RESPIRATORY TRACT TUMORS
(Conceptos / Keywords: NSCLC; SCLC, Mesotheliomas; Tracheal tumors; Bronchial tumors; etc).
AbriI - Mayo 2013 / April - May 2013

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wijbrandts CA; van Schaardenburg D
INSTITUCIÓN / INSTITUTION: - Academic Medical Center, Amsterdam, The Netherlands.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wijbrandts CA; van Schaardenburg D
INSTITUCIÓN / INSTITUTION: - Academic Medical Center, Amsterdam, The Netherlands.

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[1] Enlace al texto completo (gratuito o de pago) 1056/NEJMicm1212346
[2] Enlace al texto completo (gratuito o de pago) 1200/JCO.2012.46.9783
PURPOSE We assessed whether chemotherapy selection based on in situ ERCC1 and RRM1 protein levels would improve survival in patients with advanced non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS Eligible patients were randomly assigned 2:1 to the trial’s experimental arm, which consisted of gemcitabine/carboplatin if RRM1 and ERCC1 were low, docetaxel/carboplatin if RRM1 was high and ERCC1 was low, gemcitabine/docetaxel if RRM1 was low and ERCC1 was high, and docetaxel/vinorelbine if both were high. In the control arm, patients received gemcitabine/carboplatin. The trial was powered for a 32% improvement in 6-month progression-free survival (PFS).

RESULTS Of 331 patients registered, 275 were eligible. The median number of cycles given was four in both arms. A tumor rebiopsy specifically for expression analysis was required in 17% of patients. The median time from informed consent to expression analysis was 11 days. We found no statistically significant differences between the experimental arm and the control arm in PFS (6.1 months vs 6.9 months) or overall survival (11.0 months vs 11.3 months). A subset analysis revealed that patients with low levels for both proteins who received the same treatment in both treatment arms had a statistically better PFS (P = .02) in the control arm (8.1 months) compared with the experimental arm (5.0 months). CONCLUSION This demonstrates that protein expression analysis for therapeutic decision making is feasible in newly diagnosed patients with advanced-stage NSCLC. A tumor rebiopsy is safe, required in 17%, and acceptable to 89% (47 of 53) of patients.


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

BACKGROUND: This was a post hoc analysis of patients with non-squamous histology from a phase III maintenance pemetrexed study in advanced non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: The six symptom items'[average symptom burden index (ASBI)] mean at baseline was calculated using the lung cancer symptom scale (LCSS). Low and high symptom burden (LSB, ASBI < 25; HSB, ASBI >/= 25) and performance status (PS: 0, 1) subgroups were analyzed for treatment effect on progression-free survival (PFS) and overall survival (OS) using the Cox proportional hazard models adjusted for demographic/clinical factors.

RESULTS: Significantly longer PFS and OS for pemetrexed versus placebo occurred in LSB patients [PFS: median 5.1 versus 2.4 months, hazard ratio (HR) 0.49, P < 0.0001; OS: median 17.5 versus 11.0 months, HR 0.63, P = 0.0012] and PS 0 patients (PFS: median 5.5 versus 1.7 months, HR 0.36, P < 0.0001; OS: median 17.7 versus 10.3 months, HR 0.54, P = 0.0019). Significantly longer PFS, but not OS, occurred in HSB patients (median 3.7 versus 2.8 months, HR 0.50, P = 0.0033) and PS 1 patients (median 4.4 versus 2.8 months, HR 0.60, P = 0.0002). CONCLUSIONS: ASBI and PS are associated with survival for non-squamous NSCLC patients, suggesting that maintenance pemetrexed is useful for LSB or PS 0 patients following induction.

TÍTULO / TITLE: A Trial of Autologous Ex vivo-expanded NK Cell-enriched Lymphocytes with Docetaxel in Patients with Advanced Non-small Cell Lung Cancer as Second- or Third-line Treatment: Phase Ila Study.

RESUMEN / SUMMARY: BACKGROUND: New strategies are still needed to enhance the treatment outcome for advanced non-small cell lung cancer, in spite of recent remarkable developments. Cancer immunotherapy has been attractive since a long time, with diverse clinical attempts and results. In particular, natural killer (NK) cells have received considerable attention because of their potential role in immune surveillance in vivo by destroying infected or transformed cells. Major histocompatibility complex class I-related chain A/B (MICA/B) on tumor cells, known as the representative ligand for NKG2D.
receptor on NK cells, has been reported to be modulated by a variety of stress factors, including some chemotherapeutic agents, and it is anticipated that enhancing MICA/B expression will be contributory to anticancer treatment. With recent development of expanding autologous ex vivo NK cell-enriched lymphocytes (NKL), we designed a trial to augment the anticancer effect by co-administering NKL and docetaxel, one of the second-line agents used for treatment of patients with advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: Eligible patients were between the age of 20 and 75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and previously received one chemotherapy or two regimens including one epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, stage IIIIB/IV, histologically- or cytologically-proven NSCLC with measurable lesions. NKL were kindly prepared and provided from NK BIO Co. (Seongnam City, Korea). Feasibility, adverse effects, progression-free survival (PFS) were evaluated and compared with the historical control of weekly docetaxel regimen. RESULTS: Nineteen patients were enrolled before early closure. NKL production and administration were feasible in all cases, even in those with disseminated disease. No additional adverse events were observed in addition to those reported for docetaxel-alone. PFS of 3 months and 10.5% response rate (RR), with two cases of partial response, were observed and were similar to the historical control (PFS=2.9 months, RR=8.0%).

CONCLUSION: To our knowledge, this is the first report on the combination of NKL with docetaxel in patients with advanced NSCLC. Autologous NKL production and co-administration with docetaxel were feasible without further toxicity or complication. Benefit in PFS and RR, as compared with the historical control, was not detected in this study population with advanced NSCLC. In order to determine whether the combination of NKL and chemotherapy has any anticancer effect, an additional study should be performed in patients with low tumor burden, such as those with less advanced disease or those in remission.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Garrido P; Rosell R; Arellano A; Andreu F; Domine M; Perez-Casas A; Cardenal F; Armaiz MD; Moran T; Morera R; Isla D; Valencia J; Cobo M; Delgado R; Garcia-Gomez R; Calvo F; Zamora J; Ramos A; Massuti B
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RESUMEN / SUMMARY: - The optimal schedule and regimen of chemotherapy (CT) in association with chemoradiation has not been established in stage III non-small-cell lung cancer (NSCLC). We have compared three schedules of non-platinum-based CT plus either radiotherapy or chemoradiation. From May 2001 to June 2006, 158 patients with unresectable stage III NSCLC were enrolled in a randomized phase II trial with overall response rate (ORR) as the primary endpoint. The initial design included three arms: sequential CT followed by thoracic radiation (TRT); concurrent CT/TRT followed by consolidation CT; and induction CT followed by concurrent CT/TRT. However, based on the preliminary results of the RTOG 9410 trial, the sequential arm was closed when 19 patients had been enrolled. All patients received two cycles of docetaxel 40mg/m2 days 1 and 8 plus gemcitabine 1200mg/m2 days 1 and 8, as either induction or consolidation therapy. Concurrent CT/TRT consisted of docetaxel 20mg/m2 and carboplatin AUC 2 weekly plus 60Gy TRT. No differences were found in ORR between the two arms (56% and 57%). Hematological toxicity was mild but significantly superior with consolidation CT; the esophagitis rate was similar in both arms (16% and 15%). With a median follow-up of 57 months, no differences were found in median survival (13.07 and 13.8 months) or 5-year survival (16.4% and 22%). This regimen cannot be recommended as an alternative to platinum-based CT/TRT although it has an acceptable toxicity profile and encouraging long-term survival data (ClinicalTrials.gov NCT01652820).

[6]


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


AUTORES / AUTHORS: - Morabito A; Gebbia V; Di Maio M; Cinieri S; Vigano MG; Bianco R; Barbera S; Cavanna L; De Marinis F; Montesarchio V; Costanzo R; Sandomenico C; Montanino A; Mancuso G; Russo P; Nacci A; Giordano P; Daniele G; Piccirillo MC; Rocco G; Gridelli C; Gallo C; Perrone F

INSTITUCIÓN / INSTITUTION: - National Cancer Institute - “G. Pascale” Foundation, via M. Semmola, 80131 Napoli, Italy.
Platinum-based chemotherapy is the standard treatment for patients with advanced non-small cell lung cancer (NSCLC), but the evidence of its efficacy among ECOG performance status (PS)2 patients is weak because these patients are usually excluded from clinical trials; concern exists about tolerability and feasibility of standard chemotherapy in these patients. No prospective randomized trial has tested the addition of cisplatin to single-agent chemotherapy in patients with advanced NSCLC and PS2. CAPPA-2 was a multicenter, randomized phase 3 study for first-line treatment of PS2 patients with advanced NSCLC. Patients, aged 18-70, were eligible if they had stage IV or IIB with malignant pleural effusion or metastatic supraclavicular nodes (TNM VI edition) and adequate organ function. Patients in standard arm received gemcitabine 1200mg/m² days 1 and 8. Patients in experimental arm received cisplatin 60mg/m² day 1 plus gemcitabine 1000mg/m² days 1 and 8. All treatments were repeated every 3 weeks, up to 4 cycles, unless disease progression or unacceptable toxicity. Primary endpoint was overall survival (OS). To have 80% power of detecting hazard ratio (HR) 0.71, corresponding to an increase in median OS from 4.8 to 6.8 months, 285 deaths were required. The study was stopped in June 2012 after the enrolment of 57 patients, due to the slow accrual and the report of positive results from a similar study. Median OS was 3.0 months with single-agent gemcitabine and 5.9 months with cisplatin plus gemcitabine (HR 0.52, 95% CI 0.28-0.98, p=0.039). Combination chemotherapy produced longer PFS (median 1.7 vs. 3.3 months, HR 0.49, 95% CI 0.27-0.89, p=0.017) and higher response rate (4% vs. 18%, p=0.19), without substantial increase in toxicity. The addition of cisplatin to single-agent gemcitabine improves survival as first-line treatment of PS2 patients with advanced NSCLC.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary  
AUTORES / AUTHORS: Church TR; Black WC; Aberle DR; Berg CD; Clingan KL; Duan F; Fagerstrom RM; Gareen IF; Gierada DS; Jones GC; Mahon I; Marcus PM; Sicks JD; Jain A; Baum S  
RESUMEN / SUMMARY: BACKGROUND: Lung cancer is the largest contributor to mortality from cancer. The National Lung Screening Trial (NLST) showed that screening with low-dose helical computed tomography (CT) rather than with chest radiography reduced mortality from lung cancer. We describe the screening, diagnosis, and limited treatment results from the initial round of
screening in the NLST to inform and improve lung-cancer-screening programs.

METHODS: At 33 U.S. centers, from August 2002 through April 2004, we enrolled asymptomatic participants, 55 to 74 years of age, with a history of at least 30 pack-years of smoking. The participants were randomly assigned to undergo annual screening, with the use of either low-dose CT or chest radiography, for 3 years. Nodules or other suspicious findings were classified as positive results. This article reports findings from the initial screening examination. RESULTS: A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography); 26,309 participants (98.5%) and 26,035 (97.4%), respectively, underwent screening. A total of 7191 participants (27.3%) in the low-dose CT group and 2387 (9.2%) in the radiography group had a positive screening result; in the respective groups, 6369 participants (90.4%) and 2176 (92.7%) had at least one follow-up diagnostic procedure, including imaging in 5717 (81.1%) and 2010 (85.6%) and surgery in 297 (4.2%) and 121 (5.2%). Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants and stage IIIB to IV in 120 vs. 112). Sensitivity and specificity were 93.8% and 73.4% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.

CONCLUSIONS: The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT and chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT. (Funded by the National Cancer Institute; NLST ClinicalTrials.gov number, NCT00047385.).

[8]

TÍTULO / TITLE: - Pooled Analysis of the Prognostic and Predictive Effects of KRAS Mutation Status and KRAS Mutation Subtype in Early-Stage Resected Non-Small-Cell Lung Cancer in Four Trials of Adjuvant Chemotherapy.

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


AUTORES / AUTHORS: - Shepherd FA; Domerg C; Hainaut P; Janne PA; Pignon JP; Graziano S; Douillard JY; Brambilla E; Le Chevalier T; Seymour L; Bourredjem A; Le Teuff G; Pirker R; Filipits M; Rosell R; Kratzke R; Bandarchi B; Ma X; Capelletti M; Soria JC; Tsao MS

INSTITUCIÓN / INSTITUTION: - Frances A. Shepherd, Bizhan Bandarchi, and Ming-Sound Tsao, University Health Network, Princess Margaret Hospital, and the University of Toronto, Toronto; Lesley Seymour, National Cancer Institute of Canada Clinical Trials Group, Queen’s University, Kingston, Ontario, Canada; Caroline Domerg, Jean-Pierre Pignon, Thierry Le Chevalier, Abderrahmane
RESUMEN / SUMMARY: PURPOSE We undertook this analysis of KRAS mutation in four trials of adjuvant chemotherapy (ACT) versus observation (OBS) to clarify the prognostic/predictive roles of KRAS in non-small-cell lung cancer (NSCLC). METHODSKRAS mutation was determined in blinded fashion. Exploratory analyses were performed to characterize relationships between mutation status and subtype and survival outcomes using a multivariable Cox model. RESULTS: G12A or G12R (HR = 0.66; P = .48), G12C or G12V (HR = 0.94; P = .77) and G12D or G12S (HR = 1.39; P = .48; comparison of four HRs, including WT, interaction P = .76). OBS patients with KRAS-mutated tumors were more likely to develop second primary cancers (HR = 2.76, 95% CI, 1.34 to 5.70; P = .005) but not ACT patients (HR = 0.66; 95% CI, 0.25 to 1.75; P = .40; interaction, P = .02). CONCLUSIONKRAS mutation status is not significantly prognostic. The potential interaction in patients with codon-13 mutations requires validation. At this time, KRAS status cannot be recommended to select patients with NSCLC for ACT.
TÍTULO / TITLE: - Randomized Phase II Study of Ixabepilone or Paclitaxel Plus Carboplatin in Patients With Non-Small-Cell Lung Cancer Prospectively Stratified by Beta-3 Tubulin Status.

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


AUTORES / AUTHORS: - Edelman MJ; Schneider CP; Tsai CM; Kim HT; Quoix E; Luft AV; Kaleta R; Mukhopadhyay P; Trifan OC; Whitaker L; Reck M

INSTITUCIÓN / INSTITUTION: - University of Maryland Greenebaum Cancer Center, Division of Hematology/Oncology, 22 South Green St, Baltimore, MD 21201-1595; medelman@umm.edu.

RESUMEN / SUMMARY: - PURPOSE Retrospective studies have reported that tumor expression of the beta-3 tubulin (beta3T) isoform is an unfavorable prognostic factor in non-small-cell lung cancer (NSCLC) treated with tubulin-inhibiting chemotherapy. Ixabepilone is a tubulin-inhibiting agent with low susceptibility to multiple resistance mechanisms including beta3T isoform expression in several tumor models. This randomized phase II study evaluated ixabepilone-based chemotherapy in stage IIIb/IV NSCLC, compared with paclitaxel-based chemotherapy. Tumor specimens were prospectively evaluated for beta3T expression. PATIENTS AND METHODS Patients were stratified by beta3T status (positive v negative) and randomly assigned at a ratio of 1:1 to receive ixabepilone (32 mg/m²) and carboplatin (area under concentration-time curve [AUC], 6) or paclitaxel (200 mg/m²) and carboplatin (AUC, 6) for up to six cycles. The primary end point was progression-free survival (PFS) in the beta3T-positive subgroup. Results Ninety-five patients (beta3T positive, 52; beta3T negative, 43) received ixabepilone plus carboplatin; 96 patients (beta3T positive, 49; beta3T negative, 47) received paclitaxel plus carboplatin. No significant differences in median PFS were observed between arms for either subgroup (beta3T positive, 4.3 months in both arms; beta3T negative, 5.8 v 5.3 months). Ixabepilone did not significantly improve overall survival (OS) for the beta3T-positive subset or the overall population. Adverse events were similar between the two arms and comparable with those in previous studies. CONCLUSION There was no predictive value of beta3T in differentiating clinical activity of ixabepilone- or paclitaxel-containing regimens. Ixabepilone did not improve PFS or OS in patients with beta3T-positive tumors. beta3T-positive patients had worse PFS relative to beta3T-negative patients, regardless of treatment; hence, beta3T expression seems to be a negative prognostic factor, but not a predictive factor, in advanced NSCLC treated with either ixabepilone or paclitaxel platinum-based doublets.

[11]

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


AUTORES / AUTHORS: - Gondi V; Paulus R; Bruner DW; Meyers CA; Gore EM; Wolfson A; Werner-Wasik M; Sun AY; Choy H; Movsas B

INSTITUCIÓN / INSTITUTION: - Central Dupage Hospital Cancer Center, Warrenville, Illinois; University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin. Electronic address: vgondi@chicagocancer.org.

RESUMEN / SUMMARY: - PURPOSE: To assess the impact of prophylactic cranial irradiation (PCI) on self-reported cognitive functioning (SRCF), a functional scale on the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). METHODS AND MATERIALS: Radiation Therapy Oncology Group (RTOG) protocol 0214 randomized patients with locally advanced non-small cell lung cancer to PCI or observation; RTOG 0212 randomized patients with limited-disease small cell lung cancer to high- or standard-dose PCI. In both trials, Hopkins Verbal Learning Test (HVLT)-Recall and -Delayed Recall and SRCF were assessed at baseline (after locoregional therapy but before PCI or observation) and at 6 and 12 months. Patients developing brain relapse before follow-up evaluation were excluded. Decline was defined using the reliable change index method and correlated with receipt of PCI versus observation using logistic regression modeling. Fisher’s exact test correlated decline in SRCF with HVLT decline. RESULTS: Of the eligible patients pooled from RTOG 0212 and RTOG 0214, 410 (93%) receiving PCI and 173 (96%) undergoing observation completed baseline HVLT or EORTC QLQ-C30 testing and were included in this analysis. Prophylactic cranial irradiation was associated with a higher risk of decline in SRCF at 6 months (odds ratio 3.60, 95% confidence interval 2.34-6.37, P<.0001) and 12 months (odds ratio 3.44, 95% confidence interval 1.84-6.44, P<.0001). Decline on HVLT-Recall at 6 and 12 months was also associated with PCI (P=.002 and P=.002, respectively) but was not closely correlated with decline in SRCF at the same time points (P=.05 and P=.86, respectively). CONCLUSIONS: In lung cancer patients who do not develop brain relapse, PCI is associated with decline in HVLT-tested and self-reported cognitive functioning. Decline in HVLT and decline in SRCF are not closely correlated, suggesting that they may represent distinct elements of the cognitive spectrum.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Aerts JG; Hegmans JP
INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Diseases, Erasmus Medical Center, Rotterdam, The Netherlands. j.aerts@erasmusmc.nl
RESUMEN / SUMMARY: - There is growing evidence that activation of the immune system may be an effective treatment for patients with either small cell lung cancer or non-small cell lung cancer (NSCLC). Immunomodulatory antibodies directed against cytotoxic T cell-associated antigen 4 (CTLA-4/CD152) and programmed cell death ligand 1 (PDL1/CD274) showed clinical efficacy in patients with lung cancer. The key immune cells responsible for antitumor activity are the CTLs. The presence of these tumor-directed CTLs, both in number and functionality, is a prerequisite for the immune system to attack cancer cells. Immunomodulatory agents attempt to increase the efficacy of CTL activity. Thus, the limited number of patients who benefit from immunomodulatory antibodies may be caused by either an inadequate number or the impairment of CTL activity by the hostile environment created by the tumor. In this review, we discuss tumor-induced impairment of CTLs and experimental treatments that can stimulate T-cell responses and optimize specific CTL function. We discuss 2 types of immune cells with known suppressive capacity on CTLs that are of pivotal importance in patients with lung cancer: regulatory T cells and myeloid-derived suppressor cells.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Varlotto J; Fakiris A; Flickinger J; Medford-Davis L; Liss A; Shelkey J; Belani C; Deluca J; Recht A; Maheshwari N; Barriger R; Yao N; Decamp M
INSTITUCIÓN / INSTITUTION: - Penn State Hershey Cancer Institute, Hershey, Pennsylvania; Penn State College of Medicine, Hershey, Pennsylvania.
RESUMEN / SUMMARY: - BACKGROUND: Stereotactic body radiotherapy (SBRT) is an alternative to surgery for clinical stage I non-small cell lung cancer (NSCLC), but comparing its effectiveness is difficult because of differences in patient selection and staging. METHODS: Two databases were combined which contained patients treated from 1999 to 2008 by lobectomy (LR, n = 132), sublobar resection (SLR, n = 48), and SBRT (n = 137) after negative staging. Univariate and multivariate analysis were performed for survival (OS), total recurrence control (TRC comprises local-regional and distant control), and locoregional control (LRC) in our entire population. A matched-pair analysis was also performed that compared surgery and SBRT results. Median follow-up for the entire study population was 25.8 months. RESULTS: On univariate analysis, OS was significantly worse with SBRT and also correlated with histology, the Charlson comorbidity index, tumor size, and aspirin use; TRC correlated only with histology; and no variable significantly correlated with LRC. OS was significantly poorer for SBRT in the matched-pair analysis than for patients treated with surgery, but TRC and LRC were not significantly different between these groups. Multivariate analyses including propensity score as a covariate (controlling for all factors affecting treatment selection) found that OS correlated only with Charlson comorbidity index, and TRC correlated only with tumor grade. LRC correlated only with tumor size with or without propensity score correction. CONCLUSIONS: This retrospective study has demonstrated similar OS, LRC, and TRC with SBRT or surgery after controlling for prognostic and patient selection factors. Randomized clinical trials are needed to better compare the effectiveness of these treatments. Cancer 2013. © 2013 American Cancer Society.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mac Manus MP; Everitt S; Bayne M; Ball D; Plumridge N; Binns D; Herschtal A; Cruickshank D; Bressel M; Hicks RJ
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia.
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RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: This prospective study investigated the impact of radiotherapy (RT)-planning FDG-PET/CT on
management of non-small cell lung cancer (NSCLC). MATERIALS AND METHODS: Patients still eligible for radical RT after conventional staging underwent RT-planning PET/CT and, if disease was still treatable to 60 Gy, they entered our planning study, where visually-contoured tumour volumes derived with and without PET information were compared. If PET/CT detected advanced disease, palliative therapy was given. Overall survival (OS) for palliative and curative patients was compared. RESULTS: Of 76 eligible patients, only 50 (66%) received radical chemoradiotherapy after PET/CT while 26 (34%) received palliative therapies because PET/CT detected advanced disease. Without PET, FDG-avid tumour would reside outside the planning target volume (PTV) in 36% of radical cases and in 25% <90% of the PTV would have received >95% prescribed dose. OS for all patients was 56.8% and 24.9% at 1 and 4 years, respectively. OS for patients given chemoradiotherapy was 77.5% and 35.6% at 1 and 4 years, respectively and was 32% for stage IIIA patients at 4 years. OS for patients treated palliatively was inferior (P<0.001); 16.3% and 4.1% at 1 and 4 years, respectively. CONCLUSIONS: Planning PET/CT frequently changed management and was associated with excellent survival. Survival data from this study were presented in part at the 2011 World Lung Cancer Conference, Amsterdam and planning data at the 2010 Annual Scientific Meeting of the American Society for Therapeutic Radiology and Oncology, Chicago.

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[15]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang RX; Zhu JH; Fan J; Ji XQ
INSTITUCIÓN / INSTITUTION: - Department of Oncologic Surgery, First Affiliated Hospital, Bengbu Medical College, Bengbu, People’s Republic of China.
RESUMEN / SUMMARY: - PURPOSE: In a previous study, we found a hyaluronidase 3 (HYAL3) gene mutation in exon 2 at position 188 by genome sequencing in a lung squamous cell carcinoma patient. The mutation results in substitution of serine for alanine. The aim of the study was to screen the HYAL3 gene mutation in Chinese lung squamous cell carcinoma patients and explore the correlation between mutation of HYAL3 with clinical and pathological characteristics in lung squamous cell carcinoma patients in China. METHODS: We applied polymerase chain reaction to examine the HYAL3 gene mutations in cancer tissues and their adjacent normal tissues from 39 cases of lung squamous cell carcinoma patients. RESULTS: 1) The incidence rate of HYAL3
mutation in 39 cases of lung squamous cell carcinoma was 10.26% (4/39) and none in adjacent normal lung tissues (0/39). 2) The mutations of HYAL3 in the 4 cases were all heterozygous: 3 of them were located in exon 1 (G-T) and one in exon 2 (G-T). 3) Mutations of the HYAL3 gene were not correlated with the distribution of patient gender, age, tumor size, histological grade, smoking history, TNM stage or distant metastasis (P >0.05). The gene mutation was correlated with lymph node status (P = 0.044). CONCLUSION: Mutations of the HYAL3 gene are rare in Chinese lung squamous cell carcinoma patients and might contribute to lymph node metastasis.

[16]
**TÍTULO / TITLE:** - A Phase I Trial of Sunitinib and Rapamycin in Patients with Advanced Non-Small Cell Lung Cancer.

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

  - Enlace al texto completo (gratuito o de pago) 1159/000348584

**AUTORES / AUTHORS:** - Waqar SN; Gopalan PK; Williams K; Devarakonda S; Govindan R

**INSTITUCIÓN / INSTITUTION:** - Division of Medical Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo., USA.

**RESUMEN / SUMMARY:** - Background: Sunitinib is an oral multitargeted tyrosine kinase inhibitor, with single-agent activity in non-small cell lung cancer (NSCLC). Resistance to tyrosine kinase inhibitor therapy is mediated by the mammalian target of rapamycin (mTOR) pathway, and may be reversed by using mTOR inhibitors. Methods: We performed a phase I study evaluating the combination of sunitinib and rapamycin in patients with advanced NSCLC. Results: Nineteen patients were enrolled in the study. The dose-limiting toxicities included infection, pneumonia, diarrhea/dehydration and treatment delay due to thrombocytopenia in 1 patient each. Sunitinib 25 mg orally daily and rapamycin 2 mg orally daily with 4 weeks on and 2 weeks off therapy were determined to be the maximum tolerated dose. No objective responses were noted, and 6 patients had stable disease as a best response. Conclusion: The combination of sunitinib and rapamycin is well-tolerated and warrants further investigation in the phase II setting.

[17]
**TÍTULO / TITLE:** - A Multicenter Phase II Study of Ganetespib Monotherapy in Patients with Genotypically Defined Advanced Non-Small Cell Lung Cancer.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
PURPOSE: Ganetespib is a novel inhibitor of the heat shock protein 90 (Hsp90), a chaperone protein critical to tumor growth and proliferation. In this phase II study, we evaluated the activity and tolerability of ganetespib in previously treated patients with non-small cell lung cancer (NSCLC). EXPERIMENTAL DESIGN: Patients were enrolled into cohort A (mutant EGFR), B (mutant KRAS), or C (no EGFR or KRAS mutations). Patients were treated with 200 mg/m2 ganetespib by intravenous infusion once weekly for 3 weeks followed by 1 week of rest, until disease progression. The primary endpoint was progression-free survival (PFS) at 16 weeks. Secondary endpoints included objective response (ORR), duration of treatment, tolerability, median PFS, overall survival (OS), and correlative studies. RESULTS: Ninety-nine patients with a median of 2 prior systemic therapies were enrolled; 98 were assigned to cohort A (n = 15), B (n = 17), or C (n = 66), with PFS rates at 16 weeks of 13.3%, 5.9%, and 19.7%, respectively. Four patients (4%) achieved partial response (PR); all had disease that harbored anaplastic lymphoma kinase (ALK) gene rearrangement, retrospectively detected by FISH (n = 1) or PCR-based assays (n = 3), in crizotinib-naive patients enrolled to cohort C. Eight patients (8.1%) experienced treatment-related serious adverse events (AE); 2 of these (cardiac arrest and renal failure) resulted in death. The most common AEs were diarrhea, fatigue, nausea, and anorexia. CONCLUSIONS: Ganetespib monotherapy showed a manageable side effect profile as well as
clinical activity in heavily pretreated patients with advanced NSCLCs, particularly in patients with tumors harboring ALK gene rearrangement. Clin Cancer Res; 19(11); 3068-77. ©2013 AACR.

[18] TÍTULO / TITLE: - Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Sun JM; Ahn YC; Choi EK; Ahn MJ; Ahn JS; Lee SH; Lee DH; Pyo H; Song SY; Jung SH; Jo JS; Jo J; Sohn HJ; Suh C; Lee JS; Kim SW; Park K

INSTITUCIÓN / INSTITUTION: - Department of Medicine.
RESUMEN / SUMMARY: - BACKGROUND: We compared late thoracic radiotherapy (TRT) with early TRT in the treatment of limited-disease small-cell lung cancer (LD-SCLC). PATIENTS AND METHODS: Patients with LD-SCLC received four cycles of etoposide plus cisplatin every 21 days. Patients were randomly assigned to receive either TRT administered concurrently with the first cycle (early TRT) or the third cycle (late TRT) of chemotherapy. The primary end point was complete response rate. RESULTS: Two hundred twenty-two patients were randomly assigned. Late TRT was not inferior to early TRT in terms of the complete response rate (early versus late; 36.0% versus 38.0%). Other efficacy measures including overall survival [median, 24.1 versus 26.8 months; hazard ratio (HR) 0.90; 95% CI 0.18-1.62] and progression-free survival (median, 12.4 versus 11.2 months; HR 1.10; 95% CI 0.37-1.84) were not different between two arms. No statistical difference was noted in the pattern of treatment failures. However, neutropenic fever occurred more commonly in the early TRT arm than the late TRT arm (21.6% versus 10.2%; P = 0.02). CONCLUSION: In LD-SCLC treatment, TRT starting in the third cycle of chemotherapy seemed to be noninferior to early TRT, and had a more favorable profile with regard to neutropenic fever.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Myeloid-derived suppressor cells (MDSC) are one of the major factors limiting the efficacy of immune therapy. In a clinical trial of patients with extensive stage small cell lung cancer (SCLC), we tested the possibility that targeting MDSC can improve the induction of immune responses by a cancer vaccine. Forty-one patients with extensive stage SCLC were randomized into three arms: arm A-control, arm B-vaccination with dendritic cells transduced with wild-type p53, and arm C-vaccination in combination with MDSC targeted therapy with all-trans-retinoic acid (ATRA).

Interim results of the ongoing clinical trial are presented. Pretreatment levels of MDSC populations in patients from all three arms were similar. Vaccine alone did not affect the proportion of MDSC, whereas in patients treated with ATRA, the MDSC decreased more than twofold (p = 0.02). Before the start of treatment, no patients had detectable p53-specific responses in IFN-gamma ELISPOT. Sequential measurements did not show positive p53 responses in any of the 14 patients from arm A. After immunization, only 3 out of 15 patients (20 %) from arm B developed a p53-specific response (p = 0.22). In contrast, in arm C, 5 out of 12 patients (41.7 %) had detectable p53 responses (p = 0.012). The proportion of granzyme B-positive CD8(+) T cells was increased only in patients from arm C but not in arm B. Depletion of MDSC substantially improved the immune response to vaccination, suggesting that this approach can be used to enhance the effect of immune interventions in cancer.
trends in reporting of outcome measures in phase II and phase III trials conducted in advanced non-small-cell lung cancer (NSCLC) patients.

METHODS: Data from September 2000 to September 2012 were extracted from the ClinicalTrials.gov database, and a descriptive-comparative analysis was performed to evaluate outcome-measures reporting for the two phases.

RESULTS: We identified 459 phase II and 128 phase III trials that met our inclusion criteria. The frequently reported primary outcomes in phase II trials were progression-free survival (PFS; 32 %), response rate (RR; 21.4 %), and safety and toxicity (adverse events [AEs]; 14.6 %). In contrast, overall survival (OS; 60.9 %) and PFS (26.6 %) were frequently reported primary outcomes in phase III trials. AEs were reported as a secondary outcome measure in 50.1 and 64.8 % of phase II and phase III trials, respectively. Improvement in quality of life was identified as a secondary outcome measure significantly more frequently in phase III than in phase II trials. CONCLUSIONS: Our study identified recent trends in reports of outcome measures in advanced-stage NSCLC phase II and phase III trials. The outcomes of this study can be valuable for investigators with minimal or some experience in the field of oncology who are conducting clinical research.
in archived primary tumors from patients with NSCLC with those identified in metachronous or synchronous metastases. PATIENTS AND METHODS Primary and matched metastatic tumor pairs from 15 patients were analyzed by using a targeted next-generation sequencing assay in a Clinical Laboratory Improvement Amendments laboratory. Genomic libraries were captured for 3,230 exons in 182 cancer-related genes plus 37 introns from 14 genes often rearranged in cancer and sequenced to high coverage. Results Among 30 tumors, 311 genomic alterations were identified of which 63 were known recurrent (32 in primary tumor, 31 in metastasis) and 248 were nonrecurrent (likely passenger). TP53 mutations were the most frequently observed recurrent alterations (12 patients). Tumors harbored two or more (maximum four) recurrent alterations in 10 patients. Comparative analysis of recurrent alterations between primary tumor and matched metastasis revealed a concordance rate of 94% compared with 63% for likely passenger alterations. CONCLUSION This high concordance suggests that for the purposes of genomic profiling, use of archived primary tumor can identify the key recurrent somatic alterations present in matched NSCLC metastases and may provide much of the relevant genomic information required to guide treatment on recurrence.

[22]
TÍTULO / TITLE: - Combination of protein coding and non-coding gene expression as a robust prognostic classifier in stage I lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Akagi I; Okayama H; Schetter AJ; Robles AI; Kohno T; Bowman ED; Kazandjian D; Welsh JA; Oue N; Saito M; Miyashita M; Uchida E; Takizawa T; Takenoshita S; Skaug V; Mollerup S; Haugen A; Yokota J; Harris CC
INSTITUCIÓN / INSTITUTION: - Laboratory of Human Carcinogenesis, National Cancer Institute.
RESUMEN / SUMMARY: - Prognostic tests for early stage lung cancer patients may provide needed guidance on postoperative surveillance and therapeutic decisions. We used a novel strategy to develop and validate a prognostic classifier for early stage lung cancer. Specifically, we focused on 42 genes with roles in lung cancer or cancer prognosis. Expression of these biologically relevant genes and their association with relapse-free survival were evaluated using microarray data from 148 stage I lung adenocarcinoma patients. Seven genes associated with relapse-free survival were further examined by quantitative RT-PCR in 291 lung adenocarcinoma tissues from Japan, the
United States and Norway. Only BRCA1, HIF1A, DLC1, and XPO1 were each significantly associated with prognosis in the Japan and US/Norway cohorts. A Cox regression-based classifier was developed using these four genes on the Japan cohort and validated in stage I lung adenocarcinoma from the US/Norway cohort and three publically available lung adenocarcinoma expression profiling datasets. The results suggest that the classifier is robust across ethnically and geographically diverse populations regardless of the technology used to measure gene expression. We evaluated the combination of the four-gene classifier with microRNA miR-21 (MIR21) expression and found that the combination improved associations with prognosis, which were significant in stratified analyses on stage IA and stage IB patients. Thus, the four coding gene classifier, alone or with miR-21 expression, may provide a clinically useful tool to identify high risk patients and guide recommendations regarding adjuvant therapy and postoperative surveillance of stage I lung adenocarcinoma patients.

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TÍTULO / TITLE: - A phase I clinical trial of weekly oral topotecan for relapsed small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Agelaki S; Kontopodis E; Kotsakis A; Chandrinos V; Bompolaki I; Zafeiriou Z; Papadimitraki E; Stoltidis D; Kalbakis K; Georgoulias V
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University General Hospital of Heraklion, PO Box 1352, 71110, Heraklion, Crete, Greece, agelaki@med.uoc.gr.
RESUMEN / SUMMARY: - PURPOSE: To determine the dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of oral topotecan administered weekly in patients with relapsed small cell lung cancer (SCLC). PATIENTS AND METHODS: Patients were treated with oral topotecan on days 1, 8, and 15, every 28 days. The dose was escalated by 0.5 mg/m2 increments from the starting dose of 3 mg/m2 until the MTD was reached. DLTs were defined as grade 4 neutropenia, febrile neutropenia, grade 4 thrombocytopenia, non-hematologic toxicity >/=grade 3, any toxicity precluding the treatment on days 8 or 15 of the first cycle, or delay of the second cycle for more than 7 days. RESULTS: Eighteen patients were enrolled. Thirteen patients received oral topotecan as second-line and five as third- or further-line treatment. The DLT level was reached at 4.5 mg/m2, and the MTD was determined to be 4 mg/m2. DLTs consisted of grade 2/3 neutropenia and grade 2 thrombocytopenia precluding treatment on day 15 of the first cycle or on day 1 of the second cycle.
The most frequent toxicities were grade 2-3 neutropenia (27.8% of patients), grade 2-3 anemia (33.3%), grade 2 thrombocytopenia (16.7%), and grade 2-3 fatigue (44.4%). The response rate was 11.1%, the median progression-free survival 2.3 months, and the median overall survival 5.1 months.

CONCLUSION: The recommended phase II dose of weekly oral topotecan in pretreated patients with SCLC is 4 mg/m² on days 1, 8, and 15 every 28 days.
**TÍTULO / TITLE:** - Clinical Significance of ABCG2 Haplotype-tagging Single Nucleotide Polymorphisms in Patients With Unresectable Non-Small Cell Lung Cancer Treated With First-line Platinum-based Chemotherapy.

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


**AUTORES / AUTHORS:** - Kim SH; Kim MJ; Cho YJ; Jeong YY; Kim HC; Lee JD; Hwang YS; Kim IS; Lee S; Oh SY; Ling H; Lee GW

**INSTITUCIÓN / INSTITUTION:** - *Department of Internal Medicine, Division of Hematology and Medical Oncology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon daggerDepartment of Internal Medicine, Division of Hematology-Oncology, Gyeongsang National University School of Medicine double daggerDepartment of Internal Medicine, Division of Pulmonology, Gyeongsang National University Hospital, Jinju section signDepartment of Laboratory Medicine, Pusan National University School of Medicine, Busan parallelDepartment of Internal Medicine, Division of Hematology-Oncology, Dong-A University Medical Center, Busan, Republic of Korea paragraph signDepartment of Experimental Therapeutics, M.D. Anderson Cancer Center, University of Texas, Houston, TX.

