness of resection and the pathologic nodal status.

[967]
RESUMEN / SUMMARY: Autophagic elimination of defective mitochondria suppresses oxidative stress and preserves mitochondrial function. Here, the essential autophagy gene Atg7 was deleted in a mouse model of BRAFV600E-induced lung cancer in the presence or absence of the tumor suppressor TRPV5. Atg7 deletion initially induced
oxidative stress and accelerated tumor cell proliferation in a manner indistinguishable from Nrf2 ablation. Compound deletion of Atg7 and Nrf2 had no additive effect suggesting that both genes modulate tumorigenesis by regulating oxidative stress, revealing a potential mechanism of autophagy-mediated tumor suppression. At later stages of tumorigenesis, Atg7 deficiency resulted in an accumulation of defective mitochondria, proliferative defects, reduced tumor burden, conversion of adenomas and adenocarcinomas to oncocytomas, and increased mouse lifespan. Autophagy-defective tumor-derived cell lines were impaired in their ability to respire, survive starvation and were glutamine-dependent, suggesting that autophagy-supplied substrates from protein degradation sustains BRAFV600E-tumor growth and metabolism.

[968]

TÍTULO / TITLE: Respiratory bronchiolitis and lung carcinoma.
RESUMEN / SUMMARY: Enlace a Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1016/j.resinv.2013.03.003
AUTORES / AUTHORS: Yamada Y; Terada J; Tatsumi K; Kono C; Tanno M; Takemura T; Yamaguchi T
INSTITUCIÓN / INSTITUTION: Department of Chest Medicine, Japan Railway Tokyo General Hospital, Japan.
RESUMEN / SUMMARY: BACKGROUND: Cigarette smoking is the primary causative factor for lung carcinoma and respiratory bronchiolitis (RB), particularly RB-associated interstitial lung disease (RB-ILD). However, the link between lung cancer and RB/RL-ILD remains undefined. We examined whether pathological fibrosis lesions exist simultaneously in patients with lung carcinoma because the fibrous lesions could be precancerous. METHODS: Clinical, radiological, and pathological features were consecutively evaluated in 67 current smokers, 22 ex-smokers, and 35 nonsmokers who underwent surgical resection for lung carcinoma. The presence of interstitial changes was evaluated by high-resolution computed tomography (HRCT). The pathological examination focused on RB, RB with fibrosis, and coexistent interstitial changes.

RESULTS: RB with fibrosis was observed in 13/67 current smokers with centrilobular nodular and/or patchy ground-glass opacities patterns or emphysema on HRCT. RB without fibrosis was observed in 12/67 current smokers with a centrilobular pattern, emphysema, or a normal pattern on HRCT. The Brinkman smoking index was significantly higher in the RB with fibrosis group (1278+/-133) than in the RB without fibrosis group (791+/-131). No RB with/without fibrosis features were noted in nonsmokers or ex-smokers. Squamous cell carcinoma was observed in 11/13 patients with RB with fibrosis, whereas adenocarcinoma was observed in 7/12 patients with RB without fibrosis. CONCLUSIONS: Squamous cell carcinoma located in peripheral areas
was primarily observed in patients with RB with fibrosis, whereas adenocarcinoma was primarily observed in patients with RB without fibrosis. Interstitial fibrosis with RB caused by continuous heavy cigarette smoking may increase the risk of developing squamous cell carcinoma.

[969]
**TÍTULO / TITLE**: Late-onset distant metastatic upper urinary tract urothelial carcinoma mimicking lung adenocarcinoma.

**RESUMEN / SUMMARY**: Urothelial carcinomas (UCs) can occur in the upper urinary tract or lower urinary tract. Upper urinary tract urothelial carcinoma (UUT-UC) is relatively a rare disease and accounts for only about 5% of UC cases. Sporadic cases of late-onset metastasis, associated with UC of the bladder, have occasionally been reported. In contrast, no late-onset distant metastatic UUT-UC without local recurrence has, to the best of our knowledge, been reported in the English literature. We report an extremely rare case of distant metastatic UC, mimicking lung adenocarcinoma that originated from UUT-UC 12 years previously.

[970]
**TÍTULO / TITLE**: Tracking lung tumors in orthogonal X-rays.

**RESUMEN / SUMMARY**: This paper presents a computationally very efficient, robust, automatic tracking method that does not require any implanted fiducials for low-contrast tumors. First, it generates a set of motion hypotheses and computes corresponding feature vectors in local windows within orthogonal-axis X-ray images. Then, it fits a regression model that maps features to 3D tumor motions by minimizing geodesic distances on motion manifold. These hypotheses can be jointly generated in
3D to learn a single 3D regression model or in 2D through back projection to learn two 2D models separately. Tumor is tracked by applying regression to the consecutive image pairs while selecting optimal window size at every time. Evaluations are performed on orthogonal X-ray videos of 10 patients. Comparative experimental results demonstrate superior accuracy (~1 pixel average error) and robustness to varying imaging artifacts and noise at the same time.