**RESUMEN / SUMMARY:** - OBJECTIVES:: The ATP-binding cassette (ABC) ABCG2, involved in multidrug resistance (MDR) in cancer cells, plays an integral role in drug resistance. Single nucleotide polymorphisms (SNPs) have been identified in many MDR-associated ABC genes that seem to influence drug sensitivity/resistance through various mechanisms. Therefore, we investigated whether ABCG2 haplotype-tagging SNPs (htSNPs) were associated with clinical outcomes in patients with unresectable non-small cell lung cancer (NSCLC) treated with front-line platinum-based chemotherapy.

**PATIENTS AND METHODS::** We genotyped 4 ABCG2 htSNPs for 129 unresectable NSCLC cases treated with first-line platinum-based chemotherapy. Clinical characteristics, treatment outcomes, and predictive value of the htSNPs in patient response, survival, and adverse events related to platinum-based chemotherapy were analyzed according to each ABCG2 htSNP using the chi test, Kaplan-Meier method, and Cox proportional hazard model. RESULTS:: The rs2725264 was significantly related to overall survival (OS) (P=0.018, log-rank test). The median survival duration (in months) for patients with the rs2725264 T/T, T/C, and C/C genotypes was 35.75 [95% confidence interval (CI), 24.25-47.25], 34.25 [hazard ratio (HR) 1.27 (0.68 to 2.35); 95% CI, 27.16-41.34], and 14.89 [HR 3.22 (1.26 to 8.24), 95% CI, 13.86-15.92], respectively. The rs2725264 was identified as an independent factor by
Cox proportional hazard model analysis (P=0.028). In the taxane-based groups, OS was associated with rs2725264 (P=0.041), whereas in the gemcitabine-based groups, OS was associated with rs4148149 (P=0.014).

CONCLUSIONS: Our data suggest ABCG2 htSNPs rs2725264 (overall group and taxane-platinum combination group) and rs4148149 (gemcitabine-platinum combination group) were associated with OS in unresectable NSCLC patients treated with first-line platinum-based chemotherapy. Thus, the ABCG2 htSNP rs2725264 may be independently associated with OS in unresectable NSCLC patients treated with first-line platinum-based chemotherapy.

[26]
TÍTULO / TITLE: - Microcavity Array System for Size-Based Enrichment of Circulating Tumor Cells from the Blood of Patients with Small-Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hosokawa M; Yoshikawa T; Negishi R; Yoshino T; Koh Y; Kenmotsu H; Naito T; Takahashi T; Yamamoto N; Kikuhara Y; Kanbara H; Tanaka T; Yamaguchi K; Matsunaga T
RESUMEN / SUMMARY: - In this study, we present a method for efficient enrichment of small-sized circulating tumor cells (CTCs) such as those found in the blood of small cell lung cancer (SCLC) patients using a microcavity array (MCA) system. To enrich CTCs from whole blood, a microfabricated nickel filter with a rectangular MCA (104 cavities/filter) was integrated with a miniaturized device, allowing for the isolation of tumor cells based on differences in size and deformability between tumor and blood cells. The shape and porosity of the MCA were optimized to efficiently capture small tumor cells on the microcavities under low flow resistance conditions, while allowing other blood cells to effectively pass through. Under optimized conditions, approximately 80% of SCLC (NCI-H69 and NCI-H82) cells spiked in 1 mL of whole blood, were successfully recovered. In clinical samples, CTCs were detectable in 16 of 16 SCLC patients. In addition, the number of leukocytes captured on the rectangular MCA was significantly lower than that on the circular MCA (p < 0.001), suggesting that use of the rectangular MCA diminishes a considerable number of carryover leukocytes. Therefore, our system has potential as a tool for the detection of CTCs in small cell-type tumors and detailed molecular analyses of CTCs.

[27]
TÍTULO / TITLE: - Comparing end-of-life care for hospitalized patients with chronic obstructive pulmonary disease and lung cancer in Taiwan.
RESUMEN / SUMMARY: Cuando se trata de cuidados finales de vida, los pacientes con enfermedad obstructiva crónica respiratoria (COPD) son a menudo tratados de manera diferente a los pacientes con cáncer de pulmón. Sin embargo, pocos informes se comparan sobre la atención final de vida entre estas dos grupos. Se investigó la diferencia entre pacientes con enfermedad terminal COPD y enfermedad terminal cáncer de pulmón basado en los síntomas de final de vida y patrones de práctica clínica utilizando un estudio retrospectivo de pacientes con COPD y cáncer de pulmón que murieron en un hospital de atención aguda en Taiwán. Los pacientes con enfermedad terminal COPD tenían más comorbilidades y más días en la unidad de cuidados intensivos (ICU) que los pacientes con enfermedad terminal cáncer de pulmón. Se les dio más probabilidades de morir en la ICU y menos probabilidades de recibir atención hospice. Los pacientes con COPD también tenían más procedimientos invasivos, eran menos propensos a usar fármacos narcóticos y sedantes, y eran menos propensos a haber dado consentimiento do-not-resuscitate. Los síntomas fueron similares entre estos dos grupos. Diferencias en tratamiento sugieren que los pacientes con COPD reciben más cuidado dirigido a prolongar la vida que cuidado dirigido a aliviar los síntomas y proporcionar apoyo final de vida. Podría ser más difícil determinar cuando los pacientes con COPD están en el final de vida que cuando los pacientes con cáncer de pulmón están en ese mismo estado. Nuestros hallazgos indican que en Taiwán, se debe hacer más esfuerzo por dar el mismo acceso a la atención hospice a los pacientes con enfermedad terminal COPD que a los pacientes con enfermedad terminal cáncer de pulmón.

[28]


RESUMEN / SUMMARY: Gefitinib is a tyrosine kinase inhibitor, indicated in advanced non-small cell lung cancer in all lines of treatment for patients harboring EGFR mutations. It has a favorable toxicity profile but may induce unexpected adverse effects, such as an inflammatory reaction in the bladder.
We report a rare case of hemorrhagic cystitis, an unusual side effect, in a patient with non-small cell lung cancer treated with gefitinib, which did not compromise the clinical response.

[29]

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


AUTORES / AUTHORS: Hoang T; Dahlberg SE; Schiller JH; Johnson DH

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RESUMEN / SUMMARY: INTRODUCTION: We conducted this analysis to determine whether survival of advanced NSCLC patients treated with platin-based chemotherapy doublets involving paclitaxel, docetaxel or gemcitabine was dependent on histological subtypes and treatment regimen. METHODS: We retrospectively analyzed data from E1594, a front-line phase III study in which advanced NSCLC patients were randomized to receive one of four regimens: cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-paclitaxel. Patients were classified into four histology groups: squamous cell (SCC), adeno- (AC), large cell (LCC) and others including not otherwise specified (O/NOS) carcinoma. Logrank test was performed to compare overall survival (OS) and progression free survival (PFS) distributions according to histology as well as treatment. RESULTS: Of 1139 patients including 716 men and 423 women, AC was the most common subtype (56.8%), followed by SCC (19.7%), O/NOS (17.0%) and LCC (6.5%). Men were more likely to have SCC and women were more likely to have AC (p=0.002). Among the four histology groups, there was no imbalance in regard to race, performance status, weight loss, brain metastasis or treatment. In each histology group, we found no significant difference in OS and PFS between the four chemotherapy regimens. Conversely, in each treatment arm, the survival outcome was similar between the four histology subtypes. CONCLUSIONS: Our analysis suggests that histology does not predict survival benefit in advanced NSCLC patients treated with first-line platin-based doublets involving paclitaxel, docetaxel or gemcitabine.
NeuroD1 regulates survival and migration of neuroendocrine lung carcinomas via signaling molecules TrkB and NCAM.

Small-cell lung cancer and other aggressive neuroendocrine cancers are often associated with early dissemination and frequent metastases. We demonstrate that neurogenic differentiation 1 (NeuroD1) is a regulatory hub securing cross talk among survival and migratory-inducing signaling pathways in neuroendocrine lung carcinomas. We find that NeuroD1 promotes tumor cell survival and metastasis in aggressive neuroendocrine lung tumors through regulation of the receptor tyrosine kinase tropomyosin-related kinase B (TrkB). Like TrkB, the prometastatic signaling molecule neural cell adhesion molecule (NCAM) is a downstream target of NeuroD1, whose impaired expression mirrors loss of NeuroD1. TrkB and NCAM may be therapeutic targets for aggressive neuroendocrine cancers that express NeuroD1.

Impact of preoperative radiation on survival of patients with T3N0 >7-cm non-small cell lung cancers treated with anatomic resection using the Surveillance, Epidemiology, and End Results database.

Very large non-small cell lung cancers (NSCLC) remain a therapeutic challenge. The objective of this study was to evaluate the effect of surgery in the presence and absence of neoadjuvant radiation (NRT) on survival of patients with T3N0 >7-cm NSCLCs.
was used to identify patients undergoing lobectomy or pneumonectomy for T3N0 NSCLC tumors >7 cm from 1999-2008. Patients were categorized into groups based on type of surgery performed and whether NRT was used. Five-year overall (OS) and lung cancer-specific survival (LCSS) were estimated by the Kaplan-Meier method and comparisons made using log-rank tests and Cox regression models. RESULTS: There were 1301 patients evaluated, including 1232 undergoing primary surgical therapy (PST) and 69 receiving NRT. NRT was not associated with improvements in 5-y OS (48% versus 41%, P = 0.062) or LCSS (59% versus 52%, P = 0.116) compared with PST. Lobectomies were associated with better 5-y OS (43% versus 33%; P = 0.006) and LCSS (54% versus 43%, P = 0.005) compared with pneumonectomies. On multivariate analysis, NRT did not produce any significant advantage in OS (P = 0.242) and LCSS (P = 0.208). Pneumonectomies were associated with significantly worse OS (hazard ratio, 1.32; P = 0.007) and LCSS (hazard ratio, 1.38; P = 0.005) when compared with lobectomies. CONCLUSIONS: NRT, which most likely was a combination of chemotherapy and radiation, was not associated with improvements in OS or LCSS in patients with T3N0 >7-cm NSCLC compared with PST. When feasible, lobectomy appears more beneficial than pneumonectomy in terms of long-term survival for very large tumors.

[32]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lee CK; Brown C; Gralla RJ; Hirsh V; Thongprasert S; Tsai CM; Tan EH; Ho JC; Chu da T; Zaatar A; Osorio Sanchez JA; Vu VV; Au JS; Inoue A; Lee SM; Gebski V; Yang JC
INSTITUCIÓN / INSTITUTION: - Graduate Institute of Oncology and Cancer Research Center, National Taiwan University College of Medicine, Taipei 10051, Taiwan. chih.yang@ntu.edu.tw.
RESUMEN / SUMMARY: - Background The epidermal growth factor receptor (EGFR) signaling pathway is crucial for regulating tumorigenesis and cell survival and may be important in the development and progression of non-small cell lung cancer (NSCLC). We examined the impact of EGFR-tyrosine kinase inhibitors (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations. Methods Randomized trials that compared EGFR-TKIs monotherapy or combination EGFR-TKIs-chemotherapy with chemotherapy or placebo were included. We used published hazard ratios (HRs), if available, or derived treatment estimates
from other survival data. Pooled estimates of treatment efficacy of EGFR-TKIs for the EGFR mutation-positive (EGFRmut(+)) and EGFR mutation-negative (EGFRmut(-)) subgroups were calculated with the fixed-effects inverse variance weighted method. All statistical tests were two-sided. Results We included 23 eligible trials (13 front-line, 7 second-line, 3 maintenance; n = 14570). EGFR mutation status was known in 31% of patients. EGFR-TKIs treatment prolonged PFS in EGFRmut(+) patients, and EGFR mutation was predictive of PFS in all settings: The front-line hazard ratio for EGFRmut(+) was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; P < .001), and the front-line hazard ratio for EGFRmut(-) was 1.06 (95% CI = 0.94 to 1.19; P = .35; P interaction < .001). The second-line hazard ratio for EGFRmut(+) was 0.34 (95% CI = 0.20 to 0.60; P < .001), and the second-line hazard ratio for EGFRmut(-) was 1.23 (95% CI = 1.05 to 1.46; P = .01; P interaction < .001). The maintenance hazard ratio for EGFRmut(+) was 0.15 (95% CI = 0.08 to 0.27; P < .001), and the maintenance hazard ratio for EGFRmut(-) was 0.81 (95% CI = 0.68 to 0.97; P = .02; P interaction < .001). EGFR-TKIs treatment had no impact on OS for EGFRmut(+) and EGFRmut(-) patients. Conclusions EGFR-TKIs therapy statistically significantly delays disease progression in EGFRmut(+) patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of PFS benefit with EGFR-TKIs treatment in all settings. These findings support EGFR mutation assessment before initiation of treatment. EGFR-TKIs should be considered as front-line therapy in EGFRmut(+) advanced NSCLC patients.

[33]
TITULO / TITLE: - Lung tumor NF-kappaB signaling promotes T cell-mediated immune surveillance.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hopewell EL; Zhao W; Fulp WJ; Bronk CC; Lopez AS; Massengill M; Antonia S; Celis E; Haura EB; Enkemann SA; Chen DT; Beg AA
RESUMEN / SUMMARY: - NF-kappaB is constitutively activated in many cancer types and is a potential key mediator of tumor-associated inflammation, tumor growth, and metastasis. We investigated the role of cancer cell NF-kappaB activity in T cell-mediated antitumor responses. In tumors rendered immunogenic by model antigen expression or following administration of antitumor vaccines, we found that high NF-kappaB activity leads to tumor rejection and/or growth suppression in mice. Using a global RNA expression microarray, we demonstrated that NF-kappaB enhanced expression of several T cell chemokines, including Ccl2, and decreased CCL2 expression was associated with enhanced tumor growth in a mouse lung cancer model. To
investigate NF-kappaB function in human lung tumors, we identified a gene expression signature in human lung adenocarcinoma cell lines that was associated with NF-kappaB activity level. In patient tumor samples, overall lung tumor NF-kappaB activity was strongly associated with T cell infiltration but not with cancer cell proliferation. These results therefore indicate that NF-kappaB activity mediates immune surveillance and promotes antitumor T cell responses in both murine and human lung cancer.

[34]

**TITULO / TITLE:** - Tumor response and health-related quality of life in clinically selected patients from Asia with advanced non-small-cell lung cancer treated with first-line gefitinib: Post hoc analyses from the IPASS study.

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


●●Enlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.03.004

**AUTORES / AUTHORS:** - Wu YL; Fukuoka M; Mok TS; Saijo N; Thongprasert S; Yang JC; Chu DT; Yang JJ; Rukazenkov Y

**INSTITUCION / INSTITUTION:** - Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China. Electronic address: syylwu@live.cn

**RESUMEN / SUMMARY:** - BACKGROUND: In IPASS (NCT00322452), progression-free survival (PFS, primary endpoint) was significantly longer with first-line gefitinib versus carboplatin/paclitaxel in never/light ex-smokers with advanced pulmonary adenocarcinoma in Asia, both in the overall intent-to-treat (ITT) population and in the EGFR mutation-positive subgroup. To further characterize the clinical relevance of these data, we investigated objective response rate (ORR) and health-related quality of life (HRQoL) in patients treated with gefitinib. METHODS: Objective response was assessed (RECIST) 6-weekly (previously reported). Post hoc assessments included median time to response, median duration of response and change in tumor size. The analysis of response population included those patients treated with gefitinib who responded (n=262 from ITT; n=94 from EGFR mutation-positive subgroup). The percentage of patients with deterioration in HRQoL (Functional Assessment of Cancer Therapy-Lung [FACT-L], Trial Outcome Index [TOI]) and symptoms (Lung Cancer Subscales [LCS]) at 4 months post-randomization was analyzed according to progression status (EFQ population grouped by progressors/non-progressors in both treatment arms). The ORR (ITT) and incidence of skin rash/acne (evaluable-for-safety) were summarized. RESULTS: In patients whose tumors responded to gefitinib, median time to response was 6.1 weeks in the ITT population (n=262) and 6.0 weeks in the EGFR mutation-positive
subgroup (n=94); median duration of response was 9.7 and 8.7 months in these groups, respectively. There was significant tumor shrinkage with gefitinib. A greater percentage of patients in the EFQ population whose tumors progressed experienced deterioration in HRQoL and symptoms at 4 months versus patients whose tumors did not progress (FACT-L 33.7% vs 16.3%; TOI 33.7% vs 13.2%; LCS 31.7% vs 15.5%). In the gefitinib arm of the EFS population, incidence of rash was 75.8% and 68.1% in EGFR mutation-positive and -negative subgroups, respectively (with ORR for the gefitinib arm of the ITT 71.2% vs 1.1%, respectively). CONCLUSIONS: Patients whose tumors responded to first-line gefitinib experienced significant tumor shrinkage and a rapid, durable response. Deterioration in HRQoL and lung cancer symptoms at 4 months post-randomization was found to be associated with tumor progression, highlighting the role of patient-reported outcomes in the evaluation of advanced NSCLC disease. Rash was not supported as a predictive marker of response to gefitinib.

[35]
**TÍTULO / TITLE:** Gynaecomastia, galactorrhoea, and lung cancer in a man.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

[36]
**TÍTULO / TITLE:** Risk factors for predicting the occult nodal metastasis in TNM NSCLC patients staged by PET/CT: Potential value in the clinic.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
PET/CT, further investigate the potential risk factors for nodal involvement, since a successful prediction could be helpful in selection appropriate candidates for SABR or limited surgery. METHODS: We retrospectively reviewed the records of 189 patients who diagnosed as clinical stage I NSCLC by 18F-FDG PET/CT from January 2004 to July 2011. All patients underwent lobectomy and systematic lymph node dissection and preoperative 18F-FDG PET/CT scanning. The prevalence of occult nodal metastasis in patients as clinical N0 was analyzed according to clinicopathological factors such as tumor location, tumor size, tumor subtype, grade of differentiation and primary tumor SUVmax. Risk factors for occult nodal metastasis were defined by univariate and multivariate analysis. RESULTS: Occult nodal metastasis was detected in 18.0% (34/189) of the patients. SUVmax of the primary tumor and tumor size were independent predictors of occult nodal metastasis for patients with clinical N0 NSCLC by FDG PET/CT. Accordingly we divided our patients into three groups: group 1 (low-risk group) ~T<=3cm and SUVmax<=4.3; group 2 (moderate-risk group) ~T<=3cm and SUVmax>4.3 or SUVmax<=4.3 and T>3cm; group 3 (high-risk group) ~T>3cm and SUVmax>4.3. The occult lymph node metastasis rate in groups 1, 2, 3 was 1/82 (1.2%), 19/75 (25.3%) and 14/32 (43%) respectively. CONCLUSIONS: T1-2N0M0 NSCLC patients by PET/CT showing larger tumor size and high SUVmax constitute a high-risk group for occult nodal metastasis. The combined information of primary tumor SUVmax and tumor size before treatment have potential values in the clinic. These findings would be helpful in selection of SABR or limited surgery candidates.

RESUMEN / SUMMARY: BACKGROUND: Standard chemotherapy does not lead to long-term survival in patients with malignant pleural mesothelioma. Malignant pleural mesothelioma is strongly dependent on vasculature with high vessel
counts and high concentrations of serum vascular growth factors. Thalidomide has shown antiangiogenic activity, and we hypothesised that its use in the maintenance setting could improve outcomes. METHODS: In this open-label, multicentre, randomised phase 3 study, eligible patients had proven malignant pleural or peritoneal mesothelioma and had received a minimum of four cycles of first-line treatment containing at least pemetrexed, with or without cisplatin or carboplatin, and had not progressed on this treatment. Patients were randomly assigned (in a 1:1 ratio, stratified by previous first-line chemotherapy, histological subtype, and recruiting hospital) to receive thalidomide 200 mg per day (including a 2 week run in of 100 mg per day) plus active supportive care or active supportive care alone until disease progression. Patients were required to be registered and to start treatment with thalidomide within 10 weeks after the end of the first-line chemotherapy. Thalidomide was given for a maximum of 1 year or until unacceptable toxicity. The primary endpoint was time to progression. The primary analyses were by intention to treat. The study is registered, ISRCTN13632914. FINDINGS: Between May 11, 2004, and Dec 23, 2009, we randomly assigned 222 patients, 111 in each group (one patient on active supportive care later withdrew consent and was excluded from analyses). At the time of this final analysis, median follow-up was 33.1 months (IQR 22.3-66.8), and physician-reported disease progression had occurred in 104 patients in the thalidomide group and 107 in the active supportive care group; 92 patients in the thalidomide group and 93 in the active supportive care group had died. Median time to progression in the thalidomide group was 3.6 months (95% CI 3.2-4.1) compared with 3.5 months (2.3-4.8) in the active supportive care group (hazard ratio 0.95, 95% CI 0.73-1.20, p=0.72). 43 (39%) grade 3 or 4 adverse events were reported in the thalidomide group and 31 (28%) in the active supportive care group; neurosensory events were reported by two (2%) patients on thalidomide and none on active supportive care, cardiac events by two (2%) patients on thalidomide and three (3%) on active supportive care, and thromboembolic events by three (3%) patients on thalidomide and none on active supportive care. INTERPRETATION: No benefit was noted in time to progression with the addition of thalidomide maintenance to first-line chemotherapy. Different treatment strategies are needed to improve outcomes in patients with malignant mesothelioma. FUNDING: Dutch Cancer Society (KWF), Eli Lilly, NSW Dust Disease Compensation Board, University of Sydney, and Cancer Australia.

[38]

**TÍTULO / TITLE:** - The theoretical foundation and research progress for WBRT combined with erlotinib for the treatment of multiple brain metastases in patients with lung adenocarcinoma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)

AUTORES / AUTHORS: - Zhuang H; Wang J; Zhao L; Yuan Z; Wang P

INSTITUCIÓN / INSTITUTION: - Department of Radiotherapy, Tianjin Cancer Institute & Hospital, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin Lung Cancer Center, Tianjin, PR, China.

RESUMEN / SUMMARY: - Tyrosine kinase inhibitors (TKIs) have revolutionised the treatment of lung adenocarcinoma, and a theoretical basis exists for utilising whole brain radiotherapy (WBRT) combined with erlotinib for the treatment for brain metastases in patients with lung adenocarcinoma. This therapeutic regimen has the potential to be a revolutionary treatment for which the most appropriate indication is lung adenocarcinoma. Currently, there is no difference in the treatment of brain metastasis, especially multiple brain metastases, in patients with lung adenocarcinoma of patients with other lung carcinomas. Furthermore, limited clinical trials that combine a TKI with WBRT to treat multiple lung adenocarcinoma metastases have been conducted, and many clinical questions remain unanswered. Lung adenocarcinoma has a high propensity to metastasise to the brain, and targeted therapy has been widely used; however, clinical trials are necessary to provide data to support the combination of erlotinib and WBRT. © 2013 Wiley Periodicals, Inc.

[39]

TÍTULO / TITLE: - Tumor Heterogeneity as measured on the CT component of PET/CT Predicts Survival in Patients with Potentially Curable Non-Small Cell Lung Cancer.

RESUMEN / SUMMARY: - Enlace al resumen / Link to its summary


AUTORES / AUTHORS: - Win T; Miles K; Janes SM; Ganeshan B; Shastry M; Endozo R; Meagher M; Shortman RI; Wan S; Kayani I; Ell P; Groves AM

INSTITUCIÓN / INSTITUTION: - Chest Medicine, Lister Hospital.

RESUMEN / SUMMARY: - PURPOSE: We prospectively examined the role of tumor textural heterogeneity on positron emission tomography/computed tomography (PET/CT) in predicting survival compared to other clinical and imaging parameters in non small cell lung cancer (NSCLC) patients. EXPERIMENTAL DESIGN: The feasibility study consisted of fifty-six assessed consecutive NSCLC patients (32-males; 24-females; mean-age 67+/9.7y) that underwent combined fluorodeoxyglucose (FDG)-PET/CT. The validation study population consisted of sixty-six prospectively recruited consecutive consenting NSCLC patients (37-males; 29-females; mean-age 67*5+/7*8y) that successfully underwent combined FDG-PET/CT-dynamic contrast enhanced

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(DCE)-CT. Images were used to derive tumoral PET/CT textural heterogeneity, DCE-CT permeability, and FDG uptake (SUVmax). The mean follow-up period was 22.6+/-13.3 months and 28.5+/-13.2 months for the feasibility and validation studies. Optimum threshold was determined for clinical stage and each of the above biomarkers (where available) from the feasibility study population. Kaplan-Meier analysis assessed the ability of the biomarkers to predict survival in the validation study. Cox's-regression determined survival factor independence. RESULTS: Univariate analysis revealed that tumor CT derived heterogeneity (p<0.001), PET derived heterogeneity (p=0.003), CT derived permeability (p=0.002) and stage (p<0.001) were significant survival predictors. The thresholds used were derived from a previously performed feasibility study. Tumor SUVmax did not predict survival. Using multivariable analysis, tumor CT textural heterogeneity (p=0.021), stage (p=0.001), and permeability (p<0.001) were independent survival predictors. These predictors were independent of patient treatment. CONCLUSIONS: Tumor stage and computed tomography-derived textural heterogeneity were the best predictors of survival in NSCLC. The use of computed tomography-derived textural heterogeneity should assist the management of many patients with NSCLC.

[40]

TÍTULO / TITLE: Urethane increases reactive oxygen species and activates extracellular signal-regulated kinase in RAW 264.7 macrophages and A549 lung epithelial cells.

RESUMEN / SUMMARY: Urethane, which is used as an anesthetic for animal experiments, causes inflammation and cancer in the lung. BALB/c mice received 1 mg/g of urethane once a week for four consecutive weeks via intraperitoneal injections developed interstitial infiltration of inflammatory cells and tumors in the lung. However, the intracellular signaling events which urethane causes inflammation and cancer are largely unknown. Here we show that urethane caused overproduction of reactive oxygen species (ROS) in RAW 264.7 macrophages and A549 lung epithelial cells. Pretreatment of these cells with the antioxidant N-acetylcysteine attenuated the urethane-induced ROS production. Urethane increased heme oxygenase-1 expression to protect these cells from cytotoxicity caused by overproduced ROS. In addition, urethane
activated extracellular signal-regulated kinase (ERK) in both cell types. Overall, our data imply that urethane stimulates ROS production and ERK activation in macrophages and lung epithelial cells, and the overproduced ROS and activated ERK may promote tumor formation in the lung.

[41]
TÍTULO / TITLE: The CD36 dynamic change after radiation therapy in lung cancer patients and its correlation with symptomatic radiation pneumonitis.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Bai L; Zhao J; Yu H; Zhao N; Liu D; Zhong W; Zhao Y
INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, First Affiliated Hospital of China Medical University, People’s Republic of China.
RESUMEN / SUMMARY: This study was carried out to investigate the relationship between serum CD36 levels and radiation pneumonitis in 30 patients irradiated for lung cancer. We found CD36 may become an important index for predicting the occurrence and development of radiation pneumonitis and evaluating the curative effect.

[42]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Bos M; Gardizi M; Schildhaus HU; Heukamp LC; Geist T; Kaminsky B; Zander T; Nogova L; Scheffler M; Dietlein M; Kobe C; Holstein A; Maintz D; Buttner R; Wolf J
INSTITUCIÓN / INSTITUTION: Department I of Internal Medicine, Center for Integrated Oncology Koln-Bonn, University Hospital Cologne, Cologne, Germany.
RESUMEN / SUMMARY: A 55-year-old Caucasian woman with lung adenocarcinoma stage IV presented with repeated relapse after treatment with cytotoxic chemotherapy (carboplatin, gemcitabine, docetaxel, pemetrexed) and targeted agents (erlotinib, cetuximab, sunitinib). Comprehensive molecular
diagnostics (EGFR-, ALK-, RAS-, BRAF-, PIK3CA-, HER2- and DDR2-aberrations) were performed and failed initially to detect any driver mutation. While the patient suffered from rapid deterioration of her general condition, in particular from progressive dyspnea due to lung metastases, we implemented screening for RET- and ROS1 translocations into our molecular diagnostic program based on recent reports of these new molecular subgroups in lung adenocarcinoma. On retesting the patient’s tumor sample was found to harbor a ROS1-translocation. The patient was subsequently treated with crizotinib and experienced a pronounced clinical improvement corresponding to a complete metabolic response in 18F-FDG-PET and a good and confirmed partial response in CT (RECIST 1.1). Our case exemplifies the need for rapid implementation of newly discovered rare genetic lung cancer subtypes in routine molecular diagnostics.

[43]

**TÍTULO / TITLE:** DDX3 loss by p53 inactivation promotes tumor malignancy via the MDM2/Slug/E-cadherin pathway and poor patient outcome in non-small-cell lung cancer.

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


**AUTORES / AUTHORS:** Wu DW; Lee MC; Wang J; Chen CY; Cheng YW; Lee H

**INSTITUCIÓN / INSTITUTION:** Graduate Institute of Cancer Biology and Drug Discovery, Taipei Medical University, Taipei, Taiwan, ROC.

**RESUMEN / SUMMARY:** P53 inactivation by p53 mutation and E6 oncoprotein has a crucial role in human carcinogenesis. DDX3 has been shown to be a target of p53. In this study, we hypothesized that DDX3 loss by p53 inactivation may promote tumor malignancy and poor patients’ outcome. Mechanically, DDX3 loss by p53 knockdown and E6 overexpression was observed in A549 lung cancer cells. Conversely, DDX3 expression was markedly elevated by wild-type (WT) p53 ectopic expression in p53-null H1299 cells, E6-knockdown TL-1 lung cancer and SiHa cervical cancer cells. Interestingly, DDX3 loss promotes soft-agar growth and invasive capability; however, both capabilities were suppressed by DDX3 overexpression. We next expected that DDX3 loss might result in Slug-suppressed E-cadherin expression via decreased MDM2-mediated Slug degradation. As expected, MDM2 transcription is suppressed by DDX3 loss via decreased SP1 binding activity to the MDM2 promoter. Consequently, Slug expression was elevated by the reduction of MDM2 because of DDX3 loss, and E-cadherin expression was suppressed by Slug. Consistent observations in the correlation of DDX3 loss with MDM2, Slug and E-cadherin were seen in lung tumors from lung cancer patients. In addition, patients with low-DDX3 tumors had poorer survival and relapse than patients
with high-DDX3 tumors. In conclusion, we suggest that DDX3 loss by p53 inactivation via MDM2/Slug/E-cadherin pathway promotes tumor malignancy and poor patient outcome. Oncogene advance online publication, 15 April 2013; doi:10.1038/onc.2013.107.

[44]

TÍTULO / TITLE: - Adjuvant MAGE-A3 Immunotherapy in Resected Non-Small-Cell Lung Cancer: Phase II Randomized Study Results.

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


AUTORES / AUTHORS: - Vansteenkiste J; Zielinski M; Linder A; Dahabreh J; Gonzalez EE; Malinowski W; Lopez-Brea M; Vanakesa T; Jassem J; Kalofonos H; Perdeus J; Bonnet R; Basko J; Janiilionis R; Passlick B; Treasure T; Gillet M; Lehmann FF; Bichard VG

INSTITUCIÓN / INSTITUTION: - Johan Vansteenkiste, University Hospital KU Leuven, Leuven; Marc Gillet, Frederic F. Lehmann, and Vincent G. Brichard, GlaxoSmithKline Biologicals, Rixensart, Belgium; Marcin Zielinski, Pulmonary Hospital, Zakopane; Wojciech Malinowski, Szpital Kopernika, Tusznin; Jacek Jassem, Medical University of Gdansk, Gdansk, Poland; Albert Linder, LungenKlinik, Hemer; Jakub Perdeus, Asklepios Fachkliniken Muenchen-Gauting, Gauting; Reiner Bonnet, Zentralklinikum Bad Berka, Bad Berka; Bernward Passlick, University of Freiburg, Baden-Wurttemberg, Germany; Jubrail Dahabreh, Athens Medical Centre, Athens; Haralabos Kalofonos, University of Patras, Patras, Greece; Emilio E. Gonzalez, Asturias Central University Hospital, Oviedo; Marta Lopez-Brea, Marques de Valdecilla University Hospital, Santander, España; Tonu Vanakesa, North Estonian Regional Hospital, Tallinn, Estonia; Jazeps Basko, P. Stradina Kliniska Universitates Slimnica, Riga, Richard Janiilionis, Vilnius University Central Hospital, Vilnius, Lithuania; and Tom Treasure, Guy’s Hospital, London, United Kingdom.

RESUMEN / SUMMARY: - PURPOSE The MAGE-A3 protein is expressed in approximately 35% of patients with resectable non-small-cell lung cancer (NSCLC). Several immunization approaches against the MAGE-A3 antigen have shown few, but often long-lasting, clinical responses in patients with metastatic melanoma. Patients and methods A double-blind, randomized, placebo-controlled phase II study was performed assessing clinical activity, immunologic response, and safety following immunization with recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) in completely resected MAGE-A3-positive stage IB to II NSCLC. The primary end point was disease-free interval (DFI). Results Patients were randomly assigned to either MAGE-A3 immunotherapeutic (n = 122) or placebo
After a median postresection period of 44 months, recurrence was observed in 35% of patients in the MAGE-A3 arm and 43% in the placebo arm. No statistically significant improvement in DFI (hazard ratio [HR], 0.75; 95% CI, 0.46 to 1.23; two-sided P = .254), disease-free survival (DFS; HR, 0.76; 95% CI, 0.48 to 1.21; P = .248), or overall survival (HR, 0.81; 95% CI, 0.47 to 1.40; P = .454) was observed. Corresponding analysis after a median of 70 months of follow-up revealed a similar trend for DFI and DFS. All patients receiving the active treatment showed a humoral immune response to the MAGE-A3 antigen, although no correlation was observed with outcome. No significant toxicity was observed. CONCLUSIONS In this early development study with a limited number of patients, postoperative MAGE-A3 immunization proved to be feasible with minimal toxicity. These results are being investigated further in a large phase III study.
was higher in the erlotinib arm. CONCLUSIONS: Both pemetrexed and erlotinib had comparable efficacy in pre-treated patients with metastatic NSCLC, and the current results indicated that genotyping of tumor cells may have an important effect on treatment efficacy. Cancer 2013; © 2013 American Cancer Society.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1038/nrc3514
AUTORES / AUTHORS: - McCarthy N

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt192
AUTORES / AUTHORS: - Kozu Y; Maniwa T; Takahashi S; Isaka M; Ohde Y; Nakajima T
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan.
RESUMEN / SUMMARY: - OBJECTIVES: Even after curative resection, a significant fraction of patients with stage I non-small-cell lung cancer (NSCLC) die primarily because of systemic relapse. The purpose of the present study was to investigate the risk factors for both recurrence and poor survival in patients with pathological (p-) stage I NSCLC. METHODS: We retrospectively reviewed 467 consecutive patients from a single institution with completely resected p-stage I NSCLC. Patients with multiple lung tumours or malignancies from other organs and those who had undergone preoperative therapies were excluded. The correlation between clinicopathological factors and surgical outcomes, including disease-free survival (DFS) and overall survival (OS), was analysed. The clinicopathological factors examined were age, gender, smoking history, serum carcinoembryonic antigen (CEA) levels, serum cytokeratin 19 fragment levels, surgical procedure, tumour histology, p-stage, angiolymphatic invasion and differentiation grade. RESULTS: The 5-year DFS and OS rates of the total study population were 91.4 and 92.8%, respectively. Multivariate analysis results indicated that high serum CEA levels (>5.0 ng/ml) and p-stage IB were independent factors for recurrence, whereas older age (>70 years), high serum CEA levels and p-stage IB were independent factors for poor
survival. The risks of recurrence and death in patients with both high serum CEA levels and p-stage IB was 10.3 and 5.2 times higher than those observed in patients with both normal serum CEA levels and p-stage IA, respectively.

CONCLUSIONS: High serum CEA levels and p-stage IB were independent factors for both recurrence and poor survival in p-stage I NSCLC patients.

[48]
TÍTULO / TITLE: - Lung Cancer That Harbors an HER2 Mutation: Epidemiologic Characteristics and Therapeutic Perspectives.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mazieres J; Peters S; Lepage B; Cortot AB; Barlesi F; Beau-Faller M; Besse B; Blons H; Mansuet-Lupo A; Urban T; Moro-Sibilot D; Dansin E; Chouaid C; Wislez M; Diebold J; Felip E; Rouquette I; Milia JD; Gautschi O
INSTITUCIÓN / INSTITUTION: - Unite d’Oncologie Cervico-Thoracique, Clinique des Voies Respiratoires, Hopital Larrey, CHU Toulouse, Chemin de Pouvourville, 31059 Toulouse Cedex, France; mazieres.j@chu-toulouse.fr.
RESUMEN / SUMMARY: - PURPOSE HER2 mutations are identified in approximately 2% of non-small-cell lung cancers (NSCLC). There are few data available that describe the clinical course of patients with HER2-mutated NSCLC. PATIENTS AND METHODS We retrospectively identified 65 NSCLC, diagnosed with a HER2 in-frame insertion in exon 20. We collected clinicopathologic characteristics, patients’ outcomes, and treatments. Results HER2 mutation was identified in 65 (1.7%) of 3,800 patients tested and was almost an exclusive driver, except for one single case with a concomitant KRAS mutation. Our population presented with a median age of 60 years (range, 31 to 86 years), a high proportion of women (45 women v 20 men; 69%), and a high proportion of never-smokers (n= 34; 52.3%). All tumors were adenocarcinomas and 50% were stage IV at diagnosis. For these latter cases, 22 anti-human epidermal growth factor receptor 2 (HER2) treatments were administered after conventional chemotherapy in 16 patients. Subsequently, four patients experienced progressive disease, seven experienced disease stabilizations, and 11 experienced partial responses (overall response rate, 50%; disease control rate [DCR], 82%). Specifically, we observed a DCR of 93% for trastuzumab-based therapies (n = 15) and a DCR of 100% for afatinib (n = 3) but no response to other HER2-targeted drugs (n = 3). Progression-free survival for patients with HER2 therapies was 5.1 months. Median survival was of 89.6 and 22.9 months for early-stage and stage IV patients, respectively.
CONCLUSION This study, the largest to date dedicated to HER2-mutated
NSCLC, reinforces the importance of screening for HER2 mutations in lung adenocarcinomas and suggests the potential efficacy of HER2-targeted drugs in this population.

[49]

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

AUTORES / AUTHORS: - Wu J; Betzing C; He TT; Fuss M; D'Souza WD
INSTITUCIÓN / INSTITUTION: - Radiation Oncology, Swedish Cancer Institute, Seattle, Washington 98104.

RESUMEN / SUMMARY: - Purpose: In this work, the authors retrospectively compared the accumulated dose over the treatment course for stereotactic body radiation therapy (SBRT) of lung cancer for three patient setup strategies. Methods: Ten patients who underwent lung SBRT were selected for this study. At each fraction, patients were immobilized using a vacuum cushion and were CT scanned. Treatment plans were performed on the simulation CT. The planning target volume (PTV) was created by adding a 5-mm uniform margin to the internal target volume derived from the 4DCT. All plans were normalized such that 99% of the PTV received 60 Gy. The plan parameters were copied onto the daily CT images for dose recalculation under three setup scenarios: skin marker, bony structure, and soft tissue based alignments. The accumulated dose was calculated by summing the dose at each fraction along the trajectory of a voxel over the treatment course through deformable image registration of each CT with the planning CT. The accumulated doses were analyzed for the comparison of setup accuracy. Results: The tumor volume receiving 60 Gy was 91.7 +/- 17.9%, 74.1 +/- 39.1%, and 99.6 +/- 1.3% for setup using skin marks, bony structure, and soft tissue based alignments, respectively. The isodose line covering 100% of the GTV was 55.5 +/- 7.1, 42.1 +/- 16.0, and 64.3 +/- 7.1 Gy, respectively. The corresponding average biologically effective dose of the tumor was 237.3 +/- 29.4, 207.4 +/- 61.2, and 258.3 +/- 17.7 Gy, respectively. The differences in lung biologically effective dose, mean dose, and V20 between the setup scenarios were insignificant. Conclusions: The authors’ results suggest that skin marks and bony structure are insufficient for aligning patients in lung SBRT. Soft tissue based alignment is needed to match the prescribed dose delivered to the tumors.

[50]

**RESUMEN / SUMMARY:** Pharmacokinetics of docetaxel can be measured in vivo using positron emission tomography (PET) and a microdose of radiolabeled docetaxel ([11C]docetaxel). The objective of this study was to investigate whether a [11C]docetaxel PET microdosing study could predict tumor uptake of therapeutic doses of docetaxel. **EXPERIMENTAL DESIGN:** Docetaxel-naive lung cancer patients underwent two [11C]docetaxel PET scans; one after bolus injection of [11C]docetaxel and another during combined infusion of [11C]docetaxel and a therapeutic dose of docetaxel (75 mg*m⁻²). Compartmental and spectral analyses were used to quantify [11C]docetaxel tumor kinetics. [11C]docetaxel PET measurements were used to estimate the area under the curve (AUC) of docetaxel in tumors. Tumor response was evaluated using computed tomography scans. **RESULTS:** Net rates of influx (Ki) of [11C]docetaxel in tumors were comparable during microdosing and therapeutic scans. [11C]docetaxel AUCTumor during the therapeutic scan could be predicted reliably using an impulse response function derived from the microdosing scan together with the plasma curve of [11C]docetaxel during the therapeutic scan. At 90 min, the accumulated amount of docetaxel in tumors was <1% of the total infused dose of docetaxel. [11C]docetaxel Ki derived from the microdosing scan correlated with AUCTumor of docetaxel (Spearman’s rho= 0.715; P= 0.004) during the therapeutic scan and with tumor response to docetaxel therapy (Spearman’s rho= -0.800; P= 0.010). **CONCLUSIONS:** Microdosing data of [11C]docetaxel PET can be used to predict tumor uptake of docetaxel during chemotherapy. The present study provides a framework for investigating the PET microdosing concept for radiolabeled anticancer drugs in patients.
BACKGROUND: Epithelial-to-mesenchymal transition (EMT) plays a pivotal role in lung cancer metastasis. The class III deacetylase sirtuin 1 (SIRT1) possesses both pro- and anticarcinogenic properties. The role of SIRT1 in lung cancer EMT is largely undefined. METHODS: The effect of SIRT1 on migration of lung cancer cells was evaluated by wound healing assay in vitro and metastasis assay in nude mice in vivo. Protein expression in human lung cancers and cultured lung cancer cells was assessed by western blotting and immunohistochemistry. Interaction between protein and DNA was measured by chromatin immunoprecipitation assay. SIRT1 promoter activity was determined by reporter assay. RESULTS: SIRT1 activation antagonized migration of lung cancer cells by suppressing EMT in vitro. Activation of SIRT1 by resveratrol also statistically significantly hampered (by 68.33%; P < .001, two-sided test) lung cancer cell metastasis in vivo. Hypoxia repressed SIRT1 transcription through promoting the competition between Sp1 and HIC1 on the SIRT1 proximal promoter in a SUMOylation-dependent manner. Disruption of SUMOylation by targeting either Ubc9 or PIASy restored SIRT1 expression and favored an epithelial-like phenotype of cancer cells, thereby preventing metastasis. Decreased SIRT1 combined with elevated PIASy expression was implicated in more-invasive types of lung cancers in humans. CONCLUSIONS: We have identified a novel pathway that links SIRT1 down-regulation to hypoxia-induced EMT in lung cancer cells and may shed light on the development of novel antitumor therapeutics.

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

AUTORES / AUTHORS: - Wu X; Wang L; Ye Y; Aakre JA; Pu X; Chang GC; Yang PC; Roth JA; Marks RS; Lippman SM; Chang JY; Lu C; Deschamps C; Su WC; Wang WC; Huang MS; Chang DW; Li Y; Pankratz VS; Minna JD; Hong WK; Hildebrandt MA; Hsiung CA; Yang P
INSTITUCIÓN / INSTITUTION: - Department of Epidemiology, University of Texas MD Anderson Cancer Center.
RESUMEN / SUMMARY: - To identify the genetic factors that influence overall survival in never smokers who have non-small cell lung cancer (NSCLC), we performed a consistency meta-analysis study utilizing genome-wide association approaches for overall survival in 327 never smoker NSCLC patients from the MD Anderson Cancer Center and 293 cases from the Mayo Clinic. We then performed a two-pronged validation of the top 25 variants that included additional validation in 1,256 NSCLC patients from Taiwan and assessment of expression quantitative trait loci (eQTL) and differential expression of genes surrounding the top loci in 70 tumors and matched normal tissues. A total of 94 loci were significant for overall survival in both MD Anderson and Mayo studies in the consistency meta-analysis phase, with the top 25 variants reaching a p-value of 10^-6. Two variants of these 25 were also significant in the Taiwanese population: rs6901416 (HR:1.44, 95%CI:1.01-2.06) and rs10766739 (HR:1.23, 95%CI:1.00-1.51). These loci resulted in a reduction in median survival time of at least 8 and 5 months in three populations, respectively. An additional six variants (rs4237904, rs7976914, rs4970833, rs954785, rs485411, and rs10906104) were validated through eQTL analysis that identified significant correlations with expression levels of six genes (LEMD3, TMBIM, ATXN7L2, SHE, ITIH2, and NUDT5, respectively) in normal lung tissue. These genes were also significantly differentially expressed between the tumor and normal lung. These findings identify several novel, candidate prognostic markers for NSCLC in never smokers, with eQTL analysis suggesting a potential biological mechanism for a subset of these observed associations.

[53]

TÍTULO / TITLE: - Clinical Significance of Expression of Cancer/testis Antigen and Down-regulation of HLA Class-I in Patients with Stage I Non-small Cell Lung Cancer.

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


AUTORES / AUTHORS: - Hanagiri T; Shigematsu Y; Shinohara S; Takenaka M; Oka S; Chikaishi Y; Nagata Y; Baba T; Uramoto H; So T; Yamada S

INSTITUCIÓN / INSTITUTION: - Second Department of Surgery, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. hanagiri@med.uoeh-u.ac.jp.

RESUMEN / SUMMARY: - Aim: The purpose of this study was to investigate the clinical significance of expression of cancer/testis (CT) antigen and down-regulation of HLA class-I in patients with stage I non-small cell lung cancer (NSCLC), which underwent complete surgical resection. PATIENTS AND METHODS: The expression of HLA class-I molecules was evaluated in 136 resected NSCLC specimens by immunohistochemistry. The results were scored as the percentage of stained tumor cells and categorized into two
groups: 0-79%, reduced expression; and >80%, normal expression. The expression of CT antigen was performed by reverse transcription-polymerase chain reaction (RT-PCR). RESULTS: The expression of HLA class-I was normal in 49 tumors (36%), and there was reduced expression in 87 tumors (64%). The expression of Melanoma antigen (MAGE)-A3, MAGE-A4, and Kita-Kyushu lung cancer antigen-1 (KK-LC-1) was positive in 34 (25.0%), 22 (16.2%), and 42 (30.9%) patients, respectively. There was no significant difference in the proportion of HLA class-I expression associated with the expression of any of the CT antigens. Among the patients with positive expression of at least one of the CT antigens, the 5-year survival rate of the patients with the normal expression of HLA class-I was 87.5%; however, it was 63.4% in patients with the reduced expression of HLA class-I (p=0.0477). CONCLUSION: Reduced expression of HLA class-I was an unfavorable prognostic factor in patients with positive expression of CT antigen, and represents an important hurdle to antigen-based cancer immunotherapy.

[54]

TÍTULO / TITLE: - Primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer harboring TKI-sensitive EGFR mutations: an exploratory study.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lee JK; Shin JY; Kim S; Lee S; Park C; Kim JY; Koh Y; Keam B; Min HS; Kim TM; Jeon YK; Kim DW; Chung DH; Heo DS; Lee SH; Kim JI
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Seoul National University Hospital, Seoul.
RESUMEN / SUMMARY: - BACKGROUND: The mechanism of primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR-mutant non-small-cell lung cancer (NSCLC) has not been clearly understood. PATIENTS AND METHODS: Eleven patients exhibiting primary resistance (disease progression <3 months) were identified among 197 consecutive NSCLC patients with TKI-sensitive EGFR mutations who received EGFR TKIs at Seoul National University Hospital. Treatment-naive tumors were examined for concurrent genetic alterations using fluorescence in situ hybridization and targeted deep sequencing of cancer-related genes. Deletion polymorphism of Bcl-2-interacting mediator of cell death (BIM) gene was examined to validate its predictive role for TKI outcome. RESULTS: The median progression-free survival (PFS) for patients receiving EGFR TKIs was 11.9 months, and the response rate 78.8%. Among the 11 patients exhibiting primary resistance, a de novo T790M mutation was identified in one patient,
and two exhibited mesenchymal-epithelial transition amplification and anaplastic lymphoma kinase fusion. Targeted deep sequencing identified no recurrent, coexistent drivers of NSCLC. Survival analysis revealed that patients with recurrent disease after surgery had a longer PFS than those with initial stage IV disease. However, BIM deletion polymorphism, line of treatment, EGFR genotype, and smoking were not predictive of PFS for EGFR TKIs.

CONCLUSIONS: We identified coexistent genetic alterations of cancer-related genes that could explain primary resistance in a small proportion of patients. Our result suggests that the mechanism of primary resistance might be heterogeneous.

[55]

TÍTULO / TITLE: - Comparison of three measurements on computed tomography for the prediction of less invasiveness in patients with clinical stage I 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.2013.02.022

AUTORES / AUTHORS: - Matsuguma H; Oki I; Nakahara R; Suzuki H; Kasai T; Kamiyama Y; Igarashi S; Mori K; Endo S; Yokoi K

INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Tochigi Cancer Center, Utsunomiya, Japan. Electronic address: hmatsugu@tcc.pref.tochigi.lg.jp.

RESUMEN / SUMMARY: - BACKGROUND: A greater proportion of ground-glass opacity (GGO) is well known to be strongly associated with less invasive lung adenocarcinoma. Recently, the solid area diameter has also been reported to be a simple and better marker for the same purpose compared with the whole nodule diameter. METHODS: From 1997 to 2009, 383 patients with clinical T1-2N0M0 non-small cell lung cancer (NSCLC) with a solid area of 3 cm or less underwent surgical resection, and their preoperative high-resolution computed tomographic images were preserved in Digital Imaging and Communications in Medicine format. Less invasive lung cancer was defined as having no vascular, lymphatic, or pleural invasion or lymph node metastasis. We compared the solid area and whole nodule diameters and proportion of GGO, with the objective of predicting less invasive lung cancer. RESULTS: Among the 383 patients, 187 were men, 335 had adenocarcinoma histologic type, 242 had less invasive lung cancer, and 43 experienced recurrence. Receiver operating characteristic (ROC) analysis to predict less invasive lung cancer showed that the area under the curve of proportion of GGO was the highest (0.848; 95% confidence interval [CI], 0.810-0.886), followed by the solid area diameter (0.785; 95% CI, 0.740-
0.829), and then whole nodule diameter (0.621; 95% CI, 0.565-0.677). Multiple logistic regression analyses revealed that proportion of GGO was the only significant predictor of less invasive lung cancer. The proportion of GGO was also found to be a significant prognostic factor of disease-free survival (DFS) along with solid area diameter by multivariate analysis. Regardless of the solid area diameter, no patient with a greater proportion of GGO (> 50%) experienced recurrence. CONCLUSIONS: Proportion of GGO remains important for predicting less invasive lung cancer.

[56]

TÍTULO / TITLE: - Rapid On-Site Evaluation Improves Needle Aspiration Sensitivity in the Diagnosis of Central Lung Cancers: A Randomized Trial.

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


AUTORES / AUTHORS: - Mondoni M; Carlucci P; Di Marco F; Rossi S; Santus P; D'Adda A; Sferrazza Papa GF; Bullamante G; Centanni S

INSTITUCIÓN / INSTITUTION: - Respiratory Unit, San Paolo Hospital, Dipartimento di Scienze della Salute, Universita degli Studi di Milano, Milan, Italy.

RESUMEN / SUMMARY: - Background: Few prospective studies have evaluated the role of endobronchial needle aspiration in diagnosing central airways neoplasms. Rapid on-site evaluation has long been used in transbronchial needle aspiration of adenopathies and peripheral lesions, but its role in sampling central malignancies has not been substantiated yet. Objectives: In this study we evaluated if endobronchial needle aspiration may increase the sensitivity of bronchoscopy for diagnosing central airways neoplasms when added to conventional diagnostic methods (forceps biopsy, brushing and bronchial washing), and if rapid on-site evaluation may be beneficial in patients undergoing endobronchial needle aspiration. Methods: 125 patients (77% males, aged 70 +/- 7 years; mean +/- SD) with central lung cancers were randomized to undergo bronchoscopy including conventional diagnostic methods and needle aspiration, with or without rapid on-site evaluation, stratifying the patients on the basis of the neoplasm growth pattern (exophytic and submucosal/peribronchial disease). Results: Needle aspiration significantly increased the sensitivity of bronchoscopy when added to conventional methods (from 76 to 91%; p < 0.001), primarily resulting from differences in submucosal/peribronchial diseases (68 vs. 90%; p < 0.001) and independently from the presence of rapid on-site evaluation; needle aspiration guided by rapid on-site evaluation guaranteed a higher improvement in bronchoscopy sensitivity than conventional needle aspiration (98 vs. 84%, respectively; p = 0.004). Needle aspiration guided by rapid on-site evaluation showed a significantly higher sensitivity than the conventional method (97 vs. 76%, respectively; p =
Conclusions: Needle aspiration increases the sensitivity of bronchoscopy in diagnosing central airways malignancies when added to conventional diagnostic methods, with a further significant improvement when guided by rapid on-site evaluation.

[57] **TÍTULO / TITLE:** - Identification of Somatic Genomic Alterations in Circulating Tumors Cells: Another Step Forward in Non-Small-Cell Lung Cancer?

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Costa DB

**INSTITUCIÓN / INSTITUTION:** - Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

[58] **TÍTULO / TITLE:** - Detection of Circulating Tumor Cells Harboring a Unique ALK Rearrangement in ALK-Positive Non-Small-Cell Lung Cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Pailler E; Adam J; Barthelemy A; Oulhen M; Auger N; Valent A; Borget I; Planchard D; Taylor M; Andre F; Soria JC; Vielh P; Besse B; Farace F

**INSTITUCIÓN / INSTITUTION:** - Institut de Cancerologie Gustave Roussy, Villejuif, France.

**RESUMEN / SUMMARY:** - PURPOSEThe diagnostic test for ALK rearrangement in non-small-cell lung cancer (NSCLC) for crizotinib treatment is currently done on tumor biopsies or fine-needle aspirations. We evaluated whether ALK rearrangement diagnosis could be performed by using circulating tumor cells (CTCs). PATIENTS AND METHODSThe presence of an ALK rearrangement was examined in CTCs of 18 ALK-positive and 14 ALK-negative patients by using a filtration enrichment technique and filter-adapted fluorescent in situ hybridization (FA-FISH), a FISH method optimized for filters. ALK-rearrangement patterns were determined in CTCs and compared with those present in tumor biopsies. ALK-rearranged CTCs and tumor specimens were characterized for epithelial (cytokeratins, E-cadherin) and mesenchymal (vimentin, N-cadherin) marker expression. ALK-rearranged CTCs were monitored in five patients treated with crizotinib. RESULTSAll ALK-positive patients had four or more ALK-rearranged CTCs per 1 mL of blood (median, nine CTCs per 1 mL; range, four to 34 CTCs per 1 mL). No or only one ALK-rearranged
CTC (median, one per 1 mL; range, zero to one per 1 mL) was detected in ALK-negative patients. ALK-rearranged CTCs harbored a unique (3'5') split pattern, and heterogeneous patterns (3'5', only 3') of splits were present in tumors. ALK-rearranged CTCs expressed a mesenchymal phenotype contrasting with heterogeneous epithelial and mesenchymal marker expressions in tumors. Variations in ALK-rearranged CTC levels were detected in patients being treated with crizotinib. CONCLUSION ALK rearrangement can be detected in CTCs of patients with ALK-positive NSCLC by using a filtration technique and FA-FISH, enabling both diagnostic testing and monitoring of crizotinib treatment. Our results suggest that CTCs harboring a unique ALK rearrangement and mesenchymal phenotype may arise from clonal selection of tumor cells that have acquired the potential to drive metastatic progression of ALK-positive NSCLC.

[59]

TÍTULO / TITLE: - The efficacy of triplet antiemetic therapy with 0.75 mg of palonosetron for chemotherapy-induced nausea and vomiting in lung cancer patients receiving highly emetogenic chemotherapy.

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


AUTORES / AUTHORS: - Miura S; Watanabe S; Sato K; Makino M; Kobayashi O; Miyao H; Iwashima A; Okajima M; Tanaka J; Tanaka H; Kagamu H; Yokoyama A; Narita I; Yoshizawa H

INSTITUCIÓN / INSTITUTION: - Department of Medicine (II), Niigata University Medical and Dental Hospital, Niigata, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Chemotherapy-induced nausea and vomiting (CINV) are some of the most problematic symptoms for cancer patients. Triplet therapy consisting of a 5HT3 receptor antagonist, aprepitant, and dexamethasone is a guideline-recommended antiemetic prophylaxis for highly emetogenic chemotherapy (HEC). The efficacy and safety of triplet therapy using a 0.75-mg dose of palonosetron have not yet been investigated. We performed a prospective phase II study using triplet antiemetic therapy with 0.75 mg of palonosetron. METHODS: Chemotherapy-naive lung cancer patients scheduled to receive HEC were enrolled. The eligible patients were pretreated with antiemetic therapy consisting of the intravenous administration of 0.75 mg of palonosetron, and 9.9 mg of dexamethasone and the oral administration of 125 mg of aprepitant on day 1, followed by the oral administration of 80 mg of aprepitant on days 2-3 and the oral administration of 8 mg of dexamethasone on days 2-4. The primary endpoint was the complete response rate (the CR rate; no vomiting and no rescue medication) during the overall phase (0-120 h).
RESULTS: The efficacy analysis was performed in 63 patients. The CR rates during the overall, acute and delayed phases were 81.0, 96.8, and 81.0 %, respectively. The no nausea and no significant nausea rate during the overall phase were 54.0 and 66.7 %, respectively. The most common adverse event was grade 1 or 2 constipation. CONCLUSIONS: Triplet antiemetic therapy using a 0.75-mg dose of palonosetron shows a promising antiemetic effect in preventing CINV in lung cancer patients receiving HEC.

[60]
TÍTULO / TITLE: - A swollen knee in a 77-year-old lung cancer patient receiving antimicrobial therapy for pneumonia.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1093/cid/cit131

[61]
TÍTULO / TITLE: - A swollen knee in a 77-year-old lung cancer patient receiving antimicrobial therapy for pneumonia.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1093/cid/cit135
AUTORES / AUTHORS: - Lin SY; Lee KM; Chen TC; Chen YH; Lien CT; Lu PL
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital.

[62]
TÍTULO / TITLE: - Efficacy of Pemetrexed as Second-Line Therapy in Advanced NSCLC after Either Treatment-Free Interval or Maintenance Therapy with Gemcitabine or Erlotinib in IFCT-GFPC 05-02 Phase III Study.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1097/JTO.0b013e31828cb505
AUTORES / AUTHORS: - Bylicki O; Ferlay C; Chouaid C; Lavole A; Barlesi F; Dubos C; Westeel V; Crequit J; Corre R; Vergnenegre A; Monnet I; Le Caer H; Fournel P; Vaylet F; Falchero L; Poudenx M; Linard P; Perol D; Zalcman G; Perol M
RESUMEN / SUMMARY: - INTRODUCTION:: Maintenance therapy in advanced non-small-cell lung cancer (NSCLC) might lead to resistance to subsequent treatments. IFCT-GFPC 0502 study showed a progression-free survival (PFS) benefit with gemcitabine or erlotinib maintenance compared with observation after cisplatin-gemcitabine chemotherapy. The trial included a pre-defined pemetrexed second-line therapy, allowing post-hoc assessment of its efficacy according to previous maintenance treatment or treatment-free interval.

METHODS:: Stage IIIB/IV NSCLC patients were randomized after four cycles of cisplatin-gemcitabine chemotherapy to either observation or to receive maintenance therapy with gemcitabine or erlotinib. Pemetrexed was given as second-line treatment on disease progression in all arms. PFS and overall survival (OS) were assessed from the beginning of pemetrexed therapy according to randomization arm. RESULTS:: Of the 464 randomized patients, 360 (78 %) received second-line pemetrexed (130 [84%], 114 [74%], and 116 [75%] in observation, gemcitabine, and erlotinib arm, respectively). Median number of pemetrexed cycles was 3 (1-40) in all arms. Median PFS did not
differ between gemcitabine and observation arms (4.2 versus 3.9 months, hazard ratio [HR] [95% confidence interval [CI] 0.81 [0.62-1.06]) or between erlotinib and observation arms (4.2 versus 3.9 months, HR 0.83 [0.64-1.09]). OS data showed a non-significant improvement with gemcitabine arm versus observation arm (8.3 versus 7.5 months, HR 0.81 [0.61-1.07]) or erlotinib arm versus observation arm (9.1 versus 7.5 months, HR 0.80 [0.61-1.05]). Results were similar for non-squamous patients. Grade 3 to 4 treatment-related adverse events (AEs) were comparable in all arms. CONCLUSIONS:: Maintenance therapy with gemcitabine continuation or erlotinib does not seem to impair efficacy of second-line pemetrexed comparatively to administration after a treatment-free interval.

[63]
TITULO / TITLE: - Identification of Stage I Non-small Cell Lung Cancer Patients at High Risk for Local Recurrence Following Sublobar Resection.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Varlotto JM; Medford-Davis LN; Recht A; Flickinger J; Yao N; Hess C; Reed MF; Toth J; Zander DS; Decamp MM
RESUMEN / SUMMARY: - OBJECTIVE: An increasing proportion of patients with stage I non-small cell lung cancer (NSCLC) is undergoing sublobar resection (L-). However, there is little information about the risks and correlates of local recurrence (LR) after such surgery, especially compared with patients undergoing lobectomy (L+). METHODS: Ninety-three and 318 consecutive patients with stage I NSCLC underwent L- and L+, respectively, from 2000 to 2006. Median follow-up was 34 months. RESULTS: In the L- group, the LR rates at 2, 3, and 5 years were 13%, 24%, and 40%, respectively. The risk of LR was significantly associated with tumor grade, tumor size, and T stage. The crude risk of LR was 33.8% (21 of 62) for patients whose tumors were grade \( \geq 2 \). In the L+ group, the LR rates at 2, 3, and 5 years were 14%, 19%, and 24%, respectively. The risk of LR significantly increased with increasing tumor size, length of hospital stay, and the presence of diabetes. The L- group experienced a significant increase in failure in the bronchial stump/staple line compared with the L+ group (10% vs 3%; \( P = .04 \)) and nonsignificant trends toward increased ipsilateral hilar and subcarinal failure rates. CONCLUSIONS: Patients with stage I NSCLC who undergo L- have an increased risk of LR compared with patients undergoing L+, particularly when they have tumors grade \( \geq 2 \) or tumor size \( \gt; 2 \) cm. If L- is considered, additional local therapy should be considered to reduce this risk of LR, especially with tumors grade \( \geq 2 \) or size \( \gt; 2 \) cm.
TÍTULO / TITLE: - Predictive Factors for Node Metastasis in Patients With Clinical Stage I Non-Small Cell Lung Cancer.

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


AUTORES / AUTHORS: - Cho S; Song IH; Yang HC; Kim K; Jheon S

INSTITUCIÓN / INSTITUTION: - Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoul, Republic of Korea; Department of Thoracic and Cardiovascular Surgery, College of Medicine, Seoul National University, Seoul, Republic of Korea. Electronic address: skcho@snubh.org.

RESUMEN / SUMMARY: - BACKGROUND: Accurate clinical staging of non-small cell lung cancer (NSCLC) is essential for developing a treatment plan and evaluating suitability for minimally invasive surgery. The aim of this study was to evaluate predictive factors for metastasis of N1 and N2 nodes in clinical stage I NSCLC. METHODS: Records of patients with clinical stage I NSCLC who had undergone pulmonary resection with systematic node dissection or node sampling between 2003 and 2011 were retrospectively reviewed. To identify predictive factors for node metastasis, univariate and multivariate logistic regression analyses were performed. RESULTS: Among the 770 patients in this study, the overall prevalence of node metastasis was 19.4%, which included 11.3% of N1 nodes and 8.1% of N2 nodes. Predictive factors for N1 node metastasis included male sex, current smoker, non-adenocarcinoma, solid consistency, centrally located tumor, clinical T stage, cytokeratin fragment 21-1 level, tumor size, maximum standardized uptake value of the mass, and ground-glass opacity proportion. Adenocarcinoma, solid consistency, clinical T stage, carciinoembryonic antigen level, tumor size, and ground-glass opacity proportion were identified as predictors for N2 node metastasis. Both tumor size and solid consistency were independent predictive values of N1 node and N2 node metastasis by multivariate analysis. CONCLUSIONS: Among the patients with clinical stage I NSCLC, 19.4% of the patients showed unexpected node metastasis, and large size and solid consistency of the tumor were predictive factors of node metastasis in clinical stage I NSCLC. Preoperative staging should be performed more thoroughly to increase the accuracy of preoperative staging, especially in those who have the larger size and solid consistency of the tumor.

[64]

Enlace al texto completo (gratis o de pago) 1016/j.athoracsur.2013.03.050
Development of a patient-centered aggregate score to predict survival after lung resection for non-small cell lung cancer.

**OBJECTIVE:** The objective of this analysis was to develop a survival aggregate score (SAS), including objective and subjective patient-based parameters, and assess its prognostic role after major anatomic resection for non-small cell lung cancer. METHODS: A total of 245 patients underwent major lung resections for non-small cell lung cancer with preoperative evaluation of quality of life (Short-Form 36v2 survey) and complete follow-up. The Cox multivariable regression and bootstrap analyses were used to identify prognostic factors of overall survival, which were weighted to construct the scoring system and summed to generate the SAS. RESULTS: Cox regression analysis showed that the factors negatively associated with overall survival and used to construct the score were 36-item short-form health survey physical component summary score less than 50 (hazard ratio [HR], 1.7; P = .008), aged older than 70 years (HR, 1.9; P = .002), and carbon monoxide lung diffusion capacity less than 70% (HR, 1.7; P = .01). Patients were grouped into 4 risk classes according to their SAS. The 5-year overall survival was 78% in class SAS0, 59% in class SAS1, 42% in class SAS2, and 14% in class SAS3 (log-rank test, P < .0001). SAS maintained its association with overall survival in patients with stages pT2 (log-rank test, P = .02), or pT3-4 (log-rank test, P = .001), and in those with stages pN1-2 (log-rank test, P = .02). The 5-year cancer-specific survival was 83% in class SAS0, 71% in class SAS1, 63% in class SAS2, and 17% in class SAS3 (log-rank test, P < .0001). CONCLUSIONS: This system may be used to refine stratification of prognosis for clinical and research purposes.
INTRODUCTION:: Optimal management of clinical stage IIIA-N2 non-small-cell lung cancer (NSCLC) is controversial. This study examines whether neoadjuvant chemoradiation plus surgery improves survival rates when compared with other recommended treatment strategies.

METHODS:: Adult patients from the National Cancer Database, with clinical stage IIIA-N2 disease definitively treated between 1998 and 2004 at American College of Surgeons Commission on Cancer accredited facilities, were included in the study. Treatment was defined as neoadjuvant chemoradiation plus either lobectomy (NeoCRT+L) or pneumonectomy (NeoCRT+P), lobectomy plus adjuvant therapy (L+AT), pneumonectomy plus adjuvant therapy (P+AT), and concurrent chemoradiation (CRT). Median follow-up and overall survival (OS) were defined from date of diagnosis to last contact. Five-year OS was estimated using Kaplan-Meier methods. Cox proportional hazard regression was used to estimate hazard ratios and 95% confidence intervals (CIs), adjusting for sociodemographic, clinical, and facility characteristics. RESULTS:: Median follow-up was 11.8 months for 11,242 eligible patients. Five-year OS was 33.5%, 20.7%, 20.3%, 13.35%, and 10.9% for NeoCRT+L, NeoCRT+P, L+AT, P+AT, and CRT, respectively (p < 0.0001). On multivariable analysis, the estimated hazard ratio was 0.51 (CI: 0.45-0.58) for NeoCRT+L; 0.77 (0.63-0.95) for NeoCRT+P; 0.66 (0.59-0.75) for L+AT; 0.69 (0.54-0.88) for P+AT; and 1.0 (reference) for the CRT group. Comorbidity did not attenuate the relationship between treatment and survival. CONCLUSION:: This large study demonstrates that patients with clinical stage IIIA-N2 NSCLC, who underwent neoadjuvant chemoradiation followed by lobectomy, were associated with an improved survival.
INTRODUCTION:: Standard therapy for limited-stage small-cell lung cancer (L-SCLC) is concurrent chemotherapy and radiotherapy (RT) followed by prophylactic cranial radiotherapy. Although many consider the standard RT regimen to be 45 Gy in 1.5 Gy twice-daily fractions, this has failed to gain widespread acceptance. We pooled data of patients assigned to receive daily RT of 70 Gy from three, consecutive prospective Cancer and Leukemia Group B L-SCLC cancer trials and report the results here. METHODS:: All patients from consecutive Cancer and Leukemia Group B L-SCLC trials (39808, 30002, and 30206) using high-dosage daily RT with concurrent chemotherapy were included, and analyzed for toxicity, disease control, and survival. Overall survival (OS) and progression-free survival (PFS) were modeled using Cox proportional hazards models. Prognostic variables for OS-rate and PFS-rate were assessed using logistic regression model. RESULTS:: Two hundred patients were included. The median follow-up was 78 months. Grade 3 or greater esophagitis was 23%. The median OS for pooled population was 19.9 months (95% confidence interval [CI]: 16.7-22.3), and 5-year OS rate was 20% (95% CI: 16-27%). The 2-year PFS was 26% (95% CI: 21-32%). Multivariate analysis found younger age (p = 0.02; hazard ratio [HR]: 1.023; 95% CI: 21-32), and female sex (p = 0.02; HR:0.69; 95% CI: 0.50-0.94) independently associated with improved overall survival. CONCLUSION:: Two-Gy daily RT to a total dosage of 70 Gy was well tolerated with similar survival to 45 Gy (1.5 Gy twice-daily). This experience may aid practitioners decide whether high-dosage daily RT with platinum-based chemotherapy is appropriate outside of a clinical trial.
Comparative effectiveness of three platinum-doublet chemotherapy regimens in elderly patients with advanced non-small cell lung cancer.

BACKGROUND: Randomized trials report equivalent efficacy among various combinations of platinum-based regimens in advanced non-small cell lung cancer (NSCLC). Their relative effectiveness and comparability based on squamous versus nonsquamous histology is uncertain.

METHODS: The authors used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data to identify first-line chemotherapy agents administered to Medicare beneficiaries with stage IIIB or IV NSCLC diagnosed from 2000 to 2007. Overall survival was compared between patients who received the 3 most common regimens: carboplatin-paclitaxel, carboplatin-gemcitabine, and carboplatin-docetaxel. Stratified analyses distinguished between the outcomes of patients with squamous versus nonsquamous cell histology. Multivariable Cox proportional hazards models and propensity score analyses facilitated adjustment for imbalance in measurable patient characteristics.

RESULTS: Of the 15,318 patients who received first-line chemotherapy, 43.1% received carboplatin-paclitaxel, 14.3% received carboplatin-gemcitabine, 8.5% received carboplatin-docetaxel, and 34.1% received other regimens. The median survival was 8.0 months (interquartile range [IQR], 3.5-17.4 months) for carboplatin-paclitaxel, 7.3 months (IQR, 3.4-15.2 months) for carboplatin-gemcitabine, and 7.5 months (IQR, 3.2-16.0 months) for carboplatin-docetaxel. Both multivariable and propensity score-adjusted Cox models demonstrated a slight inferiority associated with carboplatin-gemcitabine or carboplatin-docetaxel versus carboplatin-paclitaxel, with a hazard ratio of 1.10 (95% confidence interval, 1.04-1.15) and 1.09 (95% confidence interval, 1.02-1.16), respectively, in propensity score-stratified models. Among the subgroup of 2063 patients with squamous carcinoma, propensity score-stratified analyses had a higher risk of death (hazard ratio, 1.20; 95% confidence interval, 1.07-1.35) associated with carboplatin-gemcitabine versus carboplatin-paclitaxel. CONCLUSIONS: Carboplatin-paclitaxel was associated with slightly better survival compared with
carboplatin-gemcitabine or carboplatin-docetaxel within the Medicare population with advanced NSCLC, and this was most pronounced for patients who had squamous cell histology. Cancer 2013;119:2048-2060. © 2013 American Cancer Society.

[69] TÍTULO / TITLE: - Nrf2 prevents initiation but accelerates progression through the Kras signaling pathway during lung carcinogenesis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - Cancer Res. 2013 Apr 22.
AUTORES / AUTHORS: - Satoh H; Moriguchi T; Takai J; Ebina M; Yamamoto M
INSTITUCIÓN / INSTITUTION: - Medical Biochemistry, Tohoku University Graduate School of Medicine.
RESUMEN / SUMMARY: - Nrf2 (NFE2L2) governs cellular defenses against oxidative and electrophilic stresses and protects against chemical carcinogenesis. However, many cancers have been found to accumulate NRF2 protein, raising questions of precisely how Nrf2 contributes to carcinogenesis. In this report, we explored such questions in an established urethane-induced multistep model of lung carcinogenesis. Consistent with earlier observations, Nrf2-deficient (Nrf2/-/-) mice exhibited a relative increase in tumor foci by 8 weeks after urethane administration. However, after 16 weeks we observed a relative reduction in the number of tumors with more malignant characteristics in Nrf2/-/- mice. Furthermore, all Nrf2+/+ tumors harbored activated mutations in K-ras, whereas Nrf2/-/- tumors were rarely associated with similar K-ras mutations. Overall, our results established that Nrf2 has two roles during carcinogenesis, one of which is preventive during tumor initiation, but a second which promotes malignant progression. These findings establish Nrf2 inhibitors as rational tools to prevent malignant progression in lung cancer, whereas Nrf2 activators are more suited for lung cancer prevention.

[70] TÍTULO / TITLE: - Cross-talk between MET and EGFR in non-small cell lung cancer involves miR-27a and Sprouty2.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Acunzo M; Romano G; Palmieri D; Lagana A; Garofalo M; Balatti V; Drusco A; Chiariello M; Nana-Sinkam P; Croce CM
In the past decade, we have observed exciting advances in lung cancer therapy, including the development of targeted therapies. However, additional strategies for early detection and tumor-based therapy are still essential in improving patient outcomes. EGF receptor (EGFR) and MET (the receptor tyrosine kinase for hepatocyte growth factors) are cell-surface tyrosine kinase receptors that have been implicated in diverse cellular processes and as regulators of several microRNAs (miRNAs), thus contributing to tumor progression. Here, we demonstrate a biological link between EGFR, MET, and the miRNA cluster 23\textsuperscript{a} approximately 27\textsuperscript{a} approximately 24-2. We show that miR-27\textsuperscript{a} regulates MET, EGFR, and Sprouty2 in lung cancer. In addition, we identify both direct and indirect mechanisms by which miR-27\textsuperscript{a} can regulate both MET and EGFR. Thus, we propose a mechanism for MET and EGFR axis regulation that may lead to the development of therapeutics in lung cancer.