[971]
**TÍTULO / TITLE:** - Localized mesothelioma tumour arising synchronously with a primary contralateral lung cancer.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
**AUTORES / AUTHORS:** - Andrews W; Paul S; Narula N; Altorki NK
**INSTITUCIÓN / INSTITUTION:** - Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York Presbyterian Hospital-Weill Cornell Medical College, New York, NY, USA.
**RESUMEN / SUMMARY:** - Mesothelioma is a malignant growth of mesothelial cells found in the serosal membrane of pleural, peritoneal and pericardial surfaces as a result of prolonged exposure to asbestos. Malignant pleural mesothelioma (MPM) typically presents itself in a diffuse pattern of growth over the pleura of the lung or in more rare cases as a localized focus (LMPM). We present the first reported case of a synchronous LMPM and non-small adenocarcinoma of the lung treated by sequential resections.

[972]
**TÍTULO / TITLE:** - Website visitors asking questions online to lung cancer specialists: what do they want to know?
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
**AUTORES / AUTHORS:** - Schook RM; Linssen C; Festen J; Schramel FM; Lammers E; Zaanen P; Postmus PE
**INSTITUCIÓN / INSTITUTION:** - VU University Medical Center, Department of Pulmonary Diseases, Amsterdam, Netherlands. [r.schook@vumc.nl](mailto:r.schook@vumc.nl).
**RESUMEN / SUMMARY:** - BACKGROUND: In 2003 the Dutch Lung Cancer Information Centre (Longkanker Informatie Centrum) launched a website containing information on lung cancer accessible to anyone. OBJECTIVE: Our study aim was to inventorize the information needs of the visitors of this website by analyzing the questions they asked the lung cancer specialists in the websites interactive section “Ask the Physician”. METHODS: The first 2000 questions posted up until May 2006 have been classified by visitors’ wish, type of required information, identity, gender, and phase during
treatment course. RESULTS: Our results show that 1893 (1158/1893, 61%) of the questions were asked by a loved one/caregiver and (239/1893 13%) by patients. 1 out of 3 questions was asked by a daughter/grand-daughter. Most questions concerned specific information on lung cancer and lung cancer course (817/1893, 43%). The most inquired specific information topics were therapy side effects, diagnostics, general information on lung cancer, and regular therapy. Furthermore, questioners wanted to verify their own doctor’s information (122/1893, 6%), a diagnosis (267/1893, 14%), and a prognosis (204/1893, 11%). CONCLUSIONS: Lung cancer patients and their caregivers asked the most questions in the interactive website section. The most frequently requested information was more detailed information. These include specific information on lung cancer (regular therapy, diagnostics, and disease symptoms), verification of what the doctor has said, diagnosis, and prognosis. Most of the requested information could have been obtained from treating specialists, indicating that current information supply to lung cancer patients and their caregivers may not be matching their needs sufficiently. The further implementation of an online dialogue with lung cancer specialists might be a solution.
withdrawn 1 week after admission. The clinical course in the presence of biochemical derangement and SCLC is highly suggestive of paraneoplastic ectopic ACTH secretion.

[974]

TÍTULO / TITLE: - Rapid copper acquisition by developing murine mesothelioma: decreasing bioavailable copper slows tumor growth, normalizes vessels and promotes T cell infiltration.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - Crowe A; Jackaman C; Beddoes KM; Ricciardo B; Nelson DJ

INSTITUCIÓN / INSTITUTION: - School of Pharmacy, CHIRI Biosciences Research Precinct, Curtin University, Bentley, Perth, Western Australia, Australia.

RESUMEN / SUMMARY: - Copper, an essential trace element acquired through nutrition, is an important co-factor for pro-angiogenic factors including vascular endothelial growth factor (VEGF). Decreasing bioavailable copper has been used as an anti-angiogenic and anti-cancer strategy with promising results. However, the role of copper and its potential as a therapy in mesothelioma is not yet well understood. Therefore, we monitored copper levels in progressing murine mesothelioma tumors and analyzed the effects of lowering bioavailable copper. Copper levels in tumors and organs were assayed using atomic absorption spectrophotometry. Mesothelioma tumors rapidly sequestered copper at early stages of development, the copper was then dispersed throughout growing tumor tissues. These data imply that copper uptake may play an important role in early tumor development. Lowering bioavailable copper using the copper chelators, penicillamine, trientine or tetrathiomolybdate, slowed in vivo mesothelioma growth but did not provide any cures similar to using cisplatin chemotherapy or anti-VEGF receptor antibody therapy. The impact of copper lowering on tumor blood vessels and tumor infiltrating T cells was measured using flow cytometry and confocal microscopy. Copper lowering was associated with reduced tumor vessel diameter, reduced endothelial cell proliferation (reduced Ki67 expression) and lower surface ICAM/CD54 expression implying reduced endothelial cell activation, in a process similar to endothelial normalization. Copper lowering was also associated with a CD4(+) T cell infiltrate. In conclusion, these data suggest copper lowering is a potentially useful anti-mesothelioma treatment strategy that slows tumor growth to provide a window of opportunity for inclusion of other treatment modalities to improve patient outcomes.

[975]

TÍTULO / TITLE: - MPM: Malignant Pleural Mesothelioma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Video-atlas of radical pleurectomy for malignant pleural mesothelioma.

Video-assisted thoracoscopic extrapleural pneumonectomy for malignant pleural mesothelioma.

Extrapleural pneumonectomy and extended pleurectomy/decortication for malignant pleural mesothelioma: the Memorial Sloan-Kettering Cancer Center approach.
INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, NY 10065, USA.

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