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TÍTULO / TITLE: - Outcomes of Small Cell Lung Cancer Patients Treated With Cisplatin-Etoposide Versus Carboplatin-Etoposide.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Karam I; Jiang SY; Khaira M; Lee CW; Schellenberg D
INSTITUCIÓN / INSTITUTION: - *Division of Radiation Oncology and Radiotherapeutics - BC Cancer Agency, Vancouver Centre, Department of Radiation Oncology double daggerDivision of Medical Oncology - BC Cancer Agency, Department of Medicine section signDivision of Radiation Oncology and Radiotherapeutics - BC Cancer Agency, Department of Radiation Oncology, Fraser Valley Centre, Surrey, University of British Columbia, Vancouver, BC, Canada daggerRadiation Therapy Program, BC Cancer Agency, Fraser Valley Centre, Surrey, BC, Canada.
RESUMEN / SUMMARY: - PURPOSE: This descriptive study compares overall survival (OS) and locoregional control (LRC) rates between cisplatin-etoposide (EP) and carboplatin-etoposide (EC) at a population level in patients with limited disease (LD) and extensive disease (ED) small cell lung cancer (SCLC). MATERIALS AND METHODS: All patients diagnosed with SCLC from January 2004 to December 2008 were identified. Patients with LD SCLC treated with EP or EC and concurrent or sequential radiotherapy and those with ED SCLC treated with EP or EC were included for analysis. A retrospective review
examining prognostic features and outcomes was performed. OS and LRC curves were calculated using the Kaplan-Meier method and compared with the log-rank test. RESULTS: A total of 249 patients with LD SCLC and 287 patients with ED SCLC were identified. Patients treated with EC were significantly older for both LD (median 62 vs. 72, P<0.001) and ED (median 62 vs. 73, P<0.001). Median follow-up times were 37 and 22 months for LD and ED SCLC, respectively. Median OS for EP and EC in LD SCLC patients were 23 and 18 months (P=0.10). LRC rates at 12 months were 81% for the EP group and 68% for the EC group (P=0.97). Median OS for the EP and EC patients with ED SCLC was 10 and 11 months, respectively, (P=0.24). CONCLUSION: Despite the preferential use of EC in an older population, median OS and LRC rates were not significantly different for patients treated with EP for both LD and ED SCLC.

[72]
Título / Title: ERCC1/BRCA1 expression and gene polymorphisms as prognostic and predictive factors in advanced NSCLC treated with or without cisplatin.
Resumen / Summary: Background: The FAST was a factorial trial in first-line treatment of advanced non-small-cell lung cancer (NSCLC), addressing the role of replacing cisplatin with a non-platinum agent. The prognostic and predictive effect of ERCC1/BRCA1 expression and ERCC1/XPD/XRCC1-3 gene polymorphisms on outcomes of patients was examined. Methods: Patients were randomised to receive treatment with or without cisplatin. ERCC1/BRCA1 expression was determined by immunohistochemistry. ERCC1 (C8092A, C118T), XPD (Lys751Gln), XRCC1 (Arg399Gln) and XRCC3 (Thr241Met) gene polymorphisms were evaluated on tumour DNA by TaqMan allelic discrimination assay. Results: Tumour samples were available from 110 of 433 patients enrolled. 54.7% were ERCC1 positive and 51.4% were BRCA1 positive. Overall, ERCC1-negative patients had better response rate (P=0.004), progression-free survival (P=0.023) and overall survival (P=0.012) compared with positive ones, with no statistically significant treatment interaction. The BRCA1-positive patients showed numerically better outcomes, although not
statistically significant, with no treatment interaction. Among DNA repair gene polymorphisms, only XRCC1 Gln/Gln genotype evidenced a potential prognostic role (P=0.036). Conclusion: This study confirms the prognostic role of ERCC1 expression and XRCC1 (Arg399Gln) polymorphism in advanced NSCLC treated with first-line chemotherapy. None of these biomarkers was shown to be a specific predictive factor of cisplatin efficacy.

[73]
TITULO / TITLE: Identification of promiscuous KIF20A long peptides bearing both CD4+ and CD8+ T-cell epitopes: KIF20A-specific CD4+ T-cell immunity in patients with malignant tumor.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Tomita Y; Akira Y; Tsukamoto H; Senju S; Kuroda Y; Hirayama M; Irie A; Kawahara K; Yatsuda J; Hamada A; Jono H; Yoshida K; Tsunoda T; Kohrogi H; Yoshitake Y; Nakamura Y; Shinohara M; Nishimura Y
INSTITUCIÓN / INSTITUTION: Department of immunogenetics, Graduate School of Medical Sciences Kumamoto University.
RESUMEN / SUMMARY: PURPOSE: To identify long peptides (LPs) derived from a novel tumor-associated antigen (TAA), kinesin family member 20A (KIF20A), which induce tumor-specific T-helper type 1 (Th1) cells and CTLs.
EXPERIMENTAL DESIGN: We combined information from a recently developed computer algorithm predicting HLA class II-binding peptides with KIF20A-derived CTL-epitope sequences presented by HLA-A2 (A*02:01) or HLA-A24 (A*24:02) to select candidate promiscuous Th1 cell epitopes containing CTL-epitopes. Peripheral blood mononuclear cells (PBMC) derived from healthy donors or patients with head-and-neck malignant tumor (HNMT) were used to study the immunogenicity of KIF20A-LPs, and the in vitro cross-priming potential of KIF20A-LPs bearing CTL-epitopes. We used HLA-A24 transgenic mice to address whether vaccination with KIF20A-LP induces efficient cross-priming of CTLs in vivo. The Th1 cell response to KIF20A-LPs in HNMT patients receiving immunotherapy with TAA-derived CTL-epitope peptides was analyzed using IFN-gamma enzyme-linked immunospot assays.
RESULTS: We identified promiscuous KIF20A-LPs bearing naturally processed epitopes recognized by CD4+ T-cells and CTLs. KIF20A-specific CTLs were induced by vaccination with a KIF20A-LP in vivo. KIF20A expression was detected in 55% of HNMT by immunohistochemistry, and significant frequencies of KIF20A-specific Th1 cell responses were detected after short-term in vitro stimulation of PBMCs with KIF20A-LPs in 50% of HNMT patients, but not in healthy donors. Furthermore, these responses were associated with KIF20A
expression in HNMT tissues. CONCLUSIONS: These are the first results demonstrating the presence of KIF20A-specific Th1 cell responses in HNMT patients and underline the possible utility of KIF20A-LPs for propagation of Th1 cells and CTLs.

[74]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kiyohara Y; Yamazaki N; Kishi A
INSTITUCIÓN / INSTITUTION: - Division of Dermatology, Shizuoka Cancer Center Hospital, Shizuoka, Japan. Electronic address: y.kiyohara@scchr.jp.
RESUMEN / SUMMARY: - Skin toxicities are the most common side effects associated with the epidermal growth factor receptor inhibitor erlotinib, occurring in most patients receiving the drug. Clinical trials evaluating erlotinib for the treatment of non-small cell lung cancer have reported a range of skin disorders, the most common being acneiform rash, xeroderma (dry skin), pruritus, and paronychia. Although in the majority of cases these effects are mild and transient, they can have a considerable impact on a patient’s quality of life and, if particularly severe and persistent, may necessitate treatment interruption or cessation and compromise treatment outcome. This coupled with recent evidence to suggest a positive correlation between the incidence and severity of rash and clinical outcome among erlotinib-treated patients with advanced or metastatic non-small cell lung cancer highlights the importance of adequately managing epidermal growth factor receptor inhibitor-related skin disorders. Clear treatment strategies are therefore necessary to ensure the prevention and optimal management of erlotinib-related skin toxicities thereby enabling patients to continue erlotinib treatment. In this review we present a practical approach for the treatment of erlotinib-related cutaneous side effects in Japanese patients with advanced non-small cell lung cancer providing details of specific treatment interventions, according to symptom severity, for each of the common skin disorders. In addition, the importance of preventive skin care measures-namely maintaining cleanliness, moisturization, and protection from external stimuli—in preventing the development of serious skin disorders is discussed and guidelines for the practice of proper skin care are presented.

[75]
**TÍTULO / TITLE:** - Phase II study of weekly carboplatin and irinotecan as first-line chemotherapy for patients with advanced non-small cell lung cancer.

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


**AUTORES / AUTHORS:** - Kim HS; Kim JH; Kim B; Choi HC; Kwon JH; Choi DR

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Kangnam Sacred-Heart Hospital, Hallym University Medical Center, Hallym University College of Medicine, 948-1, Daerim-1-dong, Yeongdeungpo-gu, Seoul, 150-950, Republic of Korea.

**RESUMEN / SUMMARY:** - PURPOSE: Platinum-based doublet chemotherapy has a major role in the treatment of patients with advanced non-small cell lung cancer (NSCLC). The weekly fractionated administration of cisplatin for patients with NSCLC has been shown to be active. Irinotecan and carboplatin are effective against NSCLC and demonstrated synergism with non-cross-resistance in preclinical studies. We conducted a phase II study of weekly combination of carboplatin and irinotecan as first-line chemotherapy for patients with advanced NSCLC. METHODS: From March 2009 to November 2011, 24 patients who were diagnosed with inoperable or metastatic NSCLC were enrolled. Treatment consisted of carboplatin at an AUC 2.5 mg/mL/min over 30-min intravenous infusion and irinotecan 65 mg/m² over 90-min intravenous infusion on day 1 and day 8, respectively. The treatment was repeated every 3 weeks. RESULTS: One patient (4.2 %) achieved complete response, and seven (29.2 %) showed partial response. Overall response rate was 33.3 %, with median response duration of 4.55 months. Nine patients had stable disease, and disease control rate was 70.8 %. With median follow-up of 12.8 months, median progression-free survival was 4.5 months (95 % CI 1.8-7.2), and median overall survival was 15.5 months (95 % CI 6.9-24.1). Major toxicity was myelosuppression. Grade 3-4 neutropenia and thrombocytopenia occurred in 50 and 20.8 % of patients, respectively. Two patients experienced febrile neutropenia. Non-hematologic toxicities were generally mild. One patient suffered grade 4 diarrhea, and one treatment-related death due to pneumonia was occurred. CONCLUSION: The weekly combination of carboplatin and irinotecan showed favorable activity and manageable toxicity profiles in chemonaive patients with advanced NSCLC. Our results suggest that this regimen can be a reasonable chemotherapeutic option for patients with advanced NSCLC.

[76]

**TÍTULO / TITLE:** - Histamine-2 receptor antagonists and risk of lung cancer in diabetic patients - an exploratory analysis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1002/pds.3441
AUTORES / AUTHORS: - Hsu CL; Chang CH; Lin JW; Wu LC; Chuang LM; Lai MS
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; Department of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan.
RESUMEN / SUMMARY: - PURPOSE: Histamine-2 receptor blockers (H2RBs) might have anti-tumorogenic effect, but the clinical effect on lung cancer occurrence was unclear. METHODS: A total of 640,173 type 2 diabetic patients were identified from the Taiwan National Health Insurance claims database in 2000. Patients were followed from cohort entry to the earliest of cancer diagnosis, death, disenrollment from the national health insurance, or 31 December 2007. For each participant, H2RB use during the follow-up period was ascertained from the outpatient pharmacy prescription database. Patients with incident squamous cell carcinoma (SCC) and adenocarcinoma were included as cases and up to four age- and sex-matched controls were selected by risk-set sampling. Conditional logistic regression models were applied to estimate the association between H2RBs and lung cancer incidence.
RESULTS: A total of 1182 incident SCC and 2345 adenocarcinoma cases were identified, and 13,108 matched controls were selected. An increased risk was observed for H2RBs use <1 year with adjusted OR of 1.33 (95% confidence interval (CI): 1.22-1.44). After excluding all exposures occurring in the year before lung cancer diagnosis, H2RBs use with cumulative dosage >/= 360 “defined daily doses” was associated with a significantly decreased risk of lung cancer (OR: 0.60; 95% CI: 0.38-0.96). When we stratified on types of lung cancer, the protective association of higher cumulative use of H2RBs seemed more evident for lung adenocarcinoma, with an adjusted OR of 0.49 (95% CI: 0.26-0.90). CONCLUSIONS: Higher cumulative use of H2RBs might be associated with a reduced risk for non-small cell lung cancer in diabetic patients. Copyright © 2013 John Wiley & Sons, Ltd.

[TÍTULO / TITLE: - Phase 2 study of S-1 and carboplatin plus bevacizumab followed by maintenance S-1 and bevacizumab for chemotherapy-naive patients with advanced nonsquamous non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1002/cncr.28048
AUTORES / AUTHORS: - Urata Y; Okamoto I; Takeda M; Hattori Y; Okuno K; Shimada T; Kurata T; Kaneda H; Miyazaki M; Terashima M; Tanaka K; Morita S; Nakagawa K; Negoro S; Satouchi M
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Oncology, Hyogo Cancer Center, Akashi, Japan.
RESUMEN / SUMMARY: - BACKGROUND: A previous phase 3 trial demonstrated noninferiority in terms of overall survival for combined S-1 (an oral fluoropyrimidine) and carboplatin compared with combined paclitaxel and carboplatin as first-line treatment for advanced non-small cell lung cancer (NSCLC). In the current study, the authors evaluated the efficacy and safety of combined S-1, carboplatin, and bevacizumab followed by maintenance with S-1 and bevacizumab in chemotherapy-naive patients with advanced nonsquamous NSCLC. METHODS: Patients received carboplatin (area under the concentration-time curve, 5 mg mL(-1) per minute) and bevacizumab (15 mg/kg) on day 1 plus oral S-1 (80 mg/m(2) per day) on days 1 through 14 every 21 days for up to 6 cycles. For patients without disease progression, S-1 and bevacizumab were continued until disease progression or unacceptable toxicity developed. RESULTS: Forty-eight patients were enrolled in the phase 2 study; of these, 35 patients (72.9%) completed at least 4 cycles. Most toxicities of grade >/=3 were hematologic, and no increase in relative incidence associated with maintenance with S-1 and bevacizumab was observed. The objective response rate was 54.2% (95% confidence interval, 39.2%-68.6%), and the median progression-free survival was 6.8 months (95% confidence interval, 4.3-8.2 months). CONCLUSIONS: The regimen of combined S-1, carboplatin, and bevacizumab followed by maintenance with S-1 and bevacizumab was active and feasible as first-line treatment for advanced nonsquamous NSCLC. Cancer 2013;119:2275-2281. © 2013 American Cancer Society.

[78]
TÍTULO / TITLE: - Expression of KISS1 and KISS1R (GPR54) may be used as favorable prognostic markers for patients with non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 3892/ijo.2013.1967
AUTORES / AUTHORS: - Sun YB; Xu S
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, The First Hospital of China Medical University, Heping, Shenyang, Liaoning 110001, P.R. China.
RESUMEN / SUMMARY: - Lung cancer is the most commonly diagnosed cancer worldwide. Loss of KISS1 expression has been associated with progression and poor prognosis of various cancers, however, the precise role of KISS1 expression in non-small cell lung cancer (NSCLC) is not well defined. KISS1 receptor (KISS1R, also named GPR54) coupled to KISS1, has been shown to
play a pivotal role in suppressing cancer metastasis. In this study, 56 NSCLC specimens were divided into stage IIIB (locally advanced) and stage IV (metastatic). The mRNA and protein levels of KISS1 and KISS1R in cancer tissues were found to be lower compared to that in normal tissues using RT-PCR and western blot analysis, respectively. In addition, the expression of both KISS1 and KISS1R in stage IV NSCLC was lower compared to that in stage IIIB stage NSCLC. The cumulative survival rate of the patients with KISS1 or KISS1R expression was significantly higher compared to that without expression. KISS1 or KISS1R expression in NSCLC can be used to indicate favorable prognosis for disease outcome. Metastin, the product of the KISS1 gene, was lower in the serum of patients with stage IV NSCLC compared to that in stage IIIB NSCLC.

[79]
TÍTULO / TITLE: Quantitative X-ray Computed Tomography Peritoneography in Malignant Peritoneal Mesothelioma Patients Receiving Intraperitoneal Chemotherapy.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1245/s10434-013-2976-8
AUTORES / AUTHORS: Leinwand JC; Zhao B; Guo X; Krishnamoorthy S; Qi J; Graziano JH; Slavkovic VN; Bates GE; Lewin SN; Allendorf JD; Chabot JA; Schwartz LH; Taub RN
INSTITUCION / INSTITUTION: Division of Medical Oncology, Department of Medicine, Columbia University Medical Center, New York, NY, USA.
RESUMEN / SUMMARY: BACKGROUND: Intraperitoneal chemotherapy is used to treat peritoneal surface-spreading malignancies. We sought to determine whether volume and surface area of the intraperitoneal chemotherapy compartments are associated with overall survival and posttreatment glomerular filtration rate (GFR) in malignant peritoneal mesothelioma (MPM) patients. METHODS: Thirty-eight MPM patients underwent X-ray computed tomography peritoneograms during outpatient intraperitoneal chemotherapy. We calculated volume and surface area of contrast-filled compartments by semiautomated computer algorithm. We tested whether these were associated with overall survival and posttreatment GFR. RESULTS: Decreased likelihood of mortality was associated with larger surface areas (p = 0.0201) and smaller contrast-filled compartment volumes (p = 0.0341), controlling for age, sex, histologic subtype, and presence of residual disease >0.5 cm postoperatively. Larger volumes were associated with higher posttreatment GFR, controlling for pretreatment GFR, body surface area, surface area, and the interaction between body surface area and volume (p = 0.0167). DISCUSSION: Computed
tomography peritoneography is an appropriate modality to assess for maldistribution of intraperitoneal chemotherapy. In addition to identifying catheter failure and frank loculation, quantitative analysis of the contrast-filled compartment’s surface area and volume may predict overall survival and cisplatin-induced nephrotoxicity. Prospective studies should be undertaken to confirm and extend these findings to other diseases, including advanced ovarian carcinoma.

[80]
TÍTULO / TITLE: - Tumor cavitation among lung cancer patients receiving first-line chemotherapy at a tertiary care centre in India: association with histology and overall survival.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Singh N; Mootha VK; Madan K; Aggarwal AN; Behera D
INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Sector-12, Chandigarh, 160012, India, navneetchd@yahoo.com.
RESUMEN / SUMMARY: - Clinical significance of tumor cavitation (TC) prior to and following first-line chemotherapy of lung cancer is unclear. An evaluation of the incidence and prognostic role of TC among treatment naive lung cancer patients undergoing chemotherapy at a tertiary care institute in North India was undertaken. Retrospective data analysis and radiological review of newly diagnosed lung cancer patients initiated on chemotherapy over a 2-year period were carried out. Demographic characteristics and overall survival (OS) were compared between patients with and without TC at baseline. Patients who received 3 or more cycles of chemotherapy were included in analysis for response rates and new onset TC. Overall, 27 (7.8 %) of 347 patients had baseline TC. Among 271 non-small cell lung cancer (NSCLC) patients with (n = 26) and without (n = 245) baseline TC, histology was the only demographic characteristic that differed significantly [squamous 76.9 vs. 46.9 %; p = 0.004]. Majority (82.7 %) of NSCLC patients had advanced (stage IIIIB/IV) disease. NSCLC patients with and without baseline TC alive at 6 months, 1 and 2 years were 34.6 versus 53.9 %, 11.5 versus 25.7 % and 3.8 versus 7.8 %, respectively. NSCLC patients with baseline TC had shorter median OS than those without (174 days [95 % confidence interval (CI) 106-242 days] vs. 235 days [95 % CI 207-263 days]). On multivariate Cox proportional hazard analysis, age [hazard ratio (HR) = 1.02, 95 % CI 1.01-1.04] and baseline TC [HR = 1.66, 95 % CI 1.03-2.69] were found significant. Response rates were
similar between the two groups. Patients with TC after chemotherapy differed from those without in frequency of squamous histology (77.8 vs. 38.9 %; p < 0.001) and presence of metastatic disease (19.4 vs. 40.9 %; p = 0.016). Squamous histology has a significant association with presence of baseline TC and of new onset TC after chemotherapy. Presence of baseline TC has an independent association with shorter OS among NSCLC patients undergoing first-line chemotherapy.

[81]
TÍTULO / TITLE: - Effective method for the isolation and proliferation of primary lung cancer cells from patient lung tissues.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Seo J; Park SJ; Kim J; Choi SJ; Moon SH; Chung HM
INSTITUCIÓN / INSTITUTION: - Stem Cell Research Laboratory, CHA Stem Cell Institute, CHA University, 605-21, Yoeksam 1-dong, Gangnam-gu, Seoul, 135-907, South Korea.
RESUMEN / SUMMARY: - We have developed a technique for isolating and culturing primary lung cancer cells extracted from patient tissue to facilitate anti-cancer drug development. Patient-derived lung cancer tissues were mechanically dissociated to 40-100 mum. Dispase was then used to isolate cultured lung cancer cell populations, which were re-plated on Matrigel-coated dishes containing N2-supplemented medium and growth factors. This method allows pure populations of primary non-small cell lung cancer cells to be grown in vitro. The isolated cells exhibited hallmark cancerous properties such as abnormal chromosomes and in vivo tumor formation. The cell lines generated through this procedure may help to advance our knowledge of certain forms of lung cancer and may also be useful for developing patient-specific anti-cancer drug screening procedures.

[82]
TÍTULO / TITLE: - Employment Status and Work-Related Difficulties in Lung Cancer Survivors Compared With the General Population.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Kim YA; Yun YH; Chang YJ; Lee J; Kim MS; Lee HS; Zo JI; Kim J; Choi YS; Shim YM; Yoon SJ
RESUMEN / SUMMARY: - OBJECTIVE:: To investigate the employment status of lung cancer survivors and the work-related problems they face.
BACKGROUND:: Although the number of lung cancer survivors is increasing, little is known about their employment and work-related issues. METHODS:: We enrolled 830 lung cancer survivors 12 months after lung cancer curative surgery (median time after diagnosis, 4.11 years) and 1000 volunteers from the general population. All participants completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30-item and a questionnaire that included items relating to their jobs. We used logistic regression analysis to identify independent predictors of unemployment.
RESULTS:: The employment rate of lung cancer survivors decreased from 68.6% at the time of diagnosis to 38.8% after treatment, which was significantly lower than the employment rate of the general population (63.5%; adjusted odds ratio = 2.31, 95% confidence interval: 1.66-3.22). The posttreatment unemployment rate was higher for women than for men. Among survivors, employment was inversely associated with older age, household income, number of comorbidities, and poor social functioning. Fatigue (78.6%) was the most common work-related problem reported by survivors. CONCLUSIONS:: Lung cancer survivors experienced more difficulties in employment than did the general population. Age, monthly household income, number of comorbidities, and social functioning appear to be important factors influencing employment status. These findings suggest that lung cancer survivors need support to cope with the financial impact of cancer.

[83]
TÍTULO / TITLE: - First Experience of 18F-Alfatide in Lung Cancer Patients Using a New Lyophilized Kit for Rapid Radiofluorination.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wan W; Guo N; Pan D; Yu C; Weng Y; Luo S; Ding H; Xu Y; Wang L; Lang L; Xie Q; Yang M; Chen X
18F-FPPRGD2, which was approved for clinical study recently, has favorable properties for integrin targeting and showed potential for antiangiogenic therapy and early response monitoring. However, the time-consuming multiple-step synthesis may limit its widespread applications in the clinic. In this study, we developed a simple lyophilized kit for labeling PRGD2 peptide (18F-AlF-NOTA-PRGD2, denoted as 18F-alfatide) using a fluoride-aluminum complex that significantly simplified the labeling procedure.

METHODS: Nine patients with a primary diagnosis of lung cancer were examined by both static and dynamic PET imaging with 18F-alfatide, and 1 tuberculosis patient was investigated using both 18F-alfatide and 18F-FDG imaging. Standardized uptake values were measured in tumors and other main organs at 30 min and 1 h after injection. Kinetic parameters were calculated by Logan graphical analysis. Immunohistochemistry and staining intensity quantification were performed to confirm the expression of integrin alphavbeta3.

RESULTS: Under the optimal conditions, the whole radiosynthesis including purification was accomplished within 20 min with a decay-corrected yield of 42.1% +/- 2.0% and radiochemical purity of more than 95%. 18F-alfatide PET imaging identified all tumors, with mean standardized uptake values of 2.90 +/- 0.10. Tumor-to-muscle and tumor-to-blood ratios were 5.87 +/- 2.02 and 2.71 +/- 0.92, respectively. CONCLUSION: 18F-alfatide can be produced with excellent radiochemical yield and purity via a simple, 1-step, lyophilized kit. PET scanning with 18F-alfatide allows specific imaging of alphavbeta3 expression with good contrast in lung cancer patients. This technique might be used for the assessment of angiogenesis and for planning and response evaluation of cancer therapies that would affect angiogenesis status and integrin expression levels.
INTRODUCTION: We evaluated treatment patterns of elderly patients with stage IIIA (N2) non-small-cell lung cancer (NSCLC).

METHODS: The use of surgery, chemotherapy, and radiation for patients with stage IIIA (T1-T3N2M0) NSCLC in the Surveillance, Epidemiology, and End Results-Medicare database from 2004 to 2007 was analyzed. Treatment variability was assessed using a multivariable logistic regression model that included treatment, patient, tumor, and census track variables. Overall survival was analyzed using the Kaplan-Meier approach and Cox proportional hazard models.

RESULTS: The most common treatments for 2958 patients with stage IIIA (N2) NSCLC were radiation with chemotherapy (n = 1065, 36%), no treatment (n = 534, 18%), and radiation alone (n = 383, 13%). Surgery was performed in 709 patients (24%): 235 patients (8%) had surgery alone, 40 patients (1%) had surgery with radiation, 222 patients had surgery with chemotherapy (8%), and 212 patients (7%) had surgery, chemotherapy, and radiation. Younger age (p < 0.0001), lower T-status (p < 0.0001), female sex (p = 0.04), and living in a census track with a higher median income (p = 0.03) predicted surgery use. Older age (p < 0.0001) was the only factor that predicted that patients did not get any therapy. The 3-year overall survival was 21.8 +/- 1.5% for all patients, 42.1 +/- 3.8% for patients that had surgery, and 15.4 +/- 1.5% for patients that did not have surgery. Increasing age, higher T-stage and Charlson Comorbidity Index, and not having surgery, radiation, or chemotherapy were all risk factors for worse survival (all p values < 0.001).

CONCLUSIONS: Treatment of elderly patients with stage IIIA (N2) NSCLC is highly variable and varies not only with specific patient and tumor characteristics but also with regional income level.
RESUMEN / SUMMARY: - Genome analyses of endothelial cells identified genes specifically expressed by tumor endothelial cells, called tumor endothelial markers (TEMs). Currently there are no data available concerning the role of TEMs in non-small cell lung cancer (NSCLC). Therefore, the aim of this study was to investigate the role of TEMs in NSCLC in vitro and in vivo. First we evaluated the expression of various TEMs (Robo4, Clec14 and ECSCR) by qRT-PCR and Western blot analyses in three NSCLC cell lines (A549, Calu1, Colo699) and compared them to human umbilical vein endothelial cells (HUVECs), endothelial colony forming cells (ECFCs) and human bronchial epithelial cells (HBEpCs). Next the expression of TEMs was measured in resected tumor tissue of NSCLC patients (n=63) by qRT-PCR and compared to adjacent non-cancerous lung tissue (n=52). Further, immunohistochemical analysis of Robo4 expression in tumor tissue (n=33) and adjacent non-cancerous tissue (n=27) was performed. We found that NSCLC cell lines and HBEpC did not express TEMs on the mRNA level compared to HUVECs (p=0.001). In the contrary, a significant up-regulation of Robo4 and Clec14 was found in tumor samples (Robo4 p=0.03, Clec14 p=0.002). Both facts clearly indicate that these proteins are allocated to the tumor stromal department. Correlation with clinical data showed that increased TEM expression correlated with prolonged overall survival of operated NSCLC patients (Robo4 high 120.5 vs. Robo4 low 47.6 months, Clec14 high 108.1 vs. Clec14 low 54.5 months and ECSCR high 120.5 vs. ECSCR low 42.2 months). In summary, we found that TEMs are overexpressed in NSCLC stromal tissue and that an increased TEM expression correlated with an increased overall survival in early stage NSCLC.

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TÍTULO / TITLE: - Diagnosis of recurrence and assessment of post-recurrence survival in patients with extracranial non-small cell lung cancer evaluated by 18F-FDG PET/CT.

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


AUTORES / AUTHORS: - Jimenez-Bonilla JF; Quirce R; Martinez-Rodriguez I; Banzo I; Rubio-Vassallo AS; Del Castillo-Matos R; Ortega-Nava F; Martinez-Amador N; Ibanez-Bravo S; Carril JM

INSTITUCIÓN / INSTITUTION: - Nuclear Medicine Department, University Hospital “Marques de Valdecilla”, University of Cantabria, Santander, España. Electronic address: jjimenez@humv.es.

RESUMEN / SUMMARY: - The accurate diagnosis of recurrence of non small cell lung cancer (NSCLC) is crucial for the appropriate management of patients with
suspicion of recurrence (SOR). We evaluated prospectively in the clinical setting the contribution of FDG PET/CT in patients with SOR of NSCLC in terms of sensitivity, specificity, impact on therapy and on survival. METHODS: Of the 55 patients included in the study, recurrence was confirmed in 37 but, follow up data for survival evaluation was available in 34. There were 59 SOR in the 55 patients and in 41 recurrence was confirmed. 53 of the 59 suspicions, had a contrast enhanced CT. All patients had a FDG PET/CT scan after IV injection of 8MBq/kg of F18-FDG. RESULTS: Of the 59 SOR, FDG PET/CT was positive in all 41 in which recurrence was confirmed (100% sensitivity) and, it was negative in 15 of the 18 in which it was ruled out (specificity 83%). In 27 SOR with inconclusive CT, FDG PET/CT showed 100% sensitivity (18/18) and 78% specificity (7/9). FDG PET/CT had an impact on treatment in 42 of the 59 SOR. In all 34 patients, FDG PET/CT diagnosed recurrence and overall survival at 20 months and 5 years was 44% and 11%, respectively. When the extent of recurrence assessed by FDG PET/CT was considered, survival at 20 months and at 5 years of patients with loco-regional recurrence was 77% and 28% and in patients with distant recurrence 14% and 0% (p<0.001). CONCLUSION: Despite the small number of patients, our study demonstrates that FDG PET/CT is highly accurate for the detection of NSCLC recurrence. Therefore it has a great impact on the therapy regimen and on survival depending on the extent of the recurrent disease, survival being better for patients with local recurrence. By differentiating local from distant recurrence, it allows the selection of patients who, could potentially benefit from new therapies. The results also suggest that there are grounds to include FDG PET/CT in the guidelines for surveillance for NSCLC.

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[87]
TÍTULO / TITLE: - 5'-Triphosphate-siRNA Against Survivin Gene Induces Interferon Production and Inhibits Proliferation of Lung Cancer Cells In Vitro.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago)
1097/CJI.0b013e318294183b
AUTORES / AUTHORS: - Wang K; Chen X; Yan F; Xing Y; Yang X; Tu J; Chen Z
INSTITUCIÓN / INSTITUTION: - *Department of Biochemistry and Molecular Biology, Anhui Medical University, Hefei, Anhui Province daggerDivision of Infection and Immunity, Department of Electromagnetic and Laser Biology, Beijing Institute of Radiation Medicine, Beijing, China double daggerAustralian School of Advanced Medicine, Macquarie University, Sydney, NSW, Australia.
RESUMEN / SUMMARY: - Survivin is a new member of the inhibitors of apoptosis family and upregulated in various human malignancies including human lung
cancer. In this study, we proposed a new strategy for RNA interference (RNAi)-mediated anticancer therapy combining activation of interferon production with RNAi using 5'-triphosphate-siRNA (3p-siRNA) against survivin gene. We designed and generated 3p-siRNA targeting human survivin gene (3p-survivin-siRNA). The findings reported here demonstrated that 3p-survivin-siRNA induced a 3p-dependent type-I interferon response when transfected into human lung cancer cells. The 3p-survivin-siRNA significantly inhibited lung cancer cell proliferation in a 3p-dependent manner. The anticancer effect of 3p-survivin-siRNA was superior to that of conventional siRNA. The expression level of survivin in 3p-survivin-siRNA-treated A549 cells was significantly lower than that of siRNA. Furthermore, when 3p-survivin-siRNA silencing approach was combined with radiation treatment, 3p-survivin-siRNA increases the cytotoxicity of A549 cells and induces more cells to undergo apoptosis. In conclusion, our results suggest that 3p-survivin-siRNA could act as a powerful bifunctional molecule with potential for developing promising radiosensitization therapeutics against human lung cancer.

[88]  
TÍTULO / TITLE: Visceral pleural invasion is not predictive of survival in patients with lung cancer and smaller tumor size.  
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary  
●●Enlace al texto completo (gratuito o de pago)  
1016/j.athoracsur.2013.03.085  
AUTORES / AUTHORS: David E; Thall PF; Kalhor N; Hofstetter WL; Rice DC; Roth JA; Swisher SG; Walsh GL; Vaportyan AA; Wei C; Mehran RJ  
INSTITUCIÓN / INSTITUTION: Department of Thoracic and Cardiovascular Surgery, University of Texas, MD Anderson Cancer Center, Houston, Texas.  
RESUMEN / SUMMARY: BACKGROUND: Visceral pleural invasion (VPI) is used as an indicator of adverse prognosis in non-small cell lung cancer (NSCLC). The purpose of this retrospective study was to evaluate the impact of VPI on disease-free survival (DFS) and overall survival (OS) in patients with node-negative NSCLC. METHODS: Between 1998 and 2009, 1,166 patients with pathologic N0M0 NSCLC underwent surgical resection by lobectomy. Two hundred fourteen patients with VPI were compared with 952 patients without VPI. RESULTS: Median follow-up was 59 months. In multivariate analysis, VPI, larger tumor size, older age, female sex, and poor performance status were significantly associated with decreased OS. In contrast, larger tumor size, female sex, and poor performance, but notably not VPI, were associated with decreased DFS. After examining interactive effects of VPI and T stage subgroups, we found that VPI did not significantly affect either OS or DFS in
the subgroups of patients with smaller tumor sizes-stage T1a, stage T1b, or stage T2a. In contrast, a deleterious effect of VPI on DFS was seen for tumors larger than 5 cm-stages T2b and T3-with the VPI-stage T3 interaction effect being statistically significant for DFS but not for OS. CONCLUSIONS: The effect of VPI on survival in NSCLC varies greatly with tumor size, with VPI not strongly associated with OS or DFS in tumors smaller than 5 cm, but showing large negative effects on DFS for stage T2b and stage T3 tumors. Using VPI to upstage T1 tumors to a higher T stage is not warranted because it would misrepresent these VPI-T stage subgroup effects.

[89]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dhakal B; Eastwood D; Sukumaran S; Hassler G; Tisol W; Gasparri M; Choong N; Santana-Davila R
INSTITUCIÓN / INSTITUTION: - Divisions of General Internal Medicine, Medical College of Wisconsin, Milwaukee, Wis.
RESUMEN / SUMMARY: - BACKGROUND: Obesity is a risk factor for increased perioperative morbidity and mortality in surgical patients. There have been limited studies to correlate the morbidity of lung cancer resection with obesity.
METHODS: We performed a retrospective study of patients who underwent surgical resection for lung cancer at the Medical College of Wisconsin, Milwaukee, from 2006 to 2010. Data on patient demographics, weight, pathological findings, and hospital course were abstracted after appropriate institutional review board approval. Perioperative morbidity was defined as atrial fibrillation, heart failure, respiratory failure, pulmonary embolism, or any medical complications arising within 30 days after surgery. The Fisher exact test was used to test the association between body mass index (BMI) and perioperative morbidities.
RESULTS: Between 2006 and 2010, 320 lung resections were performed for lung cancer. The median age was 67 (interquartile range, 59-75) years, and 185 (57.8%) were females. A total of 121 (37.8%) of patients had a BMI lower than 25, and 199 (62.18%) patients had a BMI of 25 or higher. The 30-day mortality rate was 1.8% (n = 6) in the whole group; only 2 of these patients had a BMI of 25 or higher. Perioperative morbidity occurred in 28 (23.14%) of patients with a normal BMI and in 47 (23.61%) of patients with a BMI of 25 or higher (P = .54). Specific morbidities encountered by patients with normal versus BMI of 25 or higher were as follows: atrial fibrillation, 11 (9.09%) versus 24 (12.06%) (P = .46); pulmonary embolism, 1 (0.83%) versus 3 (1.51%) (P = 1.0); congestive heart failure, 2 (1.65%) versus 2 (1.01%) (P = .63); renal
failure, 4 (3.3%) versus 2 (1.0%) (P = .29); respiratory failure, 12 (9.92%) versus 17 (8.54%) (P = .69); and acute respiratory distress syndrome, 2 (1.65%) versus 1 (0.50%) (P = .55). The median hospital stay was 5 days in the lower BMI group and 4 days in the BMI of 25 or higher group (P = .52).

CONCLUSIONS: Overweight and normal weight patients do not differ significantly in rates of perioperative morbidities, 30-day mortality, and length of stay. Our study indicates that potential curative surgical resections can be offered to even significantly overweight patients.

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TÍTULO / TITLE: - A Novel Targeting Therapy of Malignant Mesothelioma Using Anti-Podoplanin Antibody.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Abe S; Morita Y; Kaneko MK; Hanibuchi M; Tsujimoto Y; Goto H; Kakiuchi S; Aono Y; Huang J; Sato S; Kishuku M; Taniguchi Y; Azuma M; Kawazoe K; Sekido Y; Yano S; Akiyama SI; Sone S; Minakuchi K; Kato Y; Nishioka Y
INSTITUCIÓN / INSTITUTION: - Central Office for Clinical Pharmacy Training, Institute of Health Biosciences, University of Tokushima Graduate School, Tokushima 770-8503, Japan;
RESUMEN / SUMMARY: - Podoplanin (Aggrus), which is a type I transmembrane sialomucin-like glycoprotein, is highly expressed in malignant pleural mesothelioma (MPM). We previously reported the generation of a rat anti-human podoplanin Ab, NZ-1, which inhibited podoplanin-induced platelet aggregation and hematogenous metastasis. In this study, we examined the antitumor effector functions of NZ-1 and NZ-8, a novel rat-human chimeric Ab generated from NZ-1 including Ab-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity against MPM in vitro and in vivo. Immunostaining with NZ-1 showed the expression of podoplanin in 73% (11 out of 15) of MPM cell lines and 92% (33 out of 36) of malignant mesothelioma tissues. NZ-1 could induce potent ADCC against podoplanin-positive MPM cells mediated by rat NK (CD161a+) cells, but not murine splenocytes or human mononuclear cells. Treatment with NZ-1 significantly reduced the growth of s.c. established tumors of MPM cells (ACC-MESO-4 or podoplanin-transfected MSTO-211H) in SCID mice, only when NZ-1 was administered with rat NK cells. In in vivo imaging, NZ-1 efficiently accumulated to xenograft of MPM, and its accumulation continued for 3 wk after systemic administration. Furthermore, NZ-8 preferentially recognized podoplanin expressing in MPM, but not in normal tissues. NZ-8 could induce higher ADCC mediated by human NK cells and complement-dependent cytotoxicity as compared with NZ-1. Treatment with NZ-
8 and human NK cells significantly inhibited the growth of MPM cells in vivo. These results strongly suggest that targeting therapy to podoplanin with therapeutic Abs (i.e., NZ-8) derived from NZ-1 might be useful as a novel immunotherapy against MPM.

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[91]
TÍTULO / TITLE: DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Cao J; Song Y; Bi N; Shen J; Liu W; Fan J; Sun G; Tong T; He J; Shi Y; Zhang X; Lu N; He Y; Zhang H; Ma K; Luo X; Lv L; Deng H; Cheng J; Zhu J; Wang L; Zhan Q
INSTITUCION / INSTITUTION: Authors’ Affiliations: State Key Laboratory of Molecular Oncology; Departments of Radiation Oncology, Thoracic Surgery, Medical Oncology, and Pathology, Cancer Hospital and Cancer Institute, Chinese Academy of Medical Sciences & Peking Union Medical College; National Engineering Research Center for Biochip Technology, Beijing; Shanghai Cancer Institute, Shanghai; and Cancer Epigenetic Laboratory, Anhui Cancer Hospital, Hefei, China.
RESUMEN / SUMMARY: Small cell lung cancer (SCLC) is one of the most aggressive types of cancer, yet the pathologic mechanisms underlying its devastating clinical outcome remain elusive. In this report, we surveyed 924 miRNA (miR) for their expressions in the formalin-fixed paraffin-embedded specimens from 42 patients with SCLC, and found that the downregulated miR-886-3p is closely correlated with the shorter survival of SCLC. This correlation was validated with another 40 cases. It was further discovered that loss of miR-886-3p expression was mediated by DNA hypermethylation of its promoter in both cultured SCLC cells and tumor samples. Moreover, miR-886-3p potently repressed cell proliferation, migration, and invasion of NCI-H446 cell in cell culture via suppression of the expression of its target genes: PLK1 and TGF-beta1 at posttranscription levels. Forced upregulation of miR-886-3p greatly inhibited in vivo tumor growth, bone/muscle invasion, and lung metastasis of NCI-H446 cells. This newly identified miR-886-3p-PLK1/TGF-beta1 nexus that modulates SCLC aggression suggests that both loss of miR-886-3p expression and hypermethylation of the miR-886 promoter are the promising indicators for poor outcome of as well as new therapeutic targets for SCLC. Cancer Res; 73(11); 3326-35. ©2013 AACR.
A microRNA-135ª/b binding polymorphism in CD133 confers decreased risk and favorable prognosis of lung cancer in Chinese by reducing CD133 expression.

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

AUTORES / AUTHORS: - Cheng M; Yang L; Yang R; Yang X; Deng J; Yu B; Huang D; Zhang S; Wang H; Qiu F; Zhou Y; Lu J
INSTITUCIÓN / INSTITUTION: - The Institute for Chemical Carcinogenesis, The State Key Lab of Respiratory Disease, Guangzhou Medical University, 195 Dongfengxi Road, Guangzhou 510182, China.

RESUMEN / SUMMARY: - CD133 is a pivotal marker of cancer stem cells (CSCs) that is involved in tumorigenesis and cancer progression. Recent studies have identified CD133 to be a prognostic factor for cancer rested with its expression and genetic variants. Here, we hypothesized that the single nuclear polymorphisms (SNP) in CD133 may be associated with lung cancer risk and prognosis. Based on three independent case-control analyses with a total of 2,332 lung cancer cases and 2,457 controls, the gene-based association analysis with 13 polymorphisms of CD133 suggested that CD133 is a susceptible gene for lung cancer (P = 0.043) and that the SNP rs2240688A>C in the 3′-untranslated region of CD133 is the most significant associated SNP with the risk of lung cancer (P = 0.020); further analysis showed that the rs2240688C variant genotypes (CA+CC) harbored a decreased risk of lung cancer (OR = 0.80; 95%CI= 0.72-0.90) and conferred a favorable survival for lung cancer patients (median survival time, MST: 15 months) when compared to AA genotype (MST: 11 months, log-rank test: P = 3.31x10^-6; Cox model: HR = 0.81, 95%CI = 0.70-0.94). Functional assays revealed that the rs2240688A to C transition gained a new binding of the microRNA hsa-miR-135/b and decreased the CD133 expression. Our data suggest that the functional polymorphism rs2240688A>C in CD133 is associated with lung cancer risk and survival. This SNP may be a functional biomarker to predict risk and prognosis of lung cancer.

[94]

TÍTULO / TITLE: - Phase-I study of sagopilone in combination with cisplatin in chemotherapy-naive patients with metastasised small-cell lung cancer.

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


AUTORES / AUTHORS: - Gauler TC; Christoph DC; Fischer J; Frickhofen N; Huber R; Gonschorek C; Roth K; Giurescu M; Eberhardt WE

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, West German Cancer Center, University Hospital Essen of the University Duisburg-Essen, Essen, Germany. Electronic address: thomas.gauler@uk-essen.de.

RESUMEN / SUMMARY: - BACKGROUND: Sagopilone (ZK219477) is a new and fully synthetic epothilone with activity against multi-drug resistant tumour cell lines. It has demonstrated clinical activity in several solid tumours like ovarian cancer and melanoma. Data about clinical efficacy of sagopilone in small-cell lung cancer are lacking. Here we report the first phase-I trial of sagopilone in
combination with cisplatin in previously untreated metastatic small-cell lung cancer patients. METHODS: Chemonaive patients with metastatic small-cell lung cancer (SCLC) received sagopilone in four different dosing schedules ranging from 12 to 22mg/m2 (on day 1 as 3-h infusion) followed by a fixed dose of cisplatin of 75mg/m2 as 1-h infusion on day 1. Chemotherapy was administered every 3weeks to a maximum of six cycles. The primary objective was determination of dose-limiting toxicities (DLTs) and the maximum-tolerated dose (MTD) in this setting. Secondary objectives were assessment of objective response rates (ORR) as well as investigation of sagopilone pharmacokinetics. RESULTS: Twenty-six patients received a total of 107 treatment cycles of the platinum-sagopilone doublet. The recommended phase-II dose (RD) and schedule was found to be 19mg/m2 sagopilone followed by 75mg/m2 cisplatin. Peripheral neuropathy turned out as dose-limiting toxicity when the combination was administered over a median of four cycles. Objective responses were observed in six out of seven SCLC patients (85.7%) treated with the RD. CONCLUSIONS: Sagopilone and cisplatin can be safely combined in the first-line treatment of metastasised SCLC. This combination demonstrated preliminary efficacy and should be further evaluated within phase-II trials.

[95]

TÍTULO / TITLE: - Detection of epidermal growth factor receptor mutations in formalin fixed paraffin embedded biopsies in Malaysian non-small cell lung cancer patients.

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


AUTORES / AUTHORS: - Shi Yeen TN; Pathmanathan R; Shiran MS; Ahmad Zaid FA; Cheah YK

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia. ykcheah@medic.upm.edu.my.

RESUMEN / SUMMARY: - BACKGROUND: Somatic mutations of the epidermal growth factor receptor (EGFR) are reportedly associated with various responses in non-small cell lung cancer (NSCLC) patients receiving the anti-EGFR agents. Detection of the mutation therefore plays an important role in therapeutic decision making. The aim of this study was to detect EGFR mutations in formalin fixed paraffin embedded (FFPE) samples using both Scorpion ARMS and high resolution melt (HRM) assay, and to compare the sensitivity of these methods. RESULTS: All of the mutations were found in adenocarcinoma, except one that was in squamous cell carcinoma. The mutation rate was 45.7% (221/484). Complex mutations were also observed,
wherein 8 tumours carried 2 mutations and 1 tumour carried 3 mutations.

CONCLUSIONS: Both methods detected EGFR mutations in FFPE samples. HRM assays gave more EGFR positive results compared to Scorpion ARMS.

[96]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pacurari M; Addison JB; Bondalapati N; Wan YW; Luo D; Qian Y; Castranova V; Ivanov AV; Guo NL
INSTITUCIÓN / INSTITUTION: - Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV 26505, USA.
RESUMEN / SUMMARY: - Lung cancer remains the leading cause of cancer-related mortality for both men and women. Tumor recurrence and metastasis is the major cause of lung cancer treatment failure and death. The microRNA200 (miR-200) family is a powerful regulator of the epithelial-mesenchymal transition (EMT) process, which is essential in tumor metastasis. Nevertheless, miR-200 family target genes that promote metastasis in non-small cell lung cancer (NSCLC) remain largely unknown. Here, we sought to investigate whether the microRNA-200 family regulates our previously identified NSCLC prognostic marker genes associated with metastasis, as potential molecular targets. Novel miRNA targets were predicted using bioinformatics tools based on correlation analyses of miRNA and mRNA expression in 57 squamous cell lung cancer tumor samples. The predicted target genes were validated with quantitative RT-PCR assays and western blot analysis following re-expression of miR-200a, -200b and -200c in the metastatic NSCLC H1299 cell line. The results show that restoring miR-200a or miR-200c in H1299 cells induces downregulation of DLC1, ATRX and HFE. Reinforced miR-200b expression results in downregulation of DLC1, HNRNPA3 and HFE. Additionally, miR-200 family downregulates HNRNPR3, HFE and ATRX in BEAS-2B immortalized lung epithelial cells in quantitative RT-PCR and western blot assays. The miR-200 family and these potential targets are functionally involved in canonical pathways of immune response, molecular mechanisms of cancer, metastasis signaling, cell-cell communication, proliferation and DNA repair in Ingenuity pathway analysis (IPA). These results indicate that re-expression of miR-200 downregulates our previously identified NSCLC prognostic biomarkers in metastatic NSCLC cells. These results provide new insights into miR-200 regulation in lung cancer metastasis and consequent clinical outcome, and may provide a potential basis for innovative therapeutic approaches for the treatment of this deadly disease.
INTRODUCTION:: After early reports of vandetanib’s efficacy in the induction setting, we evaluated the effect of combination docetaxel, carboplatin, and vandetanib, followed by maintenance therapy with either vandetanib, or placebo on progression-free survival (PFS) in patients with advanced non-small-cell lung cancer. METHODS:: Patients with advanced non-small-cell lung cancer were randomized to induction docetaxel (75 mg/m²) + carboplatin (area under the curve of 6) on day 1 of a 21-day cycle, and daily vandetanib (100 mg/day orally) for four cycles, followed by daily vandetanib (300 mg/day orally) or placebo until progression. Eligible patients had measurable disease, Eastern Cooperative Oncology Group performance status 0 of 1, and no prior cytotoxic or targeted agents for advanced disease. RESULTS:: One hundred sixty-two patients were randomized; 158 began induction treatment. Fifty-eight patients began maintenance vandetanib or placebo (median, 3.5 cycles). Median PFS for patients randomized to maintenance vandetanib was 4.5 months (95% confidence interval, 3.3-5.8 months), and for patients randomized to maintenance placebo was 4.2 months (95% confidence interval, 2.8-4.9 months). An exploratory analysis showed prolonged PFS for patients randomized to vandetanib maintenance (stratified log-rank p = 0.07) as also in a multivariate model adjusting for sex and stage (p = 0.02). Differences in PFS were not observed among patients who began
maintenance therapy. Toxicities were similar to other studies of these agents.

CONCLUSION:: Neither arm showed improvement over historical median PFS of 4.6 months, although patients who began maintenance and were randomized to vandetanib had somewhat better outcomes than those randomized to placebo. Given its acceptable toxicity profile, there may be a role for vandetanib in maintenance.

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

AUTORES / AUTHORS: - Du G; Yang Y; Zhang Y; Sun T; Liu W; Wang Y; Li J; Zhang H
INSTITUCIÓN / INSTITUTION: - Institute of Pharmacy, Pharmacy College of Henan University, Jinming street, Kaifeng, 475004, Henan, China, kfdgj@sohu.com.

[99] TÍTULO / TITLE: - Relationships between pulmonary microRNA and proteome profiles, systemic cytogenetic damage, and lung tumors in cigarette smoke-exposed mice treated with chemopreventive agents.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Izzotti A; Balansky R; D’Agostini F; Longobardi M; Cartiglia C; La Maestra S; Micale RT; Camoirano A; Ganchev G; Iltcheva M; Steele VE; De Flora S
INSTITUCIÓN / INSTITUTION: - Department of Health Sciences, University of Genoa, via A. Pastore 1, 16132 Genoa, Italy.
RESUMEN / SUMMARY: - Assessing the correlation between molecular end-points and cancer induction or prevention aims at validating the use of intermediate biomarkers. We previously developed murine models that are suitable to detect both the carcinogenicity of mainstream cigarette smoke (MCS) and the induction of molecular alterations. In the present study, we used 931 Swiss mice in two parallel experiments and in a preliminary toxicity study. The chemopreventive agents included vorinostat, myo-inositol, bexarotene, pioglitazone, and a combination of bexarotene and pioglitazone. Pulmonary microRNAs and proteins were evaluated by microarray analyses at 10 weeks of
age in male and female mice, either unexposed or exposed to MCS since birth, and either untreated or receiving each one of the 5 chemopreventive regimens with the diet after weaning. At 4 months of age, the frequency of micronucleated normochromatic erythrocytes was evaluated. At 7 months, the lungs were subjected to standard histopathological analysis. The results showed that exposure to MCS significantly downregulated the expression of 79/694 lung microRNAs (11.4%) and upregulated 66/1164 proteins (5.7%). Administration of chemopreventive agents modulated the baseline microRNA and proteome profiles and reversed several MCS-induced alterations, with some intergender differences. The stronger protective effects were produced by the combination of bexarotene and pioglitazone, which also inhibited the MCS-induced clastogenic damage and the yield of malignant tumors. Pioglitazone alone increased the yield of lung adenomas. Thus, microRNAs, proteins, cytogenetic damage, and lung tumors were closely related. The molecular biomarkers contributed to evaluate both protective and adverse effects of chemopreventive agents and highlighted the mechanisms involved.

[100]
TÍTULO / TITLE: Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Takeda M; Okamoto I; Nakagawa K
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Kinki University Faculty of Medicine, Ohno-higashi, Osaka-Sayama, Osaka, Japan.
RESUMEN / SUMMARY: - INTRODUCTION: Although crizotinib manifests marked antitumor activity in individuals with non-small-cell lung cancer positive for ALK abnormalities, all treated patients ultimately develop resistance to this drug. The central nervous system (CNS) is a frequent site of disease progression in such patients, with palliative radiotherapy usually being administered for the CNS metastasis. However, subsequent chemotherapy has not been optimized in these patients. METHODS: We retrospectively evaluated the continuation of crizotinib treatment after radiotherapy for isolated CNS progression in ALK-rearrangement-positive non-small-cell lung cancer patients. RESULTS: Among 21 ALK-rearrangement-positive patients treated with crizotinib, seven individuals resumed daily crizotinib administration after the completion of radiotherapy for isolated CNS failure. All these patients continued to receive crizotinib for at least 4 months after radiotherapy without disease progression.
One patient experienced a recurrent isolated CNS failure during the second period of crizotinib administration but subsequently resumed crizotinib treatment again for at least 8.5 months after another application of radiotherapy.

CONCLUSIONS: Development of isolated CNS metastasis is emerging as a clinical concern for patients treated with crizotinib. Our data suggest that continued administration of crizotinib after radiotherapy for isolated CNS progression is a potential treatment option for such patients.

[101]

TÍTULO / TITLE: - Serum miR-19a expression correlates with worse prognosis of patients with non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Lin Q; Chen T; Lin Q; Lin G; Lin J; Chen G; Guo L
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Affiliated Hospital of Putian University, Putian, Fujian, China.

RESUMEN / SUMMARY: - OBJECTIVES: The aim of this study was to investigate the expression levels of miR-19a in non-small cell lung cancer (NSCLC) tissue and serum, and to clarify the relationships of serum miR-19a expression with clinical factors and prognosis of NSCLC patients. METHODS: Expression levels of miR-19a in 25 paired NSCLC, paracancerous tissues and serum, and sera from 103 controls and 201 NSCLC patients were respectively detected using real-time quantitative PCR. RESULTS: Compared with the paracancerous tissue, miR-19a was overexpressed in NSCLC tissue (P = 0.006), and there was a strong correlation between expression levels of miR-19a in 25 paired sera and tissues (P = 0.001). Serum miR-19a expression in NSCLC patients was significantly upregulated compared with those in healthy individuals (P = 0.001). High serum miR-19a expression was significantly correlated with TNM stage and lymph node metastasis (P = 0.004 and 0.017, respectively). Survival analysis revealed that overall survival rate of patients with high serum miR-19a expression was significantly worse than those of patients with low serum miR-19a expression (hazard ratio = 1.438, 95% confidence interval 1.007-2.052, P = 0.046). CONCLUSION: High serum miR-19a expression may be an independent poor prognostic factor for survival in NSCLC patients. J. Surg. Oncol. 2013;107:767-771. © 2013 Wiley Periodicals, Inc.
TÍTULO / TITLE: - Effects of surgery, general anesthesia, and perioperative epidural analgesia on the immune function of patients with non-small cell lung cancer.

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


AUTORES / AUTHORS: - Cata JP; Bauer M; Sokari T; Ramirez MF; Mason D; Plautz G; Kurz A

INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Electronic address: jcata@mdanderson.org.

RESUMEN / SUMMARY: - STUDY OBJECTIVE: To assess preoperative and postoperative immune function in patients undergoing surgical resection of non-small cell lung cancer during general anesthesia and postoperative epidural analgesia. DESIGN: Observational single-center study. SETTING: University-affiliated academic center. PATIENTS: 24 adult, ASA physical status 3 and 4 patients with stage 1, 2, or 3 non-small cell lung cancer. No study patient received preoperative chemotherapy or radiation. INTERVENTIONS: Patients underwent thoracotomy with general anesthesia and postoperative epidural analgesia. MEASUREMENTS: Bispectral index monitoring, sevoflurane requirements, and intraoperative transfusions were recorded. Total fentanyl consumption and pain (verbal numeric rating scale) were recorded 24 hours after surgery. Preoperative and 24-hour postoperative natural killer cell percentage and function and percentages of natural killer T cells, T helper cells (CD4+), and cytotoxic T lymphocytes (CD8+) were measured. Plasma concentrations of the TH1 cytokine interleukin-2 and interferon-gamma and the TH2 cytokines interleukin-4 were measured at same time points. RESULTS: The percentage (preoperative, 13.07 +/- 9.81% vs postoperative, 9.6 +/- 6.57%, P < 0.001) and function (preoperative, 31.61 +/- 21.96%; postoperative, 13.61 +/- 9.36%; P < 0.001) of natural killer cells was significantly decreased after surgery, but the percentage of natural killer T cells, T helper cells (CD4+), and cytotoxic T lymphocytes (CD8+) remained unchanged postoperatively; thus, the CD4/CD8 ratio remained unchanged. Postoperative plasma concentrations of the three cytokines were similar to preoperative levels; therefore, the TH1/TH2 ratio also remained unchanged. CONCLUSIONS: Innate immunity is depressed in patients with non-small cell lung cancer after surgical resection, and immunity is not preserved by the use of postoperative epidural analgesia.

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[103]
**TÍTULO / TITLE:** Clinical characteristics of 274 non-small cell lung cancer patients in China.

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


**AUTORES / AUTHORS:** Chen Y; Han S; Zheng MJ; Xue Y; Liu WC

**INSTITUCIÓN / INSTITUTION:** Department of Oncology, Xi’jing Hospital, The Fourth Military Medical University, Xi’an, PR China.

**RESUMEN / SUMMARY:** Background: The mortality from non-small cell lung cancer (NSCLC) in China is increasing, and studies about clinical characteristics of recent NSCLC are rare. The primary objective of this study was to explore clinical features in a large general hospital in Northwest China, and to determine risk factors for stage, pathology and survival, with a view to prevention and treatment of NSCLC as well as establishment and improvement of national medical insurance policies. Patients and Methods: We retrospectively analyzed the characteristics of NSCLC patients (n = 274), as well as risk factors for advanced stage and squamous cell carcinoma (SCC). Survival features in different groups were analyzed, as well as risk factors of survival. Follow-up was at least 3 years. Results: 179 were male (65.3%); 136 had adenocarcinoma (49.6%) and 109 had SCC (39.8%); 186 (67.9%) had advanced-stage disease (IIIB-IV); 130 (47.4%) had smoking habits; 195 came from an urban area (71.2%); 69 had local urban resident basic medical insurance; 58% were younger than 60 years. Female, adenocarcinoma, rural patients were significantly younger than male, SCC, and urban patients. Pathology was the only independent risk factor for advanced stage. Age, sex, and smoking status were independent prognostic factors for SCC. The proportion of male SCC was higher than female SCC even without the influence of smoking. Without local urban resident basic medical insurance, higher stage and not having surgery, but not smoking status, were independent risk factors for lower median progression-free survival (PFS). Patients with adenocarcinoma and SCC in advanced stage accepting EGFR-TKI during treatment had a higher 1-year survival rate and longer overall survival (OS) compared with those never accepting EGFR-TKI. EGFR-TKI treatment and chemotherapy regimen numbers were independent risk factor for median OS in advanced adenocarcinoma and SCC patients. Conclusion: More prevention and screening should be carried out for the female and rural population. EGFR-TKI could benefit advanced NSCLCs. China’s medical insurance policy has some adverse effect on NSCLC survival calling for further improvement.

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[104]
TÍTULO / TITLE: - Postoperative survival of lung cancer patients: are there predictors beyond TNM?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Friedel G; Fritz P; Goletz S; Kristen R; Brinkmann F; Dierkesmann R; Schwab M; Ott G; Dippon J; Alscher MD
INSTITUCIÓN / INSTITUTION: - Klinik Schillerhohe Center for Pneumology and Thoracic Surgery, Gerlingen, Germany.
RESUMEN / SUMMARY: - BACKGROUND/AIM: We report on survival data of 595 patients with stage I-III lung cancer with respect to TNM classification.
MATERIALS AND METHODS: We constructed a basic model consisting of stage and grade, and assessed the improvement of survival prediction after adding comorbidity data, spirometric data, clinical and laboratory parameters.
RESULTS: Body mass index (BMI) and presence of a cardiac disease reached statistical significance for prediction of overall survival in a Cox regression model. In addition to BMI (<25 kg/m(2)) and the presence of cardiovascular disease, the spirometric variable (FEV1) predicted early death (less than five months postoperatively). When the survival random forest method was employed to predict disease outcome, creatinine levels and VO2 max became additional variables of interest for predicting survival. CONCLUSION: We propose that our lung cancer database may help to identify variables (aside from histomorphological variables) that are suitable for identifying patients at risk of death after surgical treatment of lung cancer.

[105]
TÍTULO / TITLE: - A patient with lung adenocarcinoma and RET fusion treated with vandetanib.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gautschi O; Zander T; Keller FA; Strobel K; Hirschmann A; Aebi S; Diebold J
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Cantonal Hospital, Luzern, Switzerland. liver.gautschi@luks.ch

[106]
TÍTULO / TITLE: - Cytoglobin has bimodal: tumour suppressor and oncogene functions in lung cancer cell lines.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Cytoglobin (CYGB) is frequently downregulated in many types of human malignancies, and its exogenous overexpression reduces proliferation of cancer cells. Despite its implied tumour suppressor (TSG) functions, its exact role in carcinogenesis remains unclear as CYGB upregulation is also associated with tumour hypoxia and aggressiveness. In this study, we explore the TSG role of CYGB, its influence on the phenotype of cancerous cells under stress conditions and the clinical significance of CYGB expression and promoter methylation in non-small cell lung cancer (NSCLC). DNA methylation-dependent expression silencing of CYGB is demonstrated in both clinical samples and cell lines. CYGB promoter was more frequently methylated in lung adenocarcinomas (P = 1.4 x 10^-4). Demethylation by 5’-azadeoxycytidine partially restored CYGB expression in cell lines. Interestingly, trichostatin A triggered upregulation of CYGB expression in cancer cell lines and downregulation in non-tumourigenic ones. CYGB mRNA expression in NSCLC surgical specimens correlated with that of HIF1alpha and VEGFa (P < 1 x 10^-4). Overexpression of CYGB in cancer cell lines reduced cell migration, invasion and anchorage-independent growth. Moreover, CYGB impaired cell proliferation, but only in the lung adenocarcinoma cell line (H358). Upon hydrogen peroxide treatment, CYGB protected cell viability, migratory potential and anchorage independence by attenuating oxidative injury. In hypoxia, CYGB overexpression decreased cell viability, augmented migration and anchorage independence in a cell-type-specific manner. In conclusion, CYGB revealed TSG properties in normoxia but promoted tumourigenic potential of the cells exposed to stress, suggesting a bimodal function in lung tumourigenesis, depending on cell type and microenvironmental conditions.
Probable human carcinogens are generated during Chinese-style high-temperature cooking of meat and have been detected in the ambient air and on the meat surface. Although the inhalation of these compounds is an established risk factor for lung cancer, exposure via fried meat consumption has not yet been prospectively evaluated as a risk factor. The relationship between fried meat intake and lung cancer risk was investigated using data from a prospective cohort study among Chinese in Singapore. Lung cancer cases (n = 1130) were identified from 61,321 men and women, 70% of whom were lifetime never smokers. Proportional hazards regression methods were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Overall, there was no association between fried meat intake and risk of all lung cancers combined. For lung adenocarcinoma, fried meat intake had a statistically significant association with increased risk. The association between fried meat intake and risk of lung adenocarcinoma became stronger when analyses were restricted to lifetime never smokers. Compared with the lowest tertile of fried meat intake, the HRs (95% CIs) for the second and third tertiles were 1.43 (0.98, 2.08) and 1.51 (1.03, 2.22), respectively (P for trend = 0.04). The positive association was present among both men and women. There was no association between fried meat intake and risk of non-adenocarcinomas of the lung. Our prospective results for fried meat intake support consumption as an important route of exposure to compounds from Chinese-style high-temperature cooking for the development of lung adenocarcinoma.

[108]

Myeloid cell RelA/p65 promotes lung cancer proliferation through Wnt/beta-catenin signaling in murine and human tumor cells.

Smoking is the most important risk factor for both lung cancer (LC) and chronic obstructive pulmonary disease. The aim of this study was to investigate the role of myeloid cell nuclear factor-kappaB in the regulation of tumor cell growth signaling. We subjected mice lacking myeloid
RelA/p65 (relaDelta/-) to a metastatic LC model. Cigarette smoke (CS) exposure significantly increased the proliferation of Lewis lung carcinoma cell tumors in wild-type mice. In CS-exposed relaDelta/- mice, the tumor growth was largely inhibited. Transcriptome and pathway analysis of cancer tissue revealed a fundamental impact of myeloid cells on various growth signaling pathways, including the Wnt/beta-catenin pathway. In conclusion, myeloid RelA/p65 is necessary to link smoke-induced inflammation with LC growth and has a role in the activation of Wnt/beta-catenin signaling in tumor cells. Oncogene advance online publication, 8 April 2013; doi:10.1038/onc.2013.75.

[109]
TÍTULO / TITLE: - Analysis of Predictive Factors for Postoperative Survival for Non Small Cell Lung Carcinoma Patients with Unexpected Mediastinal Lymph Nodes Metastasis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wang S; Zhou W; Zhang H; Zhao M; Chen X
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China.
RESUMEN / SUMMARY: - Objectives To discuss the predictive factors of postoperative survival for non small cell lung carcinoma (NSCLC) patients with clinical N0 stage but postoperative pathological N2 stage (cN0-pN2). Methods From January 1, 2005, to December 31, 2009, the clinical data of NSCLC patients with cN0-pN2 after radical surgery were retrospectively collected, and their survival information was collected through follow-up. The expiration date for follow-up was December 31, 2011. The predictive factors of postoperative survival for NSCLC patients with unexpected mediastinal lymph node metastasis were analyzed using Cox proportional hazards regression. Results A total of 263 patients were enrolled. The follow-up rate was 91.63%. The overall 1-, 3-, and 5-year survival rates were 94.6, 55.2, and 26.3%, respectively. Video-assisted thoracotomy surgery (VATS; odds ratio [OR] 0.659; 95% confidence interval [CI] 0.469 to 0.927; p = 0.017), multiple stations of metastatic mediastinal lymph nodes (OR 1.605; 95% CI 1.180 to 2.183; p = 0.003), and no adjuvant chemotherapy (OR 1.576; 95% CI 1.105 to 2.246; p = 0.012) were independent predictive factors for unexpected N2 patients. The median survival after VATS was superior to that after thoracotomy for patients with a single station of metastatic mediastinal lymph node (48.45 m vs 37.34 m, p = 0.018). The median survival without any adjuvant chemotherapy was inferior to that after adjuvant chemotherapy for patients with multiple stations of metastatic mediastinal lymph nodes (20.32 m vs 31.55 m, p =
Conclusion: The postoperative survival for NSCLC patients with cN0-pN2 was related to operational method, adjuvant chemotherapy, and the number of metastatic mediastinal lymph node stations. Patients with a single station of metastatic mediastinal lymph node are likely to benefit from VATS, whereas patients with multiple stations of metastatic mediastinal lymph nodes are likely to benefit from adjuvant chemotherapy.
with RFS or OS. Further research of chronic inflammation in NSCLC is warranted.

[111]
TÍTULO / TITLE: - Histology and Smoking Status Predict Survival of Patients with Advanced Non-Small-Cell Lung Cancer: Results of West Japan Oncology Group (WJOG) Study 3906L.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Kogure Y; Ando M; Saka H; Chiba Y; Yamamoto N; Asami K; Hirashima T; Seto T; Nagase S; Otsuka K; Yanagihara K; Takeda K; Okamoto I; Aoki T; Takayama K; Yamasaki M; Kudoh S; Katakami N; Miyazaki M; Nakagawa K

INSTITUCIÓN / INSTITUTION: - *Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan; daggerCenter for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan; double daggerDivision of Biostatistics, double daggerDepartment of Medical Oncology, Clinical Research Center, Kinki University School of Medicine, Osaka, Japan; section signThoracic Oncology Division, Shizuoka Cancer Center, Nagaizumi, Japan; ||Department of Medical Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan; paragraph signDepartment of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Japan; #Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan; **Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan; daggerdaggerDepartment of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; double daggerdouble daggerDepartment of Translational Clinical Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; section sign signDepartment of Clinical Oncology, Osaka City General Hospital, Osaka, Japan; ||||Department of Internal Medicine, Division of Respiratory Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan; paragraph sign paragraph signGraduate School of Medical Sciences, Research Institute for Diseases of the Chest, Kyushu University, Fukuoka, Japan; ##Department of Respiratory Disease, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan; ***Department of Respiratory Medicine, Osaka City University Medical School, Osaka, Japan; daggerdaggerdaggerDivision of Integrated Oncology, Institute of Biomedical Research and Innovation Hospital, Kobe, Japan; and double daggerdouble daggerDepartment of
INTRODUCTION: Smoking status is one of the prognostic factors in advanced non-small-cell lung cancer (NSCLC). Currently, adenocarcinoma (Ad) histology is considered a predictive factor in advanced NSCLC. We investigated the correlation between histology or smoking status and survival of NSCLC patients receiving chemotherapy. METHODS: We retrospectively reviewed clinical data from stage IIIB or IV NSCLC patients who started first-line chemotherapy at affiliated institutions of West Japan Oncology Group from 2004 to 2005. We also collected information on pack-years of cigarette smoking and years since cessation. Overall survival was compared using log-rank test, and Cox regression analysis was used to identify independent prognostic factors. RESULTS: In total, 2542 consecutive patients were enrolled at 40 institutions. Of those, 71 were excluded because of unknown smoking history. The median overall survival of non-smoking Ad patients (593 days) was longer than that of smoking Ad, nonsmoking non-Ad, and smoking non-Ad patients (384, 374, and 319 days, respectively; p < 0.001). In Cox regression with sex, age, stage, performance, and treatment as covariates, we found significant interaction (p = 0.039) between histology (Ad/non-Ad) and smoking status (smoker/nonsmoker); smoking conferred a hazard ratio of 1.34 (95% confidence interval, 1.15-1.55) in Ad, but only 0.99 (0.75-1.31) in non-Ad. Higher pack-years and shorter period since cessation were significantly associated with poorer survival in Ad (p < 0.001), but not in non-Ad (p >/= 0.434). CONCLUSION: Ad histology is associated with better prognosis, and only smoking status had a prognostic impact in Ad.

[112]
TÍTULO / TITLE: - Social deprivation does not affect lung cancer stage at presentation or disease outcome.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Cheyne L; Taylor A; Milton R; Fear J; Callister ME
INSTITUCIÓN / INSTITUTION: - Leeds Teaching Hospitals NHS Trust, United Kingdom. Electronic address: leanne.cheyne@nhs.net.
RESUMEN / SUMMARY: - INTRODUCTION: Lung cancer mortality rates are higher in more deprived populations. This may simply reflect higher incidence of the disease, or additionally delayed presentation and worse outcomes amongst more deprived patients. Low socio-economic status (SES) has also been linked to cancer fatalism which might account for such differences. We determined the
interaction between SES, patient’s characteristics at presentation with lung cancer, and disease outcome at a large UK teaching hospital. METHODS: Stage, PS at presentation, treatment and survival data, index of multiple deprivation score and ACORN group (geo-demographic segmentation tool) were analysed for 1432 patients. RESULTS: There were no significant differences in stage or PS distribution by IMD quintile or ACORN group. When patients with stage I/II disease were considered, there were no differences in IMD or ACORN group for those undergoing or not undergoing surgical resection. Similarly when the whole cohort was considered, there were no differences in these parameters between those receiving and not receiving any anti-cancer therapy. There was a non-significant trend to lower IMD score (i.e. less deprivation) in the stage IIIb/IV patients receiving palliative chemotherapy compared to those not receiving chemotherapy. There was no significant difference in median survival or one-year survival according to IMD quintile or ACORN group. CONCLUSION: In our patient cohort, deprivation does not appear to affect stage or performance status at presentation, nor survival from lung cancer. If cancer fatalism is more prevalent in deprived populations, this does not appear to lead to later diagnosis nor worse disease outcome.

[113]

**TÍTULO / TITLE:** - Inhomogeneous dose escalation increases expected local control for NSCLC patients with lymph node involvement without increased mean lung dose.

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

**REVISTA / JOURNAL:** - Acta Oncol. 2013 Apr 29.

**AUTORES / AUTHORS:** - Nielsen TB; Hansen O; Schytte T; Brink C

**INSTITUCIÓN / INSTITUTION:** - Institute of Clinical Research, University of Southern Denmark, Odense, Denmark.

**RESUMEN / SUMMARY:** - Background. Higher doses to NSCLC tumours are required to increase the low control rates obtained with conventional dose prescriptions. This study presents the concept of inhomogeneous dose distributions as a general way to increase local control probability, not only for isolated lung tumours but also for patients with involved lymph nodes. Material and methods. Highly modulated IMRT plans with homogeneous dose distributions with a prescribed dose of 66Gy/33F were created for 20 NSCLC patients, staged T1b-T4 N0-N3, using standard PTV dose coverage of 95-107%. For each patient, an inhomogeneous dose distribution was created with dose constraints of: PTV-coverage >/= 95%, same mean lung dose as obtained in the homogeneous dose plan, maximum doses of 45 and 66 Gy to spinal canal and oesophagus, respectively, and V74Gy < 1 cm3 for each of: aorta,
The dose was escalated using a TCP model implemented into the planning system. The difference in TCP values between the homogeneous and inhomogeneous plans were evaluated using two different TCP models. Results. Dose escalation was possible for all patients. TCP values based on assumed homogeneous distribution of clonogenic cells either in the GTV, CTV or PTV showed absolute TCP increases of approximately 15, 10 and 5 percentage points, respectively. This increase in local control was obtained without increasing the mean lung dose. However, small increases in maximum doses to the mediastinum were observed: 2.5 Gy for aorta, 4.4 Gy for the connective tissue, 1.6 Gy for the heart, and 2.6 Gy for trachea + bronchi. Conclusion. Increased target doses and TCP values using inhomogeneous dose distributions could be achieved for all patients, regardless of lymph node involvement, tumour stage, location, and size. These new treatment plans have the potential to increase the local tumour control by 10-15 percentage points without compromising the clinically acceptable lung toxicity level.

[114]

TITULO / TITLE: Mathematical modeling of tumor cell proliferation kinetics and label retention in a mouse model of lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Zheng Y; Moore H; Piryatinska A; Solis T; Sweet-Cordero EA
INSTITUCION / INSTITUTION: Pediatrics, Stanford University.

Slowly-cycling tumor cells that may be present in human tumors may evade cytotoxic therapies, which tend to be more efficient at destroying cells with faster growth rates. However, the proportion and growth rate of slowly-cycling tumor cells is often unknown in preclinical model systems used for drug discovery. Here we report a quantitative approach to quantitate slowly-cycling malignant cells in solid tumors, using a well-established mouse model of Kras-induced lung cancer (KrasG12D/+). Bromodeoxyuridine (BrdU) was administered to tumor-bearing mice and samples were collected at defined times during pulse and chase phases. Mathematical and statistical modeling of the label-retention data during the chase phase supported the existence of a slowly-cycling label-retaining population in this tumor model and permitted the estimation of its proportion and proliferation rate within a tumor. The doubling time of the slowly cycling population was estimated at ~5.7 weeks and this population represented ~31% of the total tumor cells in this model system. The mathematical modeling techniques implemented here may be useful in other
tumor models where direct observation of cell cycle kinetics is difficult and may help evaluate tumor cell subpopulations with distinct cell-cycling rates.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Shah A; Hahn SM; Stetson RL; Friedberg JS; Pechet TT; Sher DJ
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Department of Radiation Oncology, Columbia University Medical Center, New York, New York.

RESUMEN / SUMMARY: - BACKGROUND: The traditional treatment for clearly operable (CO) patients with stage I non-small cell lung cancer (NSCLC) is lobectomy, with wedge resection (WR) and stereotactic body radiation therapy (SBRT) serving as alternatives in marginally operable (MO) patients. Given an aging population with an increasing prevalence of screening, it is likely that progressively more people will be diagnosed with stage I NSCLC, and thus it is critical to compare the cost-effectiveness of these treatments. METHODS: A Markov model was created to compare the cost-effectiveness of SBRT with WR and lobectomy for MO and CO patients, respectively. Disease, treatment, and toxicity data were extracted from the literature and varied in sensitivity analyses. A payer (Medicare) perspective was used. RESULTS: In the base case, SBRT (MO cohort), SBRT (CO cohort), WR, and lobectomy were associated with mean cost and quality-adjusted life expectancies of $42,094/8.03, $40,107/8.21, $51,487/7.93, and $49,093/8.89, respectively. In MO patients, SBRT was the dominant and thus cost-effective strategy. This result was confirmed in most deterministic sensitivity analyses as well as probabilistic sensitivity analysis, in which SBRT was most likely cost-effective up to a willingness-to-pay of more than $500,000/quality-adjusted life year. For CO patients, lobectomy was the cost-effective treatment option in the base case (incremental cost-effectiveness ratio of $13,216/quality-adjusted life year) and in nearly every sensitivity analysis. CONCLUSIONS: SBRT was nearly always the most cost-effective treatment strategy for MO patients with stage I NSCLC. In contrast, for patients with CO disease, lobectomy was the most cost-effective option. Cancer 2013. © 2013 American Cancer Society.

[116]
TÍTULO / TITLE: - Tid1-L inhibits EGFR signaling in lung adenocarcinoma by enhancing EGFR ubiquitinylation and degradation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chen CY; Jan CI; Lo JF; Yang SC; Chang YL; Pan SH; Wang WL; Hong TM; Yang PC
INSTITUCIÓN / INSTITUTION: - Department of Nutrition and Health Sciences, Chang Gung University of Science and Technology.

RESUMEN / SUMMARY: - Tid1 (DNAJA3), a DnaJ co-chaperone, may promote degradation of oncogenic kinases. Tid1 has two isoforms, Tid1-L and Tid1-S, that may function differently. In this study, we investigated the role of the Tid1 isoforms in regulating EGFR signaling and lung cancer progression. We found that both Tid1-L and Tid1-S expressions were reduced in patients with non-small cell lung cancer compared with normal counterparts. Tid1-L expression correlated inversely with EGFR expression. Low Tid1-L/high EGFR expression predicted poor overall survival in lung adenocarcinoma patients. Tid1-L overexpression in lung cancer cells attenuated EGFR signaling and inhibited cell proliferation, colony formation and tumor growth in subcutaneous and orthotopic xenograft models. Conversely, depletion of Tid1 restored EGFR signaling and increased cell proliferation and colony formation. Tid1-L, but not Tid1-S interacted with EGFR/HSP70/HSP90 through the DnaJ domain, counteracting the EGFR regulatory function of HSP90 by causing EGFR ubiquitinylation and proteasomal degradation. Tid1-L inhibited EGFR signaling even more than the HSP90 inhibitor 17-allylamino-demethoxy geldanamycin. We concluded that Tid1-L acted as a tumor suppressor by inhibiting EGFR signaling through interaction with EGFR/HSP70/HSP90 and enhancing EGFR ubiquitinylation and degradation.

[117]

TÍTULO / TITLE: - Differential effects of insulin and dexamethasone on pulmonary surfactant-associated genes and proteins in A549 and H441 cells and lung tissue.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Rucka Z; Vanhara P; Koutna I; Tesarova L; Potesilova M; Stejskal S; Simara P; Dolezel J; Zvonicek V; Coufal O; Capov I
INSTITUCIÓN / INSTITUTION: - Centre for Biomedical Image Analysis, Faculty of Informatics, Masaryk University, 60200 Brno, Czech Republic.
In this study, the effects of insulin and dexamethasone on the expression and mRNA transcription of 4 pulmonary surfactant-associated proteins [surfactant protein (SFTP)A, SFTPB, SFTPC and SFTPD] were examined. The commercially available cell lines, A549 and H441, were used as acceptable models of lung surfactant-producing cells. Subsequently, the effects of insulin on the expression of surfactant-associated proteins were examined in patients with lung adenocarcinoma during lung resection. Our results demonstrated the inhibitory effects of insulin on the transcription of the SFTPB, SFTPC and SFTPD genes in H441 cells and the SFTPB gene in A549 cells. Treatment with insulin significantly decreased the protein expression of SFTPA1 and SFTPA2 in the H441 cells and that of proSFTPB in the A549 cells. Dexamethasone promoted the transcription of the SFTPB, SFTPC and SFTPD genes in the A549 and H441 cells and reduced the transcription of the SFTPA1 and SFTPA2 genes in the H441 cells (SFTPA mRNA expression was not detected in A549 cells). Furthermore, we demonstrated that the mRNA levels of the selected genes were significantly lower in the cell lines compared to the lung tissue. A549 and H441 cells represent similar cell types. Yet, in our experiments, these cells reacted differently to insulin and/or dexamethasone treatment, and the mRNA levels of their main protein products, surfactant-associated proteins, were significantly lower than those in real tissue. Therefore, the results obtained in this study challenge the suitability of A549 and H441 cells as models of type II pneumocytes and Clara cells, respectively. However, we successfully demonstrate the possibility of studying the effects of insulin on pulmonary surfactant-associated genes and proteins in patients with lung adenocarcinoma.

[118]

Título / Title: Epidermal growth factor receptor mutations in lung adenocarcinoma in malaysian patients.

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


Autor(es) / Authors: Liam CK; Wahid MI; Rajadurai P; Cheah YK; Ng TS

Institución / Institution: *Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; daggerBeacon International Specialist Center, Petaling Jaya, Malaysia; double daggerDepartment of Pathology, Monash University, Bandar Sunway, Malaysia; and section signDepartment of Biomedical Sciences, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia.
INTRODUCTION: Despite available data from other Asian countries, the prevalence of epidermal growth factor receptor (EGFR) mutations among lung adenocarcinoma patients has not been reported in Malaysia. This study sought to determine the frequency of EGFR mutations among multiethnic Malaysian patients diagnosed with lung adenocarcinoma.

METHODS: Demographic and clinical information of patients whose lung adenocarcinoma biopsy specimens were submitted for EGFR mutation testing at Sime Darby Medical Center from 2009 to 2011 were analyzed. EGFR mutations at exons 18, 19, 20, and 21 were detected either through bidirectional sequencing or real-time polymerase chain reaction.

RESULTS: Among 812 patients in the study, 49% were female, 63.7% were ethnic Chinese, 29.4% Malay, 4.8% Indian, and 2.1% other ethnic groups. Mutations were present in the tumors of 321 patients (39.5%), with mutations at exons 19 (23.5%) and 21 (14.9%) being the most common. Mutations were significantly more frequent among women than in men (52.5% versus 27.8%, p < 0.001). Although mutations were more common among Chinese (40.8%) compared with Malay (37.2%) or Indian (33.3%) patients, the difference was not statistically significant (p = 0.591). Of 211 patients with smoking history records, never-smokers had a higher mutation rate compared with ever-smokers (54.8% versus 20.7%, p < 0.001). CONCLUSION: EGFR mutations were present in 39.5% of patients. Mutations were more common in women and never-smokers with no differences in mutation frequency between different ethnicities. Because of the high mutation rates, reflex testing for EGFR mutation should be a routine practice for advanced lung adenocarcinoma patients in Malaysia.
pemetrexed monotherapy. Patients were divided into two groups: group A and group B included patients who started vitamin supplements 5-14 days versus within 4 days before the first dose of pemetrexed, respectively. Groups A and B included 294 (84.0%) and 56 (16.0%) patients, respectively. The median number of cycles of pemetrexed was three in both groups. Patients in group A and B showed similar rates of leukopenia (6.1% vs. 5.4%, respectively, P=1.00), neutropenia (5.1% vs. 3.6%, P=1.00), thrombocytopenia (3.1% vs. 7.1%, P=0.14), neutropenic fever (0.7% vs. 0%, P=1.00), fatigue (20.1% vs. 19.6%, P=0.94), and anorexia (15.0% vs. 21.4%, P=0.23) during the first cycle of pemetrexed therapy. There were no significant differences in terms of hospitalization (4.4% vs. 5.4%, P=0.73) or unscheduled visits due to pemetrexed-related adverse events (8.2% vs. 12.5%, P=0.31) between groups A and B, respectively. Multivariate logistic regression analysis demonstrated that an age of >/=65 years (odds ratio, 3.49; 95% CI 1.12-10.86) and poor performance status (odds ratio, 3.96; 95% CI 1.12-14.03) were statistically significant predictive factors for grade 3 or 4 hematologic toxicity. The duration of vitamin supplementation before the first dose of pemetrexed did not affect the development of pemetrexed-related toxicities, suggesting that the initiation of pemetrexed-based chemotherapy does not have to be delayed to accommodate a vitamin supplementation schedule.

[120]
TÍTULO / TITLE: - Lysine Acetyltransferase GCN5 Potentiates the Growth of Non-small Cell Lung Cancer via Promotion of E2F1, Cyclin D1, and Cyclin E1 Expression.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chen L; Wei T; Si X; Wang Q; Li Y; Leng Y; Deng A; Chen J; Wang G; Zhu S; Kang J
INSTITUCIÓN / INSTITUTION: - From the Clinical and Translational Research Center of Shanghai First Maternity and Infant Health Hospital, Shanghai Key Laboratory of Signaling and Disease Research at School of Life Science and Technology, Tongji University, No. 1239 Siping Road, Shanghai 200092 and.
RESUMEN / SUMMARY: - The lysine acetyltransferases play crucial but complex roles in cancer development. GCN5 is a lysine acetyltransferase that generally regulates gene expression, but its role in cancer development remains largely unknown. In this study, we report that GCN5 is highly expressed in non-small cell lung cancer tissues and that its expression correlates with tumor size. We found that the expression of GCN5 promotes cell growth and the G1/S phase transition in multiple lung cancer cell lines. Further study revealed that GCN5
regulates the expression of E2F1, cyclin D1, and cyclin E1. Our reporter assays indicated that the expression of GCN5 enhances the activities of the E2F1, cyclin D1, and cyclin E1 promoters. ChIP experiments suggested that GCN5 binds directly to these promoters and increases the extent of histone acetylation within these regions. Mechanistic studies suggested that GCN5 interacts with E2F1 and is recruited by E2F1 to the E2F1, cyclin D1, and cyclin E1 promoters. The function of GCN5 in lung cancer cells is abrogated by the knockdown of E2F1. Finally, we confirmed that GCN5 regulates the expression of E2F1, cyclin D1, and cyclin E1 and potentiates lung cancer cell growth in a mouse tumor model. Taken together, our results demonstrate that GCN5 specifically potentiates lung cancer growth by directly promoting the expression of E2F1, cyclin D1, and cyclin E1 in an E2F1-dependent manner. Our study identifies a specific and novel function of GCN5 in lung cancer development and suggests that the GCN5-E2F1 interaction represents a potential target for lung cancer treatment.

[121] TÍTULO / TITLE: Histology as a potential clinical predictor of outcome in advanced non-small-cell lung cancer treated with vinorelbine and mitomycin combination chemotherapy.

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


AUTORES / AUTHORS: Wibmer T; Berghmans T; Kropf-Sanchen C; Lafitte JJ; Rudiger S; Paesmans M; Blanta I; Scherpereel A; Stoiber KM; Rottbauer W; Sculier JP; Schumann C

INSTITUCIÓN / INSTITUTION: Department of Internal Medicine II, University Hospital of Ulm, Albert-Einstein-Allee 23, 89081, Ulm, Germany.

RESUMEN / SUMMARY: BACKGROUND: The importance of clinical predictors in the treatment of non-small-cell lung cancer (NSCLC) has increased during the last decade. This retrospective study analyzed the combined patient-level data from two phase II trials that investigated the efficacy and safety of combination chemotherapy with vinorelbine and mitomycin in patients with locally advanced or metastatic NSCLC. The aim of this analysis was to determine if patients’ baseline and disease characteristics, including histology, gender, smoking history, and expression of TTF-1, might be potential predictors of outcome. METHODS: Response rates, unadjusted survival times, and Cox covariate-adjusted hazard ratios (HRs) were calculated. Results were reported separately for each subgroup in each individual trial and in the pooled data set. RESULTS: A total of 175 patients were included in this analysis. Adjusted HRs for both
overall survival (OS) and progression free survival (PFS) favored the nonadenocarcinoma histology subgroup, achieving a statistical significance for OS in the pooled data (n = 175; HR 0.68; 95% CI 0.49-0.94; p = 0.019). TTF-1-negative immunohistochemistry was associated with a significantly higher response rate (25 vs. 0%; p = 0.04) and with a nonsignificant advantage in OS (n = 33; HR 1.23; 95% CI 0.56-2.73; p = 0.608). Gender and smoking history were not strongly related to outcome. CONCLUSIONS: The results of this analysis indicate that patients with nonadenocarcinoma histology might get superior benefit from combination chemotherapy with vinorelbine and mitomycin. These results should be confirmed in a prospective study.

[122]
TÍTULO / TITLE: - Protein kinase Calpha suppresses Kras-mediated lung tumor formation through activation of a p38 MAPK-TGFbeta signaling axis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hill KS; Erdogan E; Khoor A; Walsh MP; Leitges M; Murray NR; Fields AP
INSTITUCION / INSTITUTION: - Department of Cancer Biology, Mayo Clinic, Jacksonville, FL, USA.
RESUMEN / SUMMARY: - Protein kinase C alpha (PKCalpha) can activate both pro- and anti-tumorigenic signaling depending upon cellular context. Here, we investigated the role of PKCalpha in lung tumorigenesis in vivo. Gene expression data sets revealed that primary human non-small lung cancers (NSCLC) express significantly decreased PKCalpha levels, indicating that loss of PKCalpha expression is a recurrent event in NSCLC. We evaluated the functional relevance of PKCalpha loss during lung tumorigenesis in three murine lung adenocarcinoma models (LSL-Kras, LA2-Kras and urethane exposure). Genetic deletion of PKCalpha resulted in a significant increase in lung tumor number, size, burden and grade, bypass of oncogene-induced senescence, progression from adenoma to carcinoma and a significant decrease in survival in vivo. The tumor promoting effect of PKCalpha loss was reflected in enhanced Kras-mediated expansion of bronchio-alveolar stem cells (BASCs), putative tumor-initiating cells, both in vitro and in vivo. LSL-Kras/Prkca-/- mice exhibited a decrease in phospho-p38 MAPK in BASCs in vitro and in tumors in vivo, and treatment of LSL-Kras BASCs with a p38 inhibitor resulted in increased colony size indistinguishable from that observed in LSL-Kras/Prkca-/- BASCs. In addition, LSL-Kras/Prkca-/- BASCs exhibited a modest but reproducible increase in TGFbeta1 mRNA, and addition of exogenous TGFbeta1 to LSL-Kras BASCs results in enhanced growth similar to untreated BASCs from LSL-Kras/Prkca-/- mice. Conversely, a TGFbetaR1
inhibitor reversed the effects of PKCalpha loss in LSL-Kras/Prkca/-/- BASCs. Finally, we identified the inhibitors of DNA binding (Id) Id1-3 and the Wilm’s Tumor 1 as potential downstream targets of PKCalpha-dependent tumor suppressor activity in vitro and in vivo. We conclude that PKCalpha suppresses tumor initiation and progression, at least in part, through a PKCalpha-p38MAPK-TGFbeta signaling axis that regulates tumor cell proliferation and Kras-induced senescence. Our results provide the first direct evidence that PKCalpha exhibits tumor suppressor activity in the lung in vivo. Oncogene advance online publication, 22 April 2013; doi:10.1038/onc.2013.147.

[123] TITULO / TITLE: - Synergistic effects of metformin treatment in combination with gefitinib, a selective EGFR tyrosine kinase inhibitor, in LKB1 wild-type NSCLC cell lines.

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


AUTORES / AUTHORS: - Morgillo F; Sasso FC; Della Corte CM; Vitagliano D; D’aiuto E; Troiani T; Martinelli E; De Vita F; Orditura M; De Palma R; Ciardiello F

INSTITUCIÓN / INSTITUTION: - Dipartimento medico chirurgico di Internistica clinica e sperimentale, Second University of Naples.

RESUMEN / SUMMARY: - PURPOSE: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been found to be effective against lung cancer, but clinical resistance to these agents has developed as their usage has increased. Metformin is a widely used antidiabetic drug and also displays significant growth inhibitory and pro apoptotic effects in several cancer models, alone or in combination with chemotherapeutic drugs. Experimental design: The effects of gefitinib, a selective EGFR-TKI, and metformin on a panel of NSCLC cell lines were assessed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT), bromide assay, flow cytometry, anchorage independent growth, co-immunoprecipitation, and Western blot analysis. RESULTS: The combination of metformin with gefitinib induced a strong antiproliferative and proapoptotic effect in NSCLC cell lines which harbored wild type LKB1 gene. Treatment with metformin as single agent, however, induced an activation and phosphorylation of MAPK through an increased C-RAF:B-RAF heterodimerization. The inhibition of EGFR phosphorylation and of downstream signaling by adding gefitinib to metformin treatment abrogated this phenomenon and induced a strong apoptotic effect in vitro and in vivo. CONCLUSIONS: Metformin and gefitinib are synergistic in LKB1 wild type NSCLC cells. However, further studies are required to investigate better the
effect of metformin action on the RAS/RAF/MAPK pathway and the best context in which to use metformin in combination with molecular targeted agents.

[124]
TÍTULO / TITLE: - Pulmonary resection of lung cancer in a patient with partial anomalous pulmonary venous connection.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mikubo M; Ikeda S; Hoshino T; Yokota T; Fujii A; Mori M
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery and Pathology, Mitsui Memorial Hospital, Tokyo, Japan. Electronic address: m.mikubo1220@hotmail.com.
RESUMEN / SUMMARY: - We report a case of a 64-year-old man in whom a partial anomalous pulmonary venous connection (PAPVC) was found before right lower lobectomy for lung cancer. In addition to lung cancer, there was a right superior pulmonary vein that drained into the superior vena cava (SVC). There was a concern of right ventricular heart failure resulting from increased left-to-right shunt flow after lobectomy. Therefore cardiac catheterization was performed to calculate the pulmonary-to-systemic flow rate in the presence of blocked blood flow to the lower lobe pulmonary artery. As a result, we successfully performed lobectomy without correcting the PAPVC.

[125]
TÍTULO / TITLE: - High Performance of F-Fluorodeoxyglucose Positron Emission Tomography and Contrast-Enhanced CT in a Rapid Outpatient Diagnostic Program for Patients with Suspected Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - Respiration. 2013 Apr 16.
AUTORES / AUTHORS: - Brocken P; van der Heijden HF; Dekhuijzen PN; Peters-Bax L; de Geus-Oei LF
INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Diseases, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.
RESUMEN / SUMMARY: - Background: The diagnostic evaluation of patients presenting with possible lung cancer is often complex and time consuming. A rapid outpatient diagnostic program (RODP) including 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and contrast-enhanced computed tomography (CT) as a routine diagnostic tool may improve timeliness, however
the diagnostic performance of such a combined approach of RODP remains unclear. Objectives: We evaluated timeliness of care and diagnostic performance of FDG-PET and contrast-enhanced CT (FDG-PET/CT) in an RODP for all patients referred with a chest X-ray suspicious of lung cancer. Methods: Charts of patients referred to the 2-day RODP of our tertiary care university clinic after an abnormal chest X-ray between 1999 and 2009 were reviewed. Between 1999 and 2005 co-registered FDG-PET and CT imaging took place; from September 2005 onwards, a hybrid system was used. We analyzed timeliness of care and diagnostic performance of FDG-PET/CT to differentiate malignant from benign lesions. Results: In 386 patients available for analysis, 260 were diagnosed with lung cancer and 23 had another type of malignancy; in 78 patients benign disease was confirmed, and in another 45 the diagnosis was not pathologically confirmed but a median 24.5-month follow-up confirmed a benign outcome. Sensitivity, specificity, negative and positive predictive values and accuracy of FDG-PET/CT to differentiate lung cancer from benign disease were 97.7, 60.2, 92.5, 84.0 and 85.8%, respectively. Lung cancer patients had a median referral, diagnostic and therapeutic delay of 7, 2 and 19 days, respectively. Conclusions: FDG-PET/CT in an RODP setting for suspected lung cancer has high performance in detecting cancer and facilitates timely care.

[126]
TÍTULO / TITLE: - Perfusion CT allows prediction of therapy response in non-small cell lung cancer treated with conventional and anti-angiogenic chemotherapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Tacelli N; Santangelo T; Scherpereel A; Duhamel A; Deken V; Klotz E; Cortot A; Lafitte JJ; Wallyn F; Remy J; Remy-Jardin M
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Imaging, Hospital Calmette (EA 2694), University of Lille Nord de France, 59000, Lille, France.
RESUMEN / SUMMARY: - OBJECTIVES: To determine whether CT can depict early perfusion changes in lung cancer treated by anti-angiogenic drugs, allowing prediction of response. METHODS: Patients with non-small cell lung cancer, treated by conventional chemotherapy with (Group 1; n = 17) or without (Group 2; n = 23) anti-vascular endothelial growth factor (anti-VEGF) drug (bevacizumab) underwent CT perfusion before (TIME 0) and after 1 (TIME 1), 3 (TIME 2) and 6 (TIME 3) cycles of chemotherapy. The CT parameters evaluated included: (1) total tumour vascular volume (TVV) and total tumour extravascular flow (TEF); (2) RECIST (Response Evaluation Criteria in Solid...
Tumours) measurements. Tumour response was also assessed on the basis of the clinicians' overall evaluation. RESULTS: In Group 1, significant reduction in perfusion was identified between baseline and: (1) TIME 1 (TVV, P = 0.0395; TEF, P = 0.015); (2) TIME 2 (TVV, P = 0.0043; TEF, P < 0.0001); (3) TIME 3 (TVV, P = 0.0034; TEF, P = 0.0005) without any significant change in Group 2. In Group 1: (1) the reduction in TVV at TIME 1 was significantly higher in responders versus non-responders at TIME 2 according to RECIST (P = 0.0128) and overall clinicians' evaluation (P = 0.0079); (2) all responders at TIME 2 had a concurrent decrease in TVV and TEF at TIME 1. CONCLUSION: Perfusion CT demonstrates early changes in lung cancer vascularity under anti-angiogenic chemotherapy that may help predict therapeutic response. KEY POINTS: * Perfusion CT has the potential of providing in vivo information about tumour vasculature. * CT depicts early and specific perfusion changes in NSCLC under anti-angiogenic drugs. * Specific therapeutic effects of anti-angiogenic drugs can be detected before tumour shrinkage. * Early perfusion changes can help predict therapeutic response to anti-angiogenic treatment. * Perfusion CT could be a non-invasive tool to monitor anti-angiogenic treatment.

[127]
**TÍTULO / TITLE:** - Associations of HLA-DRB1 and -DQB1 alleles with severe recurrent respiratory papillomatosis in Korean patients.

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


**AUTORES / AUTHORS:** - Song EY; Shin S; Park KU; Park MH; Sung MW; Kim KH; Kwon TK

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul, South Korea.

**RESUMEN / SUMMARY:** - Recurrent respiratory papillomatosis (RRP) is characterized by frequent recurrences of papilloma of the larynx with significant morbidity. It is caused by human papillomavirus (HPV) types 6 and 11. Some associations of HLA genes with RRP have been reported, mainly in Caucasians. We performed HLA class II (DRB1 and DQB1) genotyping using Dynal RELI HLA-DRB1 SSO kit and PCR-single strand conformation polymorphism on 22 Korean patients with severe RRP and 207 healthy controls. The gene frequencies of HLA-DRB1*11:01 (18.2% vs 3.6%, p=0.0006, pc=0.02, odds ratio [OR]=5.9) and DQB1*03:01 (36.4% vs 14.5%, p=0.0009, pc=0.01, OR=3.4) and the haplotype frequency of DRB1*11:01-DQB1*03:01 (15.9% vs 3.6%, p=0.003, OR=5.0) was higher in RRP patients than controls.
DRB1*11:01 and DRB1*11:01-DQB1*03:01 haplotype were strongly associated with disease susceptibility to severe RRP in Koreans.

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

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
RESUMEN / SUMMARY: - OBJECTIVES: Lycoris is aurea agglutinin (LAA) has attracted rising attention due to its remarkable bioactivities. Here, we aimed at investigating its anti-tumor activities. MATERIAL AND METHODS: In vitro methods including MTT, cellular morphology observation, FCM and immunoblotting were performed. In vivo methods like detection of tumor volume, body weight and survival ratio, as well as TUNEL staining were performed. RESULTS AND CONCLUSION: LAA triggers G2/M phase cell cycle arrest via up-regulating p21 expression as well as down-regulating cdk-1/cyclinA singling pathway, and induces apoptotic cell death through inhibiting PI3K-Akt survival pathway in human lung adenocarcinoma A549 cells. While LAA has no significant cytotoxic effect toward normal human embryonic lung fibroblast HELF cells, and moreover, LAA could amplify the antineoplastic effects of cisplatin toward A549 cells. Lastly LAA also bears anti-cancer and apoptosis-inducing effects in vivo, and it could decrease the volume and weight of subcutaneous tumor mass obviously as well as expand lifespan of mice. These findings may provide a new perspective for elucidating the complicated molecular mechanisms of LAA-induced cancer cell growth-inhibition and death, providing a new opportunity of LAA as a potential candidate anti-neoplastic drug for future cancer therapeutics.

[130]
TÍTULO / TITLE: - High-grade Lung Adenocarcinoma With Fetal Lung-like Morphology: Clinicopathologic, Immunohistochemical, and Molecular Analyses of 17 Cases.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Morita S; Yoshida A; Goto A; Ota S; Tsuta K; Yokozawa K; Asamura H; Nakajima J; Takai D; Mori M; Oka T; Tamaru J; Itoyama S; Furuta K; Fukayama M; Tsuda H
INSTITUCIÓN / INSTITUTION: - Departments of *Pathology and Clinical Laboratories double daggerThoracic Oncology, Thoracic Surgery Division, National Cancer Center Hospital daggerDepartment of Pathology, Graduate School of Medicine, The University of Tokyo Departments of section signThoracic Surgery parallelClinical Laboratory, The University of Tokyo Hospital paragraph signMitsui Memorial Hospital, Tokyo #Department of Pathology, Saitama Medical Center, Saitama Medical University, Saitama, Japan.
RESUMEN / SUMMARY: - Low-grade lung adenocarcinoma of fetal lung type, which is well characterized by its unique clinicopathologic and molecular
features, is recognized as a distinct variant of lung cancer. In contrast, high-grade lung adenocarcinoma with fetal lung-like morphology (HG-LAFM) has not been studied widely. To characterize this subset better, we analyzed 17 high-grade adenocarcinomas with at least focal component resembling a developing epithelium in the pseudoglandular phase of the fetal lung. These rare (ca. 0.4%) carcinomas occurred predominantly in elderly men with a heavy smoking history, who showed elevated serum alpha-fetoprotein in 4 of 5 cases tested. Histologic examination revealed a fetal lung-like component as a focal finding accounting for 5% to 60% of the total tumor volume. It was invariably admixed with tissues having a morphology not resembling that of a fetal lung. A coexisting non-fetal lung-like element was quite heterogenous in appearance, showing various growth patterns. However, clear-cell (88%), hepatoid (29%), and large cell neuroendocrine carcinoma (24%) histology seemed overrepresented. HG-LAFM was characterized immunohistochemically by frequent expression of alpha-fetoprotein (41%), glypican-3 (88%), SALL-4 (59%), neuroendocrine markers (82%), CDX-2 (35%), and p53 (65%). HG-LAFM was molecularly heterogenous in that EGFR or KRAS mutation was observed in 22% of cases tested for both. Our data indicate that HG-LAFMs might form a coherent subgroup of lung adenocarcinomas. However, the uniformly focal nature of the fetal lung-like element, widely diverse coexisting non-fetal lung-like histology, and inhomogenous molecular profiles lead us to believe that HG-LAFM is best regarded as a morphologic pattern showing characteristic association with several clinicopathologic parameters rather than a specific tumor entity.

[131]

TÍTULO / TITLE: - Matrix metalloproteinase mmp-1 is dispensable for normal growth and fertility in mice and promotes lung cancer progression by modulating inflammatory responses.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fanjul-Fernandez M; Folgueras AR; Fueyo A; Balbin M; Suarez MF; Fernandez-Garcia MS; Shapiro SD; Freije JM; Lopez-Otin C
INSTITUCIÓN / INSTITUTION: - From the Departamento de Bioquimica y Biologia Molecular and.
RESUMEN / SUMMARY: - Human MMP-1 is a matrix metalloproteinase repeatedly associated with many pathological conditions, including cancer. Thus, MMP1 overexpression is a poor prognosis marker in a variety of advanced cancers, including colorectal, breast, and lung carcinomas. Moreover, MMP-1 plays a key role in the metastatic behavior of melanoma, breast, and prostate cancer.
cells. However, functional and mechanistic studies on the relevance of MMP-1 in cancer have been hampered by the absence of an in vivo model. In this work, we have generated mice deficient in Mmp1a, the murine ortholog of human MMP1. Mmp1a(-/-) mice are viable and fertile and do not exhibit obvious abnormalities, which has facilitated studies of cancer susceptibility. These studies have shown a decreased susceptibility to develop lung carcinomas induced by chemical carcinogens in Mmp1a(-/-) mice. Histopathological analysis indicated that tumors generated in Mmp1a(-/-) mice are smaller than those of wild-type mice, consistently with the idea that the absence of Mmp-1 hampers tumor progression. Proteomic analysis revealed decreased levels of chitinase-3-like 3 and accumulation of the receptor for advanced glycation end-products and its ligand S100A8 in lung samples from Mmp1a(-/-) mice compared with those from wild-type. These findings suggest that Mmp-1 could play a role in tumor progression by modulating the polarization of a Th1/Th2 inflammatory response to chemical carcinogens. On the basis of these results, we propose that Mmp1a knock-out mice provide an excellent in vivo model for the functional analysis of human MMP-1 in both physiological and pathological conditions.

[132]
TÍTULO / TITLE: - Longitudinal associations between caregiver burden and patient and spouse distress in couples coping with lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Milbury K; Badr H; Fossella F; Pisters KM; Carmack CL
INSTITUCIÓN / INSTITUTION: - Department of General Oncology, Unit 642, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, Houston, TX, 77030-4006, USA, kmilbury@mdanderson.org.
RESUMEN / SUMMARY: - PURPOSE: While spouses play a vital role in the care of cancer patients, caregiving exerts a physical and psychological toll. Caregiving burden may not only compromise spouses’ quality of life but also the quality of care and support they are able to provide. Consequently, spousal caregiving burden may also negatively impact patients’ psychological adjustment. However, the effect of caregiving burden on patients’ psychological distress is unknown. Thus, this 6-month longitudinal study examined the associations between caregiving burden and distress in both lung cancer patients and their spouses. METHODS: Patients and their spouses individually completed questionnaires within 1 month of treatment initiation (baseline) and at 3- and 6-month follow-up. Distress was measured with the Brief Symptom Inventory and caregiving burden with the Caregiver Reaction Assessment.
RESULTS: Multilevel modeling of data from 158 couples revealed that baseline spouses’ reports of caregiving-related health problems were significantly associated with 3-month (p < 0.001) and 6-month (p = 0.01) follow-up distress in both patients and spouses even when controlling for baseline distress and dyadic adjustment. Furthermore, there was evidence that baseline spouses’ reports of schedule disruption (p = 0.05) predicted 3-month patients’ distress and baseline spouses’ reports of financial strain (p < 0.05) and lack of support (p < 0.10) predicted their own distress at 6 months. CONCLUSION: Caregiving burden is problematic for both patients and spouses. Couples in which spouses report caregiving-related health problems may be at particular high risk of long-term elevated distress. Targets of future couple-focused interventions such as self-care and use of social support are discussed.

[133]

TÍTULO / TITLE: - High Expression of Sonic Hedgehog Signaling Proteins Is Related to the Favorable Outcome, EGFR Mutation, and Lepidic Predominant Subtype in Primary Lung Adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kim JE; Kim H; Choe JY; Sun P; Jheon S; Chung JH
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam, 463-707, Republic of Korea.
RESUMEN / SUMMARY: - BACKGROUND: Dysregulation of the Sonic hedgehog (SHH) signaling pathway has been identified in many human malignancies. However, it remains unclear whether this pathway is activated in human lung adenocarcinoma. METHODS: We investigated the expression of the SHH ligand and its downstream molecules, such as glioma-associated oncogene homologue (GLI)-1, GLI-2, GLI-3, and ATP-binding cassette G2 (ABCG2), in 166 cases of surgically resected lung adenocarcinoma by immunohistochemistry. Correlations between the expression of SHH-related proteins and clinicopathologic parameters, histologic subtypes, and prognostic significance were statistically analyzed. RESULTS: SHH was highly expressed in the 36.1 % (60/166), GLI-1, GLI-2, and ABCG2 were found in 90/164 (54.9 %), 26/166 (15.7 %), and 139/165 (84.2 %), respectively, and GLI-3 was positive in all cases. SHH was more frequently highly expressed in nonsmokers, patients with no recurrences, lepidic predominant subtype, and with EGFR mutation (p < 0.05, respectively). The high expression of SHH and GLI-1 was related to better overall survival and progression-free survival (p < 0.05).
CONCLUSIONS: The SHH signaling pathway is frequently up-regulated in a
subset of lung adenocarcinoma and is significantly associated with EGFR mutation and lepidic subtype. Although SHH signaling protein expression is not an independent prognostic marker, the expression of these proteins can predict a better prognostic outcome.

[134]

TITULO / TITLE: Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany.

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


AUTORES / AUTHORS: Iyer S; Taylor-Stokes G; Roughley A

INSTITUCION / INSTITUTION: Pfizer Oncology, 235, E.42nd Street, 219-6-1, New York, NY 10017, USA. Electronic address: shrividya.iyer@pfizer.com.

RESUMEN / SUMMARY: BACKGROUND: To assess patient reported symptom burden and impact on disease specific health related quality of life (HRQOL) in advanced non-small cell lung cancer (NSCLC) patients. METHODS: Patients with advanced (stage IIIb/IV) NSCLC in France (n=613) and Germany (n=600) were recruited into a multicenter, patient record-based cross-sectional study. Patient reported symptoms using the Lung Cancer Symptom Scale, which assesses fatigue, loss of appetite, shortness of breath, cough, pain and blood in sputum on a 0-100 visual analog scale. Disease specific and generic HRQOL were assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) and the EuroQol five-dimensional questionnaire (EQ-5D) respectively. A multivariate regression analysis was performed with total FACT-L score as the dependent variable and symptom scores as predictors. Age, gender, stage and performance status were used as control variables. RESULTS: Majority of the patients were male (67%), Caucasian (93%) with an average age of 63 years. Fatigue, loss of appetite, shortness of breath, cough and pain were reported by >/=90% of patients. The mean health utility index score was found to be 0.58 and the mean general health status score was 58.0. Fatigue (beta=-0.122; p<0.001), loss of appetite (beta=-0.170; p<0.001), pain (beta=-0.145; p<0.001), shortness of breath (beta=-0.118; p<0.001) were found to be significant predictors of lung cancer specific quality of life as measured by the FACT-L total score. CONCLUSION: Fatigue, loss of appetite, shortness of breath and pain have a significant negative impact on patient reported disease specific HRQOL in advanced NSCLC patients.

[135]
TÍTULO / TITLE: - Preclinical Evaluation of Genexol-PM, a Nanoparticle Formulation of Paclitaxel, as a Novel Radiosensitizer for the Treatment of Non-Small Cell Lung Cancer.

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


AUTORES / AUTHORS: - Werner ME; Cummings ND; Sethi M; Wang EC; Sukumar R; Moore DT; Wang AZ

INSTITUCIÓN / INSTITUTION: - Laboratory of Nano- and Translational Medicine, Department of Radiation Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina; Carolina Center for Cancer Nanotechnology Excellence, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina.

RESUMEN / SUMMARY: - PURPOSE: A key research objective in radiation oncology is to identify agents that can improve chemoradiation therapy. Nanoparticle (NP) chemotherapeutics possess several properties, such as preferential accumulation in tumors, that are uniquely suited for chemoradiation therapy. To facilitate the clinical translation of NP chemotherapeutics in chemoradiation therapy, we conducted preclinical evaluation of Genexol-PM, the only clinically approved NP chemotherapeutic with a controlled drug release profile, as a radiosensitizer using non-small cell lung cancer (NSCLC) as a model disease. METHODS AND MATERIALS: The physical characteristics and drug release profile of Genexol-PM were characterized. Genexol-PM’s efficacy as a radiosensitizer was evaluated in vitro using NSCLC cell lines and in vivo using mouse xenograft models of NSCLC. Paclitaxel dose to normal lung and liver after Genexol-PM administration were quantified and compared with that after Taxol administration. RESULTS: Genexol-PM has a size of 23.91 +/- 0.41 nm and surface charge of -8.1 +/- 3.1 mV. It releases paclitaxel in a controlled release profile. In vitro evaluation of Genexol-PM as a radiosensitizer showed it is an effective radiosensitizer and is more effective than Taxol, its small molecule counterpart, at the half maximal inhibitory concentration. In vivo study of Genexol-PM as a radiosensitizer demonstrated that it is more effective as a radiosensitizer than Taxol. We also found that Genexol-PM leads to lower paclitaxel exposure to normal lung tissue than Taxol at 6 hours postadministration. CONCLUSIONS: We have demonstrated that Genexol-PM is more effective than Taxol as a radiosensitizer in the preclinical setting and holds high potential for clinical translation. Our data support the clinical evaluation of Genexol-PM in chemoradiation therapy for NSCLC.
Microsimulation model predicts survival benefit of radiofrequency ablation and stereotactic body radiotherapy versus radiotherapy for treating inoperable stage I non-small cell lung cancer.

OBJECTIVE. A subset of patients with stage IA and IB non-small cell lung cancer (NSCLC) is ineligible for surgical resection and undergoes radiation therapy. Radiofrequency ablation (RFA) and stereotactic body radiotherapy are newer potentially attractive alternative therapies.

MATERIALS AND METHODS. We added RFA and stereotactic body radiotherapy treatment modules to a microsimulation model that simulates lung cancer’s natural history, detection, and treatment. Natural history parameters were previously estimated via calibration against tumor registry data and cohort studies; the model was validated with screening study and cohort data. RFA model parameters were calibrated against 2-year survival from the Radiofrequency Ablation of Pulmonary Tumor Response Evaluation (RAPTURE) study, and stereotactic body radiotherapy model parameters were calibrated against 3-year survival from a phase 2 prospective trial. We simulated lifetime histories of identical patients with early-stage NSCLC who were ineligible for resection, who were treated with radiation therapy, RFA, or stereotactic body radiotherapy under a range of scenarios. From 5,000,000 simulated individuals, we selected a cohort of patients with stage I medically inoperable cancer for analysis (n = 2056 per treatment scenario). Main outcomes were life expectancy gains.

RESULTS. RFA or stereotactic body radiotherapy treatment in patients with peripheral stage IA or IB NSCLC who were nonoperative candidates resulted in life expectancy gains of 1.71 and 1.46 life-years, respectively, compared with universal radiation therapy. A strategy where patients with central tumors underwent stereotactic body radiotherapy and those with peripheral tumors underwent RFA resulted in a gain of 2.02 life-years compared with universal radiation therapy. Findings were robust with respect to changes in model parameters.

CONCLUSION. Microsimulation modeling results suggest that RFA and stereotactic body radiotherapy could provide life expectancy gains to patients with stage IA or IB NSCLC who are ineligible for resection.
Resumen / Summary: The outcomes of surgery in lung cancer patients with schizophrenia.


Autores / Authors: Obuchi T; Okabayashi K; Imakiire T; Yoneda S; Iwasaki A

Institución / Institution: Department of Thoracic Surgery, St. Mary’s Hospital, Tsubuku-hon-machi 422, Kurume, 830-8543, Japan, fukuoka_obuchi@yahoo.co.jp.

Resumen / Summary: PURPOSE: There are very few reports regarding the outcome of lung cancer surgery in patients with schizophrenia, and the clinical features of such patients are still unclear. METHODS: From 2004 to 2012, 11 lung cancer patients (six male, five female; mean age, 62.7 years) with schizophrenia underwent lung resections at our institutions. All patients had been institutionalized because they were unable to live independently at home. We retrospectively evaluated their postoperative clinical outcomes and long-term results. RESULTS: Ten of the 11 patients had comorbidities, such as diabetes mellitus and chronic obstructive pulmonary disease. Preoperatively, two patients had a history of treatment for other primary cancers in other organs, and one was on hemodialysis. A lobectomy was performed in nine patients, a segmentectomy in one, and a partial resection in one. There were no hospital deaths. The postoperative morbidity included two cases of pneumonia, one of atelectasis, and one of prolonged air leakage lasting more than 7 days. Wandering was postoperatively observed in two patients; one of these fell and fractured the left femur. At the time of our investigation, two patients were deceased, and the overall 5-year survival rate was 74.1%. CONCLUSIONS: The postoperative morbidity and long-term results of schizophrenic patients with lung cancer were acceptable. Therefore, even in patients with schizophrenia, surgical treatment for lung cancer should be recommended when deemed to be necessary.


Autores / Authors: Cheng D; Kong H; Li Y
INSTITUCIÓN / INSTITUTION: - Department of Transfusion, The First Hospital of China Medical University, Shenyang, Liaoning Province, PR China.

RESUMEN / SUMMARY: - Abstract Objective: The aim of this study was to evaluate the prognostic value of VEGF and IL-8 in pleural effusion in patients with lung cancer. Materials and method: Commercially available ELISA was used to determine VEGF and IL-8 levels. Results: The level of VEGF showed significant correlations with lymph node metastasis and distant metastasis. But, IL-8 was only correlated with lymph node metastasis. Univariate and multivariate analysis revealed elevated VEGF level was an independent predictor of shorter OS and DFS. Conclusion: VEGF could be an important component that contributes to pleural effusion formation, and an important prognostic factor for lung cancer.

[139]
TÍTULO / TITLE: - Interobserver Agreement and Assay Reproducibility of Folate Receptor alpha Expression in Lung Adenocarcinoma: A Prognostic Marker and Potential Therapeutic Target.

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


●●Enlace al texto completo (gratuito o de pago) 5858/arpa.2013-0039-OA

AUTORES / AUTHORS: - Bremer RE; Scoggin TS; Somers EB; O’Shannessy DJ; Tacha DE

INSTITUCIÓN / INSTITUTION: - From the Department of Research & Development, Biocare Medical LLC, Concord, California (Drs Bremer and Tacha and Ms Scoggin); and the Department of Diagnostic Development, Morphotek Inc, Exton, Pennsylvania (Ms Somers and Dr O’Shannessy).

RESUMEN / SUMMARY: - Context.-Lung cancer is the leading cause of cancer deaths in the United States and globally. Folate-targeted drugs are among the promising new targeted therapies for lung cancer, provided predictive biomarkers can be identified for optimal patient selection. Objective.-To evaluate the interobserver agreement and reproducibility of an immunohistochemistry assay for folate receptor alpha as a potential predictive marker for folate-targeted therapies. Design.-Immunohistochemistry using anti-folate receptor alpha antibody 26B3 was performed on formalin-fixed, paraffin-embedded tissues. The M-score, a semiquantitative measure of staining intensity and proportion of tumor cells staining, was determined for each specimen. Interobserver agreement was assessed using lung adenocarcinoma specimens stained at a single site and evaluated by 3 independent pathologists. Interinstrument reproducibility assessed 20 specimens stained by 3 different automated stainers. Interlaboratory agreement was determined on 5 specimens, repeatedly stained on each of 5 days, at 3 different study sites.
Results.-Folate receptor alpha expression was identified in 39 of 54 cases of lung adenocarcinoma (72%) and 4 of 37 cases of lung squamous cell carcinoma (11%). Agreement among 3 pathologists was found in 24 of 26 cases (92%). Interinstrument reproducibility was observed in 19 of 20 cases (95%). Agreement among 3 laboratories was found for 49 of 50 specimens (98%). Conclusions.-Immunostaining of folate receptor alpha in lung adenocarcinomas is reproducible across staining platforms and among laboratories. Agreement among pathologists is achieved using a semiquantitative scoring method. An accurate and convenient method for determining folate receptor alpha expression offers a potentially invaluable tool for selecting patients for folate-targeted therapies.

[140]


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


AUTORES / AUTHORS: - Satouchi M; Okamoto I; Sakai H; Yamamoto N; Ichinose Y; Ohmatsu H; Nogami N; Takeda K; Mitsudomi T; Kasahara K; Negoro S

INSTITUCIÓN / INSTITUTION: - Hyogo Cancer Center, Hyogo, Japan. Electronic address: satouchi@hp.pref.hyogo.jp.

RESUMEN / SUMMARY: - PURPOSE: In a large multicenter international phase III study (CA031) of nab-paclitaxel (nab-P, 130nm albumin-bound paclitaxel particles)+carboplatin © vs solvent-based paclitaxel (sb-P)+C, conducted in 6 countries including Japan, nab-PC produced significantly higher overall response rate (ORR), primary end point compared with sb-PC, and acceptable safety profile. The aim of this analysis was to evaluate the efficacy and tolerability of nab-PC vs sb-PC in Japanese patients with advanced non-small-cell lung cancer (NSCLC) who were enrolled in the CA031 study. PATIENTS AND METHODS: In the CA031 study, a total of 1052 patients were randomized to receive either nab-P 100mg/m2 weekly or sb-P 200mg/m2 every 3 weeks both in combination with C at area under the concentration-time curve (AUC)=6 on day 1 of each 3-week cycle. This analysis included 149 Japanese patients with previously untreated stage IIIB or IV NSCLC. RESULTS: The baseline and histologic characteristics of patients were well balanced between the two arms. ORR was higher with nab-PC vs sb-PC (35% vs 27%; response rate ratio=1.318). Progression-free survival (median 6.9 vs 5.6 months; hazard ratio [HR]=0.845) and overall survival (median 16.7 vs 15.9 months; HR=0.930) were better with nab-PC vs sb-PC. Of the grade >/=3 treatment-related adverse
events, anemia and thrombocytopenia were more common in nab-PC arm, but sensory neuropathy was less common. CONCLUSION: The nab-PC treatment yielded promising results regarding the efficacy endpoint, and it was generally well tolerated as first-line therapy for Japanese patients with advanced NSCLC.

[141]
TÍTULO / TITLE: - Forkhead box protein A1 inhibits the expression of uncoupling protein 2 in hydrogen peroxide-induced A549 cell line.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
••Enlace al texto completo (gratuito o de pago) 10.1007/s12192-013-0433-z
AUTORES / AUTHORS: - Song L; Xu Z; Li L; Hu M; Cheng L; Chen L; Zhang B
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Hunan University of Chinese Medicine, Changsha, Hunan, 410208, China, songlan311492@163.com.
RESUMEN / SUMMARY: - Forkhead box protein A1 (FoxA1) is a transcription factor that is involved in embryonic development and cell differentiation. In this study, we show that hydrogen peroxide (H2O2) treatment upregulated expression of FoxA1 and UCP2 in the A549 cell line. Overexpression of FoxA1 by full-length complementary DNA reduced UCP2 expression, while silencing of FoxA1 expression by small interfering RNA significantly increased UCP2 levels. FoxA1 binds to a site from -919 to -913 bp relative to the UCP2 transcription start site. The overexpression of FoxA1 promoted the DNA binding activity and attenuated the transcription of UCP2 promoter as shown by electromobility shift, chromatin immunoprecipitation assays, and luciferase reporter assay. These data indicate an important role of FoxA1 in regulating expression of UCP2.

[142]
TÍTULO / TITLE: - Long-term Residential Exposure to Air Pollution and Lung Cancer Risk.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
••Enlace al texto completo (gratuito o de pago) 10.1097/EDE.0b013e3182949ae7
AUTORES / AUTHORS: - Hystad P; Demers PA; Johnson KC; Carpiano RM; Brauer M
INSTITUCIÓN / INSTITUTION: - From the aSchool of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; bOccupational Cancer Research Centre, Cancer Care Ontario, Ontario, Canada; cScience Integration Division, Centre for Chronic Disease Prevention and Control, Public Health
RESUMEN / SUMMARY: - BACKGROUND:: There is accumulating evidence that air pollution causes lung cancer. Still, questions remain about exposure misclassification, the components of air pollution responsible, and the histological subtypes of lung cancer that might be produced. METHODS:: We investigated lung cancer incidence in relation to long-term exposure to three ambient air pollutants and proximity to major roads, using a Canadian population-based case-control study. We compared 2,390 incident, histologically confirmed lung cancer cases with 3,507 population controls in eight Canadian provinces from 1994 to 1997. We developed spatiotemporal models for the whole country to estimate annual residential exposure to fine particulate matter (PM2.5), nitrogen dioxide (NO2), and ozone (O3) over a 20-year exposure period. We carried out a subanalysis in urban centers, using exposures derived from fixed-site air pollution monitors, and also examined traffic proximity measures. Hierarchical logistic regression models incorporated a comprehensive set of individual and geographic covariates. RESULTS:: The increase in lung cancer incidence (expressed as fully adjusted odds ratios [ORs]) was 1.29 (95% confidence interval = 0.95-1.76) with a ten-unit increase in PM2.5 (mug/m), 1.11 (1.00-1.24) with a ten-unit increase in NO2 (ppb), and 1.09 (0.85-1.39) with a ten-unit increase in O3 (ppb). The urban monitor-based subanalyses generally supported the national results, with larger associations for NO2 (OR = 1.34; 1.07-1.69) per 10 ppb increase. No dose-response trends were observed, and no clear relationships were found for specific histological cancer subtypes. There was the suggestion of increased risk among those living within 100 m of highways, but not among those living near major roads. CONCLUSIONS:: Lung cancer incidence in this Canadian study was increased most strongly with NO2 and PM2.5 exposure. Further investigation is needed into possible effects of O3 on development of lung cancer.

[143]

TÍTULO / TITLE: - Genetic and epigenetic alterations of the LKB1 gene and their associations with mutations in TP53 and EGFR pathway genes in Korean non-small cell lung cancers.

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


AUTORES / AUTHORS: - Lee SM; Choi JE; Na YK; Lee EJ; Lee WK; Choi YY; Yoon GS; Jeon HS; Kim DS; Park JY
INSTITUCIÓN / INSTITUTION: - Department of Anatomy, School of Medicine, Kyungpook National University, Daegu 700-422, Republic of Korea.
RESUMEN / SUMMARY: - INTRODUCTION: Liver kinase 1 (LKB1) plays a critical barrier role in lung tumorigenesis by controlling initiation, differentiation and metastasis. We searched for genetic and epigenetic alterations of the LKB1 gene in Korean non-small cell lung cancers (NSCLCs) and correlated the results with clinicopathological features. We also investigated the relationship between genetic and epigenetic alterations of LKB1 and mutations in the TP53 gene and epidermal growth factor receptor (EGFR) pathway genes. METHODS: A total of 159 NSCLCs were analyzed for loss of heterozygosity (LOH) at microsatellite loci D19S886, and D19S878. Mutations and methylation status of LKB1 were examined by direct sequencing and a methylation-specific polymerase chain reaction, respectively. RESULTS: A somatic mutation was found in one of the 159 tumors. LOH and promoter methylation was detected in 19.5% (31/159) and 13.2% (21/159) of the tumors, respectively. Four of the 159 tumors had concomitant LOH and methylation of LKB1. In total, 30.2% of the 159 NSCLCs harbored LKB1 LOH or promoter methylation, which were correlated with down-regulation of gene expression. LKB1 LOH was more frequent in males, smokers, and tumors with a TP53 mutation than in females, never-smokers, and tumors without a TP53 mutation, respectively. However, no significant correlation between LKB1 alterations and mutations in EGFR pathway genes was found. CONCLUSION: These results suggest that the prevalence of LKB1 genetic and epigenetic alterations in NSCLCs vary depending on patient ethnicity. Our results show that LKB1 alterations often occur simultaneously with mutations in EGFR pathway genes.

[144]

TÍTULO / TITLE: - C-X-C motif receptor 2, endostatin and proteinase-activated receptor 1 polymorphisms as prognostic factors in NSCLC.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Uzunoglu FG; Yavari N; Bohn BA; Nentwich MF; Reeh M; Pantel K; Perez D; Tsui TY; Bockhorn M; Mann O; Izbicki JR; Wikman H; Vashist YK

INSTITUCIÓN / INSTITUTION: - Department of General, Visceral and Thoracic Surgery, University Medical Center of Hamburg-Eppendorf, Germany.
RESUMEN / SUMMARY: - The progress of non-small cell lung cancer (NSCLC) is dependent on sufficient angiogenesis. Thrombin induced activation of proteinase-activated receptor 1 (PAR-1) on platelets leads to platelet secretion.
and aggregation. This influences cell survival, apoptosis and angiogenesis by the release of VEGF and Endostatin (ES), a potent angiogenesis inhibitor. Interleukin-8 (IL-8) induces tumor angiogenesis independent of the VEGF pathway through the chemokine C-X-C motif receptor 2 (CXCR-2). Our purpose was to evaluate germline polymorphisms of these potential therapy targets as prognostic markers for disease free survival (DFS) and overall survival (OS) in surgically treated NSCLC patients. In total 209 Caucasian patients, treated between 1996 and 2011, were included in this study. Genomic DNA was extracted from peripheral blood leucocytes. Genotyping of CXCR-2 +1208 C>T and +785 C>T, PAR-1 -506 Ins/del and -14 IvS A>T and ES +4349 G>A was performed by TaqMan® genotyping assays or by polymerase chain reaction (PCR) followed by capillary electrophoresis. Chi-square test, Kaplan-Meier estimator and cox regression hazard model were used to assess the prognostic value of selected polymorphisms. The PAR-1 -14 IvS A/A genotype was associated with advanced tumor stages (p=0.024) and, in univariate analysis, with shorter median OS in squamous cell lung carcinoma (SqCC, p=0.035). The CXCR-2 +1208T/T genotype was associated with aggressive tumor biology (p=0.038), and shorter DFS and OS (p=0.018, p=0.021) in NSCLC and especially in SqCC a negative predictor for DFS and OS (p=0.045, p=0.041). Genotyping of the CXCR-2 +1208 C>T polymorphism could be a useful tool to identify high-risk SqCC subgroups.

[145]
**TÍTULO / TITLE:** CD4/CD8 Double-negative Mycosis Fungoides Mimicking Erythema Gyratum Repens in a Patient with Underlying Lung Cancer.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 2340/00015555-1618
**AUTORES / AUTHORS:** Nagase K; Shirai R; Okawa T; Inoue T; Misago N; Narisawa Y
**INSTITUCIÓN / INSTITUTION:** Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Saga University, Nabeshima 5-1-1, Saga 849-8501, Japan. kotaro@nagase-skin.com.
**RESUMEN / SUMMARY:** Abstract is missing (Letter).

[146]
**TÍTULO / TITLE:** Methylene blue-mediated photodynamic therapy enhances apoptosis in lung cancer cells.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
ENLACE AL TEXTO COMPLETO (GRATUITO O DE PAGO) 3892/or.2013.2494

AUTORES / AUTHORS: - Lim EJ; Oak CH; Heo J; Kim YH

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology and Immunology, Kosin University College of Medicine, Busan, Republic of Korea.

RESUMEN / SUMMARY: - Combined treatment with a photosensitizer and iodide laser [photodynamic therapy (PDT)] has improved the outcome of various cancers. In this study, we investigated the effects of using the photosensitizer methylene blue (MB) in PDT in human lung adenocarcinoma cells. We found that MB enhances PDT-induced apoptosis in association with downregulation of anti-apoptotic proteins, reduced mitochondrial membrane potential (MMP), increased phosphorylation of the mitogen-activated protein kinase (MAPK) and the generation of reactive oxygen species (ROS). In MB-PDT-treated A549 cells, we observed PARP cleavage, procaspase-3 activation, downregulation of the anti-apoptotic proteins Bcl-2 and Mcl-1, and the reduction of mitochondrial membrane potential (MMP). Western blot data showed that phosphorylation of p38 was increased in MB-PDT-treated A549 cells, indicating that several signaling molecules participate in the apoptotic cascade. Our data also showed that apoptotic cell death in MB-PDT-treated cells occurred through a series of steps beginning with the photochemical generation of ROS. Demonstrating the role of ROS, pretreatment of A549 cells with the antioxidant N-acetylcysteine (NAC) followed by MB-PDT resulted in increased cell viability and reduced proteolytic cleavage of PARP.

[147]

TÍTULO / TITLE: - TMEPAI regulates EMT in lung cancer cells by modulating the ROS and IRS-1 signaling pathways.

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


AUTORES / AUTHORS: - Hu Y; He K; Wang D; Yuan X; Liu Y; Ji H; Song J

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, PR China.

RESUMEN / SUMMARY: - The epithelial-mesenchymal transition (EMT) has been implicated in various pathophysiological processes, including cancer cell migration and distal metastasis. Reactive oxygen species (ROS) and insulin receptor substrate-1 (IRS-1) are important in cancer progression and regulation of EMT. To explore the biological significance and regulatory mechanism of EMT, we determined the expression, the biological function and the signaling pathway of prostate transmembrane protein, androgen induced-1 (TMEPAI), during the induction of EMT and cell migration. Transforming growth factor (TGF)-beta1 significantly upregulated the expression of TMEPAI during EMT in
human lung adenocarcinoma. Depletion of TMEPAI abolished TGF-beta1-induced downregulation of ferritin heavy chain and the subsequent generation of ROS, thus suppressing TGF-beta1-induced EMT and cell migration. In addition, increased ROS production and overexpression of TMEPAI downregulated the level of IRS-1. Both the addition of H2O2 and IRS-1 small interfering RNA rescued the ability of TGF-beta1 to induce EMT in TMEPAI-depleted cells. Remarkably, the levels of TMEPAI in lung tumor tissues are very high, whereas its expression in normal lung epithelium is very low. Moreover, TMEPAI expression was positively correlated with the cell mesenchymal phenotype and migration potential. Our work reveals that TMEPAI contributes to TGF-beta1-induced EMT through ROS production and IRS-1 downregulation in lung cancer cells.

[148]

**TÍTULO / TITLE:** Acquired Substrate Preference for GAB1 Bestows Transforming Activity to ERBB2 Lung Cancer Mutants.

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

**REVISTA / JOURNAL:** J Biol Chem. 2013 Apr 23.

**AUTORES / AUTHORS:** Fan YX; Wong L; Marino MP; Ou W; Shen Y; Wu WJ; Wong KK; Reiser J; Johnson GR

**INSTITUCIÓN / INSTITUTION:** Food and Drug Administration, United States;

**RESUMEN / SUMMARY:** Activating mutations in the alphaC-beta4 loop of the ERBB2 kinase domain, such as ERBB2YVMA and ERBB2G776VC, have been identified in human lung cancers and found to drive tumor formation. Here, we observe that the docking protein GAB1 is hyper-phosphorylated in carcinomas from transgenic mice and in cell lines expressing these ERBB2 cancer mutants. Using dominant negative GAB1 mutants lacking canonical tyrosine residues for SHP2 and PI3K interactions or lentiviral shRNA that targets GAB1, we demonstrate that GAB1 phosphorylation is required for ERBB2 mutant-induced cell signaling, cell transformation, and tumorigenesis. An enzyme kinetic analysis comparing ERBB2YVMA to wild type using physiologically relevant peptide substrates reveals that ERBB2YVMA kinase adopts a striking preference for GAB1 phosphorylation sites as evidenced by ~150-fold increases in the specificity constants (kcat/Km) for several GAB1 peptides, and this change in substrate selectivity was predominantly attributed to the peptide binding affinities as reflected by the apparent Km values. Further, we demonstrate that ERBB2YVMA phosphorylates GAB1 protein ~70-fold faster than wild type ERBB2 in vitro. Notably, the mutation does not significantly alter the Km for ATP or sensitivity to lapatinib, suggesting that, unlike EGFR lung cancer mutants, the ATP binding cleft of the kinase is not significantly changed.
Taken together, our results indicate that the acquired substrate preference for GAB1 is critical for the ERBB2 mutant-induced oncogenesis.

[149]

TÍTULO / TITLE: - Preoperative red cell distribution width in patients undergoing pulmonary resections for non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Warwick R; Mediratta N; Shackcloth M; Shaw M; McShane J; Poullis M
INSTITUCIÓN / INSTITUTION: - Department of Cardiac Surgery, Liverpool Heart and Chest Hospital, Liverpool, UK.
RESUMEN / SUMMARY: - OBJECTIVES: Red cell distribution width (RDW) has been identified as an independent risk factor with regard to prognosis in patients with cardiac disease. We sought to investigate the association of RDW in patients undergoing lung resections for non-small-cell lung cancer with respect to in-hospital morbidity, mortality and long-term survival. METHODS: Analysis of consecutive patients on a validated prospective thoracic surgery database was performed for those undergoing potentially curative resections at a single institution. Univariate and multivariate analyses were performed for postoperative invasive and non-invasive ventilation, superficial wound infections, length of hospital stay, in-hospital mortality and long-term survival. RESULTS: Overall mortality was 1.9% for all cases (n = 917). The median follow-up was 6.8 years. Univariate analysis demonstrated that RDW has a significant effect on hospital length of stay (P < 0.001), in-hospital mortality rates (P < 0.001), postoperative invasive and non-invasive ventilation (P < 0.001), superficial wound infections (P = 0.06) and long-term survival (P < 0.0001). Multivariate analysis revealed that RDW is a significant factor determining postoperative invasive and non-invasive ventilation, superficial wound infections, length of hospital stay, in-hospital mortality and long-term survival. Confounding factor analysis revealed that in the absence of anaemia, RDW was still a significant factor in the above analysis. CONCLUSIONS: RDW is a significant factor after risk adjustment, determining in-hospital morbidity, mortality and long-term survival in patients post-potentially curative resections for non-small-cell lung cancer. Further work is needed to elucidate the exact mechanism of RDW impact on in-hospital morbidity, mortality and long-term survival. We speculate that subtle bone marrow dysfunction may be an issue.

[150]
Serial Changes in Pulmonary Function after Video-Assisted Thoracic Surgery Lobectomy in Lung Cancer Patients.

Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1055/s-0033-1343980

Seok Y; Jheon S; Cho S

Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoungnam-si, Gyeonggi-do, Republic of Korea.

Background The aim of this study is to evaluate the serial changes in pulmonary function and the recovery time for the observed postoperative values to reach the predicted postoperative values after video-assisted thoracic surgery (VATS) lobectomy for lung cancer.

Patients and Methods Patients undergoing VATS lobectomy for lung cancer were prospectively evaluated using complete preoperative and repeated postoperative pulmonary function tests (PFTs). The parameters of PFT at each time were compared according to the resected lobe as well as the presence of chronic obstructive pulmonary disease (COPD). The differences between the observed and predicted postoperative values of PFT and the recovery time for the observed values to reach the predicted values were calculated.

Results Seventy-two patients (33 men, 39 women; mean age: 63.9 years) received complete pre- and postoperative regular PFT after undergoing VATS lobectomy. Of these patients, 24 (33.3%) patients satisfied the criteria for COPD. During the immediate postoperative period, forced vital capacity (FVC) percentage of the patients who received right lower lobectomy patients was decreased most significantly compared with the preoperative values. Compared with the upper lobectomy (UL) group, the lower lobectomy (LL) group showed a significant decrease of FVC% up to 6 months. However, there was no significant difference at 12 months after surgery. Patients with COPD showed little reduction of FEV1% that persisted significantly until 1 month after the surgery in both UL and LL groups. The recovery time was shortest in the left lower lobectomy patients, and it was shorter in the LL group than in the UL group.

Conclusions Postoperative pulmonary function and recovery time were different depending on the lobe resected and presence of COPD in VATS lobectomy patients. The information obtained from postoperative serial PFT would help accurately predict postoperative pulmonary function changes and recovery time after VATS lobectomy for lung cancer.

Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fiala O; Pesek M; Finek J; Benesova L; Bortlicek Z; Minarik M
INSTITUCIÓN / INSTITUTION: - Department of Oncology and Radiotherapy, Medical School and Teaching Hospital Pilsen, Charles University, Prague, Czech Republic. fiala.o@centrum.cz
RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene (KRAS) and phosphatidylinositide-3-kinase catalytic subunit-alpha (PIK3CA) mutations are biomarkers used for the prediction of efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in advanced non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: In total, 223 patients with advanced-stage squamous cell NSCLC were tested; 179 patients were treated with EGFR-TKIs. Genetic testing was performed using a combination of denaturing capillary electrophoresis and direct Sanger sequencing. RESULTS: EGFR mutations were detected in 7.2%; KRAS mutations in 7.4% and PIK3CA mutations in 3.8% of patients. No correlation of EGFR or PIK3CA mutation status with progression-free survival (PFS) (p=0.425; p=0.197), nor overall survival (OS) (p=0.673; p=0.687), was observed. KRAS mutations correlated with shorter OS (p=0.039), but not with PFS (p=0.120). CONCLUSION: We did not observe any role of EGFR, KRAS, PIK3CA mutations in prediction of EGFR-TKIs efficacy in patients with advanced-stage squamous cell NSCLC.

[152]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt200
AUTORES / AUTHORS: - Divisi D; De Vico A; Ferrari V; Crisci R
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, University of L’Aquila, “G. Mazzini” Hospital, Teramo, Italy.

[153]
TÍTULO / TITLE: - Emergency department visits after hours by lung cancer patients in Japan.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s00520-013-1814-7
**AUTORES / AUTHORS:** - Minami S; Yamamoto S; Ogata Y; Takeuchi Y; Hamaguchi M; Koba T; Futami S; Nishijima Y; Komuta K

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka, 543-0035, Japan, seigominami@oph.gr.jp.

**RESUMEN / SUMMARY:** - PURPOSE: The aims of this study were to clarify frequency with which Japanese lung cancer patients visited an emergency department (ED) after hours and their final outcome. METHODS: This is a retrospective and single institutional study. We reviewed medical records of patients who died of lung cancer from January 2008 to June 2012 at Osaka Police Hospital who had been followed up since diagnosis of lung cancer until death. We compared patients who had visited the ED after hours on weekdays, weekends, or holidays over their lives with cancer (ED visitors) and patients who had never visited the ED (non-ED visitors). RESULTS: Overall, 245 patients met the inclusion criteria for analysis. There were 149 after hours ED visits by 106 lung cancer patients. Mean number of ED visits was 0.6 for all patients. Median interval from ED visit to death was 49 days. The most common chief compliant for these patients was respiratory problems (37.6 %). Most patients visited the ED during chemotherapy (32.9 %) or for best supportive care (42.3 %). Directly after ED visits, 56.4 % of ED visitors were finally hospitalized. In a multivariate analysis, performance status (PS) (odds ratio [OR]: 11.2, 95 % confidence interval [CI]: 2.1-59.0, p = 0.004) and cancer stage (OR: 0.003, 95 % CI: 0.0006-0.014, p < 0.001) at diagnosis were statistically associated with ED visits after hours. CONCLUSIONS: Japanese patients with lung cancer frequently visit ED after hours. An ED visit is itself an indicator of poor prognosis.

[154]

**TÍTULO / TITLE:** - RRM2 Regulates Bcl-2 in Head and Neck and Lung Cancers: A Potential Target for Cancer Therapy.

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

**REVISTA / JOURNAL:** - Clin Cancer Res. 2013 May 29.

[●●Enlace al texto completo (gratuito o de pago) 1158/1078-0432.CCR-13-0073]

**AUTORES / AUTHORS:** - Rahman MA; Amin AR; Wang D; Koenig L; Nannapaneni S; Chen Z; Wang Z; Sica GL; Deng X; Chen ZG; Shin DM

**INSTITUCION / INSTITUTION:** - Hematology and Medical Oncology, Emory University, Winship Cancer Institute.

**RESUMEN / SUMMARY:** - PURPOSE: Ribonucleotide reductase subunit M2 (RRM2) plays an active role in tumor progression. Recently, we reported that depletion of RRM2 by systemic delivery of a nanoparticle carrying RRM2-specific siRNA suppresses head and neck tumor growth. The aim of this study
is to clarify the underlying mechanism by which RRM2 depletion

EXPERIMENTAL DESIGN: siRNA-mediated gene silencing was performed to downregulate RRM2. Immunoblotting, RT-PCR, confocal microscopy, tissue fractionation, gene overexpression and knockdown were employed to analyze critical apoptosis signaling. Conventional immunohistochemistry (IHC) and quantum dot-based IHF were applied to detect RRM2 and Bcl2 expression and localization in tissue samples from patients and mice. RESULTS: Knockdown of RRM2 led to apoptosis through the intrinsic pathway in head and neck squamous cell carcinoma (HNSCC) and non-small cell lung cancer (NSCLC) cell lines. We demonstrated that Bcl-2 is a key determinant controlling apoptosis, both in vitro and in vivo and that RRM2 depletion significantly reduces Bcl-2 protein expression. We observed that RRM2 regulates Bcl-2 protein stability, with RRM2 suppression leading to increased Bcl-2 degradation, and identified their co-localization in HNSCC and NSCLC cells. In a total of 50 specimens each from HNSCC and NSCLC patients, we identified the co-localization of Bcl-2 and RRM2 and found a significant positive correlation between their expression in HNSCC (R=0.98, p<0.0001) and NSCLC (R=0.92, p<0.0001) tumor tissues. CONCLUSIONS: Our novel findings add to the knowledge of RRM2 in regulating expression of the anti-apoptotic protein Bcl-2 and reveal a critical link between RRM2 and Bcl-2 in apoptosis signaling.

[155]

TÍTULO / TITLE: Completing the audit cycle improves surgical standards in lung cancer: why do some patients still not receive the best care?

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


AUTORES / AUTHORS: Hagan ME; Williams ST; Socci L; Malik M; Internullo E; Martin-Ucar AE

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Nottingham University Hospitals, Nottingham, United Kingdom.

RESUMEN / SUMMARY: INTRODUCTION: Intraoperative gold standards in the management of lung cancer include performing anatomical resection and mediastinal lymphadenectomy. Our aim was to measure improvement in quality of surgery by reauditing anatomical resection and lymph node excision in patients undergoing lung cancer surgery as per gold standards. METHODS: A complete audit cycle was performed—an initial retrospective analysis of 100 consecutive patients with primary lung cancer operated on by a single surgeon (July 2009-October 2010), followed by a prospective reaudit of 102 patients (November 2010-October 2011). Clinical and pathological data were collected
from clinical notes, surgical database, and histopathology reports. Univariate and multivariate analyses were performed to identify further areas of potential improvement. RESULTS: The number of nonanatomical resections dropped from 12% to 6% (p = not significant). The rate of performing excision of at least 1, 2, and 3 mediastinal (N2) lymph node stations improved from 86% to 91%, 63% to 77%, and 40% to 63%, respectively (p = 0.003). On multivariate analysis, failure to perform anatomical resection was related to use of video assisted thoracic surgery (VATS) techniques, previous malignancy, and high-predicted surgical risk by European Society Objective Score .01. Less complete intraoperative lymph node excision was associated with cases performed by VATS and in octogenarians. CONCLUSIONS: There is continued adherence to the guidelines, when considering cases in terms of anatomical resections, and marked improvement in complying with the gold standards for lymph node excision. The use of the audit tool has contributed to improved quality of surgical care in patients operated for lung cancer.

[156]

TÍTULO / TITLE: - Hu/elav RNA-binding protein HuR regulates parathyroid hormone related peptide expression in human lung adenocarcinoma cells.
RESENMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lauriola L; Serini S; Granone P; Lanza P; Martini M; Calviello G; Ranelletti FO
INSTITUCIÓN / INSTITUTION: - Institute of Pathologic Anatomy, Universita Cattolica del S. Cuore, Roma, Italy.
RESEMNEN / SUMMARY: - In 54 stage I and II human lung adenocarcinomas, HuR and PTHrP levels were positively correlated and the PTHrP-HuR status of the tumor was an independent prognostic marker of the clinical outcomes of patients. The possibility that HuR could upregulate PTHrP expression in lung adenocarcinoma was investigated by immunohistochemical, Western blot and RT-PCR analyses in HCC44 and DV90 human lung adenocarcinoma cell lines. In both cell lines, knockdown of HuR by specific siRNAs reduced PTHrP mRNAs and both cellular and secreted protein. Moreover, it inhibited cell growth and induced cell apoptosis, as revealed by the increase of caspase-3 activity. These effects were partially rescued by the addition of exogenous PTHrP mRNAs and both cellular and secreted protein. Moreover, it inhibited cell growth and induced cell apoptosis, as revealed by the increase of caspase-3 activity. These effects were partially rescued by the addition of exogenous PTHrP (1-34). Analysis by actinomycin D assay revealed that in both cell lines HuR silencing produced a decrease of PTHrP mRNA half-life by about 70%. These findings add PTHrP to the list of lung cancer-associated genes, whose mRNA is stabilized by HuR.

[157]
PTTG1 Promotes Migration and Invasion of Human Non-small Cell Lung Cancer Cells and is modulated by miR-186.

RESUMEN / SUMMARY: Deeper mechanistic understanding of non-small cell lung cancer (NSCLC), a leading cause of total cancer-related deaths, may facilitate the establishment of more effective therapeutic strategies. In this study, pituitary tumor transforming gene (PTTG1) expression was associated with lymph node and distant metastasis in patients with NSCLC and was correlated with patient survival. Reduction of PTTG1 by siRNA inhibits the migration and invasion of NSCLC cells by mediating MMPs expression. To the best of our knowledge, this study is the first to report that PTTG1 promotes EGF-induced the phosphorylation of LIN-11, Isl1, and MEC-3 protein domain kinase and cofilin, a critical step in cofilin recycling and actin polymerization. Additionally, EGF-induced Akt phosphorylation was suppressed through knockdown of PTTG1. Interestingly, miR-186 can modulate PTTG1 protein expression. As observed from the animal experiment in the present study, knockdown of PTTG1 through siRNA and overexpression of miR-186 inhibited invasive activity of NSCLC cells toward the SCID mice lung. In summary, our in vitro and in vivo results indicate that PTTG1 modulated by miR-186 has an important function in NSCLC invasion/metastasis. This study identified both PTTG1 and miR-186 as potential anti-invasion targets for therapeutic intervention in NSCLC.

MicroRNA-106b-25 cluster targets beta-TRCP2, increases the expression of Snail and enhances cell migration and invasion in H1299 (non small cell lung cancer) cells.

RESUMEN / SUMMARY: Lung cancer causes high mortality without a declining trend and non small cell lung cancer represents 85% of all pulmonary
MicroRNAs (miRNAs) serve as fine regulators of proliferation, migration, invasion/metastasis and angiogenesis of normal and cancer cells. Using TargetScan6.2, we predicted that the ubiquitin ligase, beta-TRCP2, could be a target for two of the constituent miRNAs of the miR-106b-25 cluster (miR-106b and miR-93). We generated a stable clone of miR-106b-25 cluster (CL) or the empty vector (EV) in H1299 (non small cell lung cancer) cells. The expression of beta-TRCP2 mRNA was significantly lower in CL than that in EV cells. Transient expression of miR-93 but not antimiR-93 decreased the expression of beta-TRCP2 mRNA in H1299 cells. beta-TRCP2-3'UTR reporter assay revealed that its activity in CL cells was only 60% of that in EV cells. Snail protein expression was higher in CL than that in EV cells and H1299 cells exhibited an increase in the expression of Snail upon transient transfection with miR-93. miR-106b-25 cluster-induced migration of CL measured by scratch assay was more than that in EV cells and no significant difference in migration was observed between antimiR-93-transfected H1299 cells and the corresponding control-oligo-transfected cells. miR-106b-25 cluster-induced migration of CL cells was again confirmed in a Boyden chamber assay without the matrigel. CL cells were more invasive than EV cells when assessed using Boyden chambers with matrigel but there were no significant changes in the cell viabilities between EV and CL cells. Colony formation assay revealed that the CL cells formed more number of colonies than EV cells but they were smaller in size than those formed by EV cells. The supernatant from CL cells was more effective than that from EV cells in inducing tube formation in endothelial cells. Taken together, our data indicate that miR-106b-25 cluster may play an important role in the metastasis of human non-small cell lung cancer cells by directly suppressing the beta-TRCP2 gene expression with a consequent increase in the expression of Snail.

[159]

TÍTULO / TITLE: - Prognostic and predictive value of estrogen receptor 1 expression in completely resected non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1002/ijc.28209
AUTORES / AUTHORS: - Brueckl WM; Al-Batran SE; Ficker JH; Claas S; Atmaca A; Hartmann A; Rieker RJ; Wirtz RM
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, 3, Klinikum Nurnberg, Nuremberg, Germany; Comprehensive Cancer Center (CCC) Erlangen-Nuremberg, Erlangen, Germany; Paracelsus Medical University Nuremberg, Nuremberg, Germany.
RESUMEN / SUMMARY: - Adjuvant chemotherapy (ACT) leads to a modest improvement in survival among patients with completely resected non-small cell
lung cancer (NSCLC) but molecular predictors are still rare. Publicly available gene microarray, clinical and follow-up data from two different studies on early-stage NSCLC were used to determine the expression of estrogen receptor 1 (ESR1). Expression values were calculated against clinical and survival data in a training set (n = 138) and a test set (subpopulation from the adjuvant JBR.10 study) allowing the determination of the prognostic effect of ESR1 in the observational arm as well as the predictive effect of ESR1 regarding ACT. Data were well balanced in terms of ESR1 expression. ESR1 high expression was of significant positive prognostic value in the training set and this could be confirmed in the test set cohort (hazard ratio for overall survival 0.248, 95% confidence interval: 0.088-0.701; p = 0.008). Additionally, ESR1 low tumors showed a benefit from ACT in terms of 5-year survival (33.3% observation arm and 77.8% ACT arm; p = 0.003), whereas patients with ESR1 high tumors did not have any benefit from ACT (test of interaction p = 0.024). ESR1 is an independent positive prognostic factor for survival in early-stage NSCLC patients. Patients with ESR1 high tumors did not benefit from ACT.
respectively. There was no statistically significant difference in the occurrence rate of grades 3 and 4 myelotoxicity between the two groups. However, there was a significant difference in the occurrence rate of grades 3 and 4 gastrointestinal reactions and peripheral neurotoxicity between the two groups (P < 0.05). A regime combining Pemetrexed and Oxaliplatin was marginally effective and well tolerated in patients with stage IIIb or IV lung adenocarcinoma who have received Erlotinib as second-line treatment.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago)
AUTORES / AUTHORS: - Backhus L; Puneet B; Bastawrous S; Mariam M; Michael M; Varghese T Jr
INSTITUCIÓN / INSTITUTION: - Surgery Service, VA Puget Sound Health Care System, Seattle, WA; Division of Cardiothoracic Surgery, Department of Surgery, University of Washington School of Medicine, Seattle, WA. Electronic address: lbackhus@u.washington.edu.
RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer deaths in the United States. Despite many advances in treatment, surgery remains the preferred treatment modality for patients presenting with early stage disease. Imaging is critical in the preoperative evaluation of these patients being considered for a curative resection. Advanced imaging techniques provide valuable information, including primary diagnostics, staging, and intraoperative localization for suspected lung cancer. Knowledge of surgical implications of imaging findings can aid both radiologists and surgeons in delivering safe and effective care.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1002/gcc.22065
AUTORES / AUTHORS: - Lloyd SM; Lopez M; El-Zein R
INSTITUCIÓN / INSTITUTION: - Dorothy I. Height Center for Health Equity and Evaluation Research, Division of Cancer Prevention and Population Science, The UT MD Anderson Cancer Center, Houston, TX.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of all cancer-related deaths in the US. The need to develop more accurate cancer risk assessment tools is imperative to improve the ability to identify individuals at greatest risk of developing disease. The Cytokinesis-Blocked Micronucleus Cytome Assay (CBMNcyt) presents a sensitive and specific method of assessing DNA damage. We have previously reported that this assay is sensitive to genetic damage caused by the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and that binucleated cells with micronuclei, nucleoplasmic bridges and nuclear buds are strong predictors of lung cancer risk. The current study confirmed our previous findings and sought to identify the specific chromosomes involved in lung carcinogenesis. Spectral karyotyping was conducted on a subset of lung cancer cases [n = 116] and cancer-free controls [n = 126] with the highest CBMNcyt endpoints, on baseline and NNK-treated blood lymphocytes. After adjusting for age, gender, race/ethnicity, smoking status, and pack and smoke years, consistent significant associations between chromosome: 9, 19, 22, X, at baseline; chromosome: 3, 4, and 16 after NNK-induction; and chromosome: 1, 13, and 17 at both baseline and NNK-induction; and lung cancer risk (all P </= 0.05) were observed. Several of these chromosomes harbor critical genes involved in lung carcinogenesis, such as the FHIT gene, CDKN2A, PADPRP, and TP53. Our results indicate that the CBMNcyt assay when used in conjunction with other cytogenetic methodologies can increase our ability to identify specific chromosomal regions associated with DNA damage, thereby improving our understanding of the underlying mechanisms involved in individual cancer predisposition. © 2013 Wiley Periodicals, Inc.

[163]

TÍTULO / TITLE: - Early-stage pulmonary adenocarcinoma (T1N0M0): a clinical, radiological, surgical, and pathological correlation of 104 cases. The MD Anderson Cancer Center Experience.

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


●●Enlace al texto completo (gratuito o de pago) 1038/modpathol.2013.33

AUTORES / AUTHORS: - Weissferdt A; Kalhor N; Marom EM; Benveniste MF; Godoy MC; Correa AM; Swisher SG; Moran CA

INSTITUCIÓN / INSTITUTION: - Department of Pathology, MD Anderson Cancer Center, Houston, TX, USA.
RESUMEN / SUMMARY: - The recent proposal for histological subtyping of pulmonary adenocarcinoma by predominant pattern and introduction of the terms adenocarcinoma in situ and minimally invasive adenocarcinoma to replace the term bronchioloalveolar carcinoma by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society has led us to conduct a study of 104 patients with early-stage primary pulmonary adenocarcinoma (T1N0M0), with a view to histological subtype as defined by the new proposal and clinical outcome. None of the clinical parameters of our patient population (type of surgery, age, gender, tumor size, and comorbidities) showed any statistically significant correlation with outcome, except for associated malignancies, which not surprisingly appeared to have a negative impact on survival. In addition, statistical analyses of the histological characteristics to include tumor differentiation and the percentage of a lepidic or bronchioloalveolar component did not show any statistically significant values in terms of survival. Our results failed to show any statistically significant difference of survival between those T1N0M0 adenocarcinomas with a lepidic component and those without, thus questioning the use of terms such as in situ or minimally invasive adenocarcinoma. On the basis of our results, we consider that the outcome for patients with T1N0M0 disease is still best determined by appropriate staging rather than by changes in the pathology nomenclature of adenocarcinoma. Modern Pathology advance online publication, 29 March 2013; doi:10.1038/modpathol.2013.33.

[164]

TÍTULO / TITLE: - Overexpression of response gene to complement 32 (RGC32) promotes cell invasion and induces epithelial-mesenchymal transition in lung cancer cells via the NF-kappaB signaling pathway.

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


AUTORES / AUTHORS: - Sun Q; Yao X; Ning Y; Zhang W; Zhou G; Dong Y

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai, 200433, People’s Republic of China.

RESUMEN / SUMMARY: - Response gene to complement 32 (RGC32) is a novel cellular protein that has been reported to be expressed aberrantly in multiple types of human tumors. However, the role of RGC32 in cancer is still controversial, and the molecular mechanisms by which RGC32 contributes to the development of cancer remain largely unknown. In the present study, we constructed a recombinant expression vector pCDNA3.1-RGC32 and transfected it into human lung cancer A549 cells. Stable transformanded cells
were identified by real-time PCR and Western blot analysis. Functional analysis showed that forced overexpression of RGC32 increased invasive and migration capacities of lung cancer cells in vitro, and induced the acquisition of epithelial-mesenchymal transition (EMT) phenotype, as demonstrated by the spindle-like morphology, downregulation of E-cadherin, and upregulation of Vimentin, Fibronectin, Snail and Slug. Also, overexpression of RGC32 increased expression and activities of matrix metalloproteinase (MMP)-2 and MMP-9 in A549 cells. Furthermore, the downregulation of E-cadherin induced by RGC32 was remarkably attenuated by nuclear factor-kappaB (NF-kappaB) inhibitor BAY 11-7028 and small interfering RNA targeting NF-kappaB p65, suggesting a role of the NF-kappaB signaling pathway in RGC32-induced EMT. Taken together, our data suggest that RGC32 promotes cell migration and invasion and induces EMT in lung cancer cells via the NF-kappaB signaling pathway.

[165] 
TÍTULO / TITLE: - Inhibition of Platelet-Derived Growth Factor Receptor alpha by MEDI-575 Reduces Tumor Growth and Stromal Fibroblast Content in a Model of Non-Small Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Laing N; McDermott B; Wen S; Yang D; Lawson D; Collins M; Reimer C; Hall PA; Andersen H; Snaith M; Wang X; Bedian V; Cao ZA; Blakey D
INSTITUCIÓN / INSTITUTION: - AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451. Naomi.laing@astrazeneca.com.
RESUMEN / SUMMARY: - Platelet-derived growth factor receptor alpha (PDGFRalpha) is a receptor tyrosine kinase that promotes cell survival and is expressed in both the tumor and the stromal components of human cancers. We have developed a fully human monoclonal antibody, MEDI-575, that selectively binds to human PDGFRalpha with high affinity, with no observable affinity for murine PDGFRalpha. To more fully characterize the role of PDGFRalpha in the regulation of tumor stroma, we evaluated the in vivo antitumor effects of MEDI-575 in tumor-bearing severe combined immunodeficient (SCID) mice and in genetically altered SCID mice expressing human PDGFRalpha in place of murine PDGFRalpha. We used the Calu-6 non-small cell lung cancer model because it lacks an in vitro proliferative response to PDGFRalpha activation. Antitumor activity was observed when the study was performed in mice expressing the human receptor, but no activity was observed in the mice expressing the murine receptor. Immunohistologic analysis of the tumors from mice expressing human PDGFRalpha showed a highly significant
reduction in stromal fibroblast content and only minor changes in tumor proliferative index in tumors exposed to MEDI-575 compared with the results seen in vehicle-treated tumors or in tumors from mice expressing murine PDGFRalpha. Additional in vitro studies indicated that exposure of primary cancer-associated fibroblasts to MEDI-575 can directly affect proliferation and key signaling pathways in these cells. These results highlight the potential for observing antitumor activity with MEDI-575 through modulation of the stromal component of tumors and confirm that the PDGFRalpha pathway can play a role in maintaining a tumor microenvironment conducive to tumor growth.

[166]

**TÍTULO / TITLE:** Aerosol delivery of eukaryotic translation initiation factor 4E-binding protein 1 effectively suppresses lung tumorigenesis in K-ras mice.

**RESUMEN / SUMMARY:** Conventional radiotherapy or chemotherapy for the long-term survival of patients with lung cancer is still difficult for treatment in metastatic and advanced tumors. Therefore, the safe and effective approaches to the treatment of lung cancer are needed. In this study, the effect of delivered eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) on lung cancer progression was evaluated. Recombinant adeno-associated virus (rAAV)-M3/4E-BP1 was delivered into 6-week-old K-rasLA1 lung cancer model mice through a nose-only inhalation system twice a week for 4 weeks. Long-term repeated delivery of 4E-BP1 effectively reduced tumor progression in the lungs of K-rasLA1 mice. Reduction of eIF4E by overexpression of 4E-BP1 resulted in suppression of cap-dependent protein expression of basic fibroblast growth factor (bFGF or FGF-2) and vascular endothelial growth factor (VEGF). In addition, delivered 4E-BP1 inhibited the proliferation of lung cancer cells in K-rasLA1 mice model. Our results suggest that long-term repeated viral delivery of 4E-BP1 may provide a useful tool for designing lung cancer treatment. Cancer Gene Therapy advance online publication, 3 May 2013; doi:10.1038/cgt.2013.24.
TÍTULO / TITLE: - Curative radiotherapy using different radiation techniques for isolated lung metastasis from colorectal cancer.

RESUMEN / SUMMARY: - AIMS AND BACKGROUND: Surgical resection remains the mainstay for the treatment of colorectal lung metastasis, but a group of patients who are medically inoperable or unsuitable for surgery are treated with radiotherapy. The purpose of this multi-institutional study was to evaluate the clinical outcome and investigate the prognostic factors affecting local control and survival in this subset of patients. METHODS: We retrospectively analyzed 30 patients with 43 lesions who underwent curative radiotherapy for isolated lung metastasis from colorectal cancer at nine institutions from 2003 and 2008. A total dose of 42-75 Gy at the peripheral planning target volume was administered in 3-35 fractions. The median biologically equivalent dose was 84 Gy (range, 58.5-180). RESULTS: Treatment response was complete in 10 (33.3%), partial in 13 (43.3%), stable in six (20.0%), and progressive in one patient (3.3%). The median follow-up period for all patients was 29.0 months (range, 5.0-93.8). Kaplan-Meier local control at 5 years was 44%. The median survival was 46.2 months, and the 5-year overall survival was 47%. Twenty-three patients (77%) experienced treatment failure, most of which were intrapulmonary. The intrapulmonary relapse-free survival and overall relapse-free survival at 5 years were 22% and 19%, respectively. Treatment response and preradiotherapy carcinoembryonic antigen level were significant prognostic factors for local control and survival. Grade 3-5 toxicity occurred in 7 patients. Three patients had grade 5 toxicity, including radiation pneumonitis, a tracheoesophageal fistula, and hemoptysis. CONCLUSIONS: Curative radiotherapy for isolated lung metastasis from colorectal cancer in patients who are medically inoperable or unsuitable for surgery results in long-term survival, comparable to surgical resection. Curative radiotherapy could be an effective and noninvasive alternative if dose-limiting toxicity is carefully considered, particularly in patients with bilateral or central lesions.

[168]

TÍTULO / TITLE: - Identification of alpha1-antitrypsin as a potential prognostic biomarker for advanced nonsmall cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors by proteomic analysis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago)
1177/0300060513476582
AUTORES / AUTHORS: - Zhao W; Yang Z; Liu X; Tian Q; Lv Y; Liang Y; Li C; Gao X; Chen L
INSTITUCIÓN / INSTITUTION: - Respiratory Institute, People’s Liberation Army General Hospital, Beijing, China.
RESUMEN / SUMMARY: - OBJECTIVE: This retrospective study attempted to identify serum biomarkers that could help to indicate treatment response in advanced nonsmall-cell lung cancer (NSCLC) patients receiving epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI) treatment.
METHODS: Two-dimensional fluorescence difference gel electrophoresis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry were used to identify proteins expressed in serum samples from NSCLC patients with long (>6-month) progression-free survival (PFS) periods, following EGFR-TKI treatment. RESULTS: Serum amyloid P component (APCS), alpha1-antitrypsin (AAT), fibrinogen-alpha (FGA), keratin type I cytoskeletal 10 (KRT10) and serotransferrin (TF) expression differed between samples taken from 18 patients before treatment (baseline) and when progressive disease (PD) was observed, during treatment. Changes in AAT, KRT10 and APCS levels were validated by Western blot analysis in the sample pool; findings were further validated by Western blot analysis in a random sample of four patients. These proteins were also present in serum samples obtained from the same patients at the partial response (PR) timepoint during EGFR-TKI treatment. AAT was upregulated at PD compared with baseline, but downregulated during the PR phase. CONCLUSION: These observations suggest that AAT could be used as a serological biomarker for predicting the utility of EGFR-TKI treatment for advanced NSCLC.

[169]
TÍTULO / TITLE: - Nuclear EGFR protein expression predicts poor survival in early stage non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago)
1016/j.lungcan.2013.03.020
AUTORES / AUTHORS: - Traynor AM; Weigel TL; Oettel KR; Yang DT; Zhang C; Kim K; Salgia R; lida M; Brand TM; Hoang T; Campbell TC; Hernan HR; Wheeler DL

140
INTRODUCTION: Nuclear EGFR (nEGFR) has been identified in various human tumor tissues, including cancers of the breast, ovary, oropharynx, and esophagus, and has predicted poor patient outcomes. We sought to determine if protein expression of nEGFR is prognostic in early stage non-small cell lung cancer (NSCLC). METHODS: Resected stages I and II NSCLC specimens were evaluated for nEGFR protein expression using immunohistochemistry (IHC). Cases with at least one replicate core containing >/=5% of tumor cells demonstrating strong dot-like nucleolar EGFR expression were scored as nEGFR positive. RESULTS: Twenty-three (26.1% of the population) of 88 resected specimens stained positively for nEGFR. Nuclear EGFR protein expression was associated with higher disease stage (45.5% of stage II vs. 14.5% of stage I; p=0.023), histology (41.7% in squamous cell carcinoma vs. 17.1% in adenocarcinoma; p=0.028), shorter progression-free survival (PFS) (median PFS 8.7 months [95% CI 5.1-10.7 mo] for nEGFR positive vs. 14.5 months [95% CI 9.5-17.4 mo] for nEGFR negative; hazard ratio (HR) of 1.89 [95% CI 1.15-3.10]; p=0.011), and shorter overall survival (OS) (median OS 14.1 months [95% CI 10.3-22.7 mo] for nEGFR positive vs. 23.4 months [95% CI 20.1-29.4 mo] for nEGFR negative; HR of 1.83 [95% CI 1.12-2.99]; p=0.014). CONCLUSIONS: Expression of nEGFR protein was associated with higher stage and squamous cell histology, and predicted shorter PFS and OS, in this patient cohort. Nuclear EGFR serves as a useful independent prognostic variable and as a potential therapeutic target in NSCLC.

[170]

TÍTULO / TITLE: - Resistance to BH3 mimetic S1 in SCLC cells that up-regulate and phosphorylate Bcl-2 through ERK1/2.

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


AUTORES / AUTHORS: - Liu Y; Zhang Z; Song T; Liang F; Xie M; Sheng H

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Fine Chemicals, School of Chemistry, Dalian University of Technology, Dalian, China; School of Life Science and Technology, Dalian University of Technology, Dalian, China.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Bcl-2 is a central regulator of cell survival that is overexpressed in the majority of small cell lung cancers (SCLC) and contributes to both malignant transformation and therapeutic resistance. The purpose of this work was to study the key factors that determine the sensitivity of SCLC cells to BH3 mimetic S1 and the mechanism underlying the resistance of BH3 mimetics. EXPERIMENTAL
APPROACHES: Western blot was used to evaluate the contribution of Bcl-2 family members to the cellular response of SCLC cell lines to S1. Acquired resistant cells were derived from initially sensitive H1688 cells. Quantitative PCR and gene silencing were performed to investigate Bcl-2 up-regulation. KEY RESULTS: A progressive increase in the relative levels of Bcl-2 and phosphorylated Bcl-2 (pBcl-2) characterized the increased de novo and acquired resistance of SCLC cell lines. Furthermore, acute treatment of S1 induced Bcl-2 expression and phosphorylation. We showed that BH3 mimetics including S1 and ABT-737 induced ER stress and then activated MEK/ERK pathway. The dual function of MEK/ERK pathway in defining BH3 mimetics was illustrated: ERK1/2 activation leaded to Bcl-2 transcriptional up-regulation and sustained phosphorylation in naive and acquired resistant SCLC cells. pBcl-2 played a key role in creating resistance of S1 and ABT-737 not only by sequestrating pro-apoptotic proteins, but also a positive feedback to promote ERK1/2 activation. CONCLUSIONS AND IMPLICATIONS: These results provide significant novel insights into the molecular mechanisms for crosstalk between ER stress and endogenously apoptotic pathways in SCLC following BH3 mimetics treatment.

[171] TÍTULO / TITLE: RNA sequencing identifies fusion of the EWSR1 and YY1 genes in mesothelioma with t(14;22)(q32;q12).
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Panagopoulos I; Thorsen J; Gorunova L; Micci F; Haugom L; Davidson B; Heim S
INSTITUCIÓN / INSTITUTION: Section for Cancer Cytogenetics, Institute for Medical Informatics, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; Centre for Cancer Biomedicine, Faculty of Medicine, University of Oslo, Oslo, Norway.
RESUMEN / SUMMARY: Mesothelioma is a rare but very aggressive tumor derived from mesothelial cells. A number of often complex but nonrandom cytogenetic abnormalities have been found in these tumors, resulting in loss of chromosome bands 14q32 and 22q12 in more than 35% of the cases. In this study, we used RNA sequencing to search for fusion transcripts in a mesothelioma carrying a t(14;22)(q32;q12) as the sole chromosomal aberration and found an EWSR1-YY1 and its reciprocal YY1-EWSR1 fusion transcript. Screening 15 additional cases of mesothelioma from which we had RNA but no cytogenetic information, we identified one more tumor carrying an EWSR1-YY1 fusion gene but not the reciprocal YY1-EWSR1 transcript. RT-polymerase
A chain reaction and sequencing showed that in both cases exon 8 of EWSR1 (nucleotide 1,139, accession number NM_013986 version 3, former exon 7 in sequence with accession number X66899) was fused to exon 2 of YY1 (nucleotide 1,160, accession number NM_003403 version 3). The EWSR1 breakpoint in exon 8 in the EWSR1-YY1 chimeric transcript is similar to what is found in other fusions involving EWSR1 such as EWSR1-FLI1, EWSR1-DDIT3, and EWSR1-ATF1. The EWSR1-YY1-encoded protein is an abnormal transcription factor with the transactivation domain of EWSR1 and the DNA-binding domain of YY1. This is the first study to detect a specific fusion gene in mesothelioma (the reason how frequent the EWSR1-YY1 fusion is remains uncertain) and also the first time that direct involvement of YY1 in oncogenesis has been demonstrated. © 2013 Wiley Periodicals, Inc.

[172] TÍTULO / TITLE: - Phase 1 Study of Dose Escalation in Hypofractionated Proton Beam Therapy for Non-Small Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago)
1016/j.ijrobp.2013.03.035
AUTORES / AUTHORS: - Gomez DR; Gillin M; Liao Z; Wei C; Lin SH; Swanick C; Alvarado T; Komaki R; Cox JD; Chang JY
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. Electronic address: dgomez@mdanderson.org.
RESUMEN / SUMMARY: - BACKGROUND: Many patients with locally advanced non-small cell lung cancer (NSCLC) cannot undergo concurrent chemotherapy because of comorbidities or poor performance status. Hypofractionated radiation regimens, if tolerable, may provide an option to these patients for effective local control. METHODS AND MATERIALS: Twenty-five patients were enrolled in a phase 1 dose-escalation trial of proton beam therapy (PBT) from September 2010 through July 2012. Eligible patients had histologically documented lung cancer, thymic tumors, carcinoid tumors, or metastatic thyroid tumors. Concurrent chemotherapy was not allowed, but concurrent treatment with biologic agents was. The dose-escalation schema comprised 15 fractions of 3 Gy(relative biological effectiveness [RBE])/fraction, 3.5 Gy(RBE)/fraction, or 4 Gy(RBE)/fraction. Dose constraints were derived from biologically equivalent doses of standard fractionated treatment. RESULTS: The median follow-up time for patients alive at the time of analysis was 13 months (range, 8-28 months). Fifteen patients received treatment to hilar or mediastinal lymph nodes. Two patients experienced dose-limiting toxicity possibly related to treatment; 1
received 3.5-Gy(RBE) fractions and experienced an in-field tracheoesophageal fistula 9 months after PBT and 1 month after bevacizumab. The other patient received 4-Gy(RBE) fractions and was hospitalized for bacterial pneumonia/radiation pneumonitis 4 months after PBT. CONCLUSION: Hypofractionated PBT to the thorax delivered over 3 weeks was well tolerated even with significant doses to the lungs and mediastinal structures. Phase 2/3 trials are needed to compare the efficacy of this technique with standard treatment for locally advanced NSCLC.

[173]

**TÍTULO / TITLE:** Calretinin is essential for mesothelioma cell growth/survival in vitro: A potential new target for malignant mesothelioma therapy?

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


**AUTORES / AUTHORS:** Blum W; Schwaller B

**INSTITUCIÓN / INSTITUTION:** Anatomy, Department of Medicine, University of Fribourg, Route Albert-Gockel 1, CH-1700 Fribourg, Switzerland.

**RESUMEN / SUMMARY:** Malignant mesothelioma (MM) are highly aggressive asbestos-related neoplasms, which show strong chemotherapy-resistance and there is no effective cure for MM so far. Calretinin (CR) is widely used as a diagnostic marker for epithelioid and mixed (biphasic) mesothelioma, but still little is known about CR’s putative function(s) in tumorigenesis. CR protects against asbestos-induced acute cytotoxicity mediated by the AKT/PI3K pathway and furthermore, SV40 early region genes are able to up-regulate CR in mesothelial cells. However, the precise role of CR in mesothelioma is still unknown. Down-regulation of CR via lentiviral-mediated shRNA significantly decreased the viability and proliferation of mesothelioma cells in vitro. The effect was strong in epithelioid-dominated cell lines (ZL55, MSTO-211H). A weaker and delayed effect was observed in mesothelioma cells with prevalent sarcomatoid morphology (SPC111, SPC212, ZL34). The specificity of the effect was confirmed by stable eGFP-CR expression in mesothelioma cell lines and subsequent down-regulation. Depletion of CR led these cancer cell lines to enter apoptosis within 72h post-infection via strong activation of the intrinsic caspase 9-dependent pathway. Down-regulation of CR in immortalized mesothelial cells LP9/TERT-1 strongly blocked proliferation and caused a G1 block without decreasing viability or activating apoptosis pathways. Our results demonstrate that down-regulation of CR had a strong effect on the viability of MM cells and that CR is essential for cells derived from malignant mesothelioma. We anticipate these findings to reveal calretinin as a highly interesting new putative therapeutic target for mesothelioma treatment of
especially the epithelioid, but also of the mixed and sarcomatoid type. © 2013 Wiley Periodicals, Inc.

[174]
TÍTULO / TITLE: - Real-time vision of a sarcoid granuloma at bronchoscopy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Shulimzon TR
INSTITUCIÓN / INSTITUTION: - Sheba Medical Center, Interventional Pulmonology, The Pulmonary Institute, Tel Hashomer, Israel.

[175]
TÍTULO / TITLE: - Zebularine inhibits the growth of A549 lung cancer cells via cell cycle arrest and apoptosis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - You BR; Park WH
INSTITUCIÓN / INSTITUTION: - Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, Republic of Korea.

RESUMEN / SUMMARY: - Zebularine (Zeb) is a DNA methyltransferase (DNMT) inhibitor to that has an anti-tumor effect. Here, we evaluated the anti-growth effect of Zeb on A549 lung cancer cells in relation to reactive oxygen species (ROS) levels. Zeb inhibited the growth of A549 cells with an IC50 of approximately 70 microM at 72 h. Cell cycle analysis indicated that Zeb induced an S phase arrest in A549 cells. Zeb also induced A549 cell death, which was accompanied by the loss of mitochondrial membrane potential (MMP; ΔPsim), Bcl-2 decrease, Bax increase, p53 increase and activation of caspase-3 and -8. In contrast, Zeb mildly inhibited the growth of human pulmonary fibroblast (HPF) normal cells and lead to a G1 phase arrest. Zeb did not induce apoptosis in HPF cells. In relation to ROS level, Zeb increased ROS level in A549 cells and induced glutathione (GSH) depletion. The well-known antioxidant, N-acetyl cysteine (NAC) prevented the death of Zeb-treated A549 cells. Moreover, Zeb increased the level of thioredoxin reductase 1 (TrxR1) in A549 cells. While the overexpression of TrxR1 attenuated death and ROS level in Zeb-treated A549 cells, the downregulation of TrxR1 intensified death and ROS level in these cells. In conclusion, Zeb inhibited the growth of A549 lung
cancer cells via cell cycle arrest and apoptosis. The inhibition was influenced by ROS and TrxR1 levels. © 2013 Wiley Periodicals, Inc.

[176]
TÍTULO / TITLE: - Intracellular ATP-Binding Cassette Transporter A3 is Expressed in Lung Cancer Cells and Modulates Susceptibility to Cisplatin and Paclitaxel.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Overbeck TR; Hupfeld T; Krause D; Waldmann-Beushausen R; Chapuy B; Guldenzoph B; Aung T; Inagaki N; Schondube FA; Danner BC; Truemper L; Wulf GG
INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, University Medical Center Gottingen, Gottingen, Germany.
RESUMEN / SUMMARY: - Patients with advanced-stage bronchial cancer benefit from systemic cytostatic therapy, in particular from regimens integrating cisplatin and taxanes. However, eventual disease progression leads to a fatal outcome in most cases, originating from tumor cells resisting chemotherapy. We here show that the intracellular ATP-binding cassette transporter A3 (ABCA3), previously recognized as critical for the secretion of surfactant components from type 2 pneumocytes, is expressed in non-small-cell lung cancer (NSCLC) cells. With some heterogeneity in a given specimen, expression levels detected immunohistochemically in primary cancer tissue were highest in adenocarcinomas and lowest in small cell lung cancers. Genetic silencing of ABCA3 in the NSCLC cell line models A549, NCI-H1650 and NCI-H1975 significantly increased tumor cell susceptibility to the cytostatic effects of both cisplatin (in all cell lines) and paclitaxel (in two of three cell lines). Taken together, ABCA3 emerges as a modulator of NSCLC cell susceptibility to cytostatic therapy.

[177]
TÍTULO / TITLE: - Stereotactic ablative body radiation therapy for octogenarians with non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Takeda A; Sanuki N; Eriguchi T; Kaneko T; Morita S; Handa H; Aoki Y; Oku Y; Kunieda E
INSTITUCIÓN / INSTITUTION: - Radiation Oncology Center, Ofuna Chuo Hospital, Kanagawa, Japan.
RESUMEN / SUMMARY: - PURPOSE: To retrospectively investigate treatment outcomes of stereotactic ablative body radiation therapy (SABR) for octogenarians with non-small cell lung cancer (NSCLC). METHODS AND MATERIALS: Between 2005 and 2012, 109 patients aged >/=80 years with T1-2N0M0 NSCLC were treated with SABR: 47 patients had histology-unproven lung cancer; 62 patients had pathologically proven NSCLC. The prescribed doses were either 50 Gy/5 fractions for peripheral tumors or 40 Gy/5 fractions for centrally located tumors. The treatment outcomes, toxicities, and the correlating factors for overall survival (OS) were evaluated. RESULTS: The median follow-up duration after SABR was 24.2 (range, 3.0-64.6) months. Only limited toxicities were observed, except for 1 grade 5 radiation pneumonitis. The 3-year local, regional, and distant metastasis-free survival rates were 82.3%, 90.1%, and 76.8%, respectively. The OS and lung cancer-specific survival rates were 53.7% and 70.8%, respectively. Multivariate analysis revealed that medically inoperable, low body mass index, high T stage, and high C-reactive protein were the predictors for short OS. The OS for the operable octogenarians was significantly better than that for inoperable (P<.01). CONCLUSIONS: Stereotactic ablative body radiation therapy for octogenarians was feasible, with excellent OS. Multivariate analysis revealed that operability was one of the predictors for OS. For medically operable octogenarians with early-stage NSCLC, SABR should be prospectively compared with resection.

[178] TÍTULO / TITLE: - Does hydatid disease have protective effects against lung cancer?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Karadayi S; Arslan S; Sumer Z; Turan M; Sumer H; Karadayi K
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Cumhuriyet University School of Medicine, Sivas, Turkey, sulekaradayi73@yahoo.com.
RESUMEN / SUMMARY: - We hypothesized that solid tumors rarely occur in patients with hydatid disease. We obtained the serum of 14 patients diagnosed with hydatid disease, the serum of 10 patients who did not have a history of hydatid disease, and the hydatid cyst fluid from six patients. These sera and fluid samples were added at different concentrations to NCI-H209/An1 human lung small cell carcinoma cells and L929 mouse fibroblasts as a control group. Sera of patients with hydatid diseases had cytotoxic effects on NCI-H209/An1
cells, but they did not have cytotoxic effects on fibroblast cells. Sera from healthy subjects did not have a cytotoxic effect on the tumor cell line or control fibroblasts. Cyst fluid, also, did not have toxic effects on the NCI-H209/An1 cell line, but was toxic to fibroblasts up to a 1:32 dilution. Sera from patients with hydatid disease had cytotoxic effects on human small cell lung cancer cells in vitro.

[179]

TÍTULO / TITLE: - DNA repair genes polymorphism and lung cancer risk with the emphasis to sex differences.
RESUMEN / SUMMARY: - DNA repair genes polymorphism and lung cancer risk with the emphasis to sex differences.

AUTORES / AUTHORS: - Letkova L; Matakova T; Musak L; Sarlinova M; Krutakova M; Slovakova P; Kavcova E; Jakusova V; Janickova M; Drgova A; Berzinec P; Halasova E
INSTITUCIÓN / INSTITUTION: - Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4, 036 01, Martin, Slovak Republic, letkova@jfmed.uniba.sk

RESUMEN / SUMMARY: - Polymorphisms in nucleotide and base excision repair genes are associated with the variability in the risk of developing lung cancer. In the present study, we investigated the polymorphisms of following selected DNA repair genes: XPC (Lys939Gln), XPD (Lys751Gln), hOGG1 (Ser326Cys) and XRCC1 (Arg399Gln), and the risks they present towards the development of lung cancer with the emphasis to gender differences within the Slovak population. We analyzed 761 individuals comprising 382 patients with diagnosed lung cancer and 379 healthy controls. Genotypes were determined by polymerase chain reaction/restriction fragment length polymorphism method. We found out statistically significant increased risk for lung cancer development between genders. Female carrying XPC Gln/Gln, XPC Lys/Gln+Gln/Gln and XRCC1 Arg/Gln, XRCC1 Arg/Gln+Gln/Gln genotypes had significantly increased risk of lung cancer corresponding to OR = 2.06; p = 0.04, OR = 1.66; p = 0.04 and OR = 1.62; p = 0.04, OR = 1.69; p = 0.02 respectively. In total, significantly increased risk of developing lung cancer was found in the following combinations of genotypes: XPD Lys/Gln+XPC Lys/Lys (OR = 1.62; p = 0.04), XRCC1 Gln/Gln+hOGG1 Ser/Ser (OR = 2.14; p = 0.02). After stratification for genders, the following combinations of genotype were found to be significant in male: XPD Lys/Gln+XPC Lys/Lys (OR = 1.87; p = 0.03), XRCC1 Arg/Gln+XPC Lys/Lys (OR = 4.52; p = 0.0007), XRCC1 Arg/Gln+XPC Lys/Gln (OR = 5.44; p < 0.0001). In female, different combinations of the following genotypes were found to be significant: XRCC1 Arg/Gln+hOGG1 Ser/Ser (OR = 1.98; p = 0.04),
XRCC1 Gln/Gln+hOGG1 Ser/Ser (OR = 3.75; p = 0.02), XRCC1 Arg/Gln+XPC Lys/Gln (OR = 2.40; p = 0.04), XRCC1 Arg/Gln+XPC Gln/Gln (OR = 3.03; p = 0.04). We found out decreased cancer risk in genotype combinations between female patients and healthy controls: XPD Lys/Lys+XPC Lys/Gln (OR = 0.45; p = 0.02), XPD Lys/Gln+XPC Lys/Gln (OR = 0.32; p = 0.005), XPD Lys/Gln+XPC Lys/Gln (OR = 0.48; p = 0.02). Our results did not show any difference between pooled smokers and non-smokers in observed gene polymorphisms in the association to the lung cancer risk. However, gender stratification indicated the possible effect of heterozygous constitution of hOGG1 gene (Ser/Cys) on lung cancer risk in female non-smokers (OR = 0.20; p = 0.01) and heterozygous constitution of XPC gene (Lys/Gln) in male smokers (OR = 2.70; p = 0.01).

[180]

**TITULO / TITLE:** - Thymidylate synthase gene copy number as a predictive marker for response to pemetrexed treatment of lung adenocarcinoma.

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


**AUTORES / AUTHORS:** - Kasai D; Ozasa H; Oguri T; Miyazaki M; Uemura T; Takakuwa O; Kunii E; Ohkubo H; Maeno K; Niimi A

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasaki-cho, Mizuho-ku, Nagoya 467-8601, Japan. t-oguri@med.nagoya- cu.ac.jp.

**RESUMEN / SUMMARY:** - BACKGROUND: Pemetrexed is a key drug for therapy of non-small cell lung cancer (NSCLC). MATERIALS AND METHODS: In a search for biomarkers for study of the efficacy of pemetrexed treatment, we examined the thymidylate synthase (TYMS) copy number in NSCLC cell lines and in clinical NSCLC samples treated with pemetrexed, combined with platinum drugs. RESULTS: TYMS copy numbers in lung adenocarcinoma cell lines were significantly lower than in squamous cell carcinoma (p=0.0105), and a significant correlation was found between the TYMS copy number and the 50% inhibitory concentration value for pemetrexed in all 17 lung cancer cell lines tested (r=0.6814, p=0.0026). Moreover, TYMS copy number was significantly lower in clinical NSCLC samples responsive to treatment with pemetrexed combined with platinum drugs (p=0.0067). Furthermore, the decrease in the baseline CT size measurement of pemetrexed combined with platinum drug treatment correlated significantly with TYMS copy number (r=0.7967, p=0.0011). CONCLUSION: To our knowledge, this is the first report of a significant association between TYMS copy number and response to pemetrexed treatment in tumor biopsy specimens. Our results suggest that TYMS copy number could be a predictive biomarker for pemetrexed based chemotherapy.
TÍTULO / TITLE: - Improving the Quality of Lung Cancer Care in Ontario: The Lung Cancer Disease Pathway Initiative.

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


AUTORES / AUTHORS: - Evans WK; Ung YC; Assouad N; Chyjek A; Sawka C

INSTITUCIÓN / INSTITUTION: - *Department of Oncology, McMaster University and the Juravinski Hospital and Cancer Centre at Hamilton Health Sciences, Hamilton, ON, Canada; daggerDepartment of Radiation Oncology, University of Toronto and the Odette Cancer Centre at Sunnybrook Health Sciences Centre; double daggersHealth Ontario; section signCancer Care Ontario; ||Departments of Medicine, Public Health Sciences and Health Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada.

RESUMEN / SUMMARY: - BACKGROUND:: Before 2008, Cancer Care Ontario (CCO) undertook provincial cancer control quality-improvement initiatives on a programmatic basis. CCO has now added Disease Pathway Management (DPM) to its quality improvement strategy, with the intent of achieving high-quality care, processes, and patient experience across the patient pathway for specific cancers. OBJECTIVES:: The three goals of DPM are: to describe and share evidence-based best practice along the cancer continuum for specific cancers; identify quality-improvement priorities for specific cancers and catalyze action; monitor performance against best practice for specific cancers. The objective of this article is to describe the process by which the CCO lung cancer (LC) DPM was initiated and some of its early successes. METHODS:: In 2009, LC DPM began with a draft LC disease pathway map and the establishment of five multidisciplinary working groups, each focused on a phase of the LC patient journey: prevention, screening, and early detection; diagnosis; treatment; palliative care, end-of-life care, and survivorship; and patient experience. The working groups held 25 meetings of 2-hour duration and developed concepts for 17 quality-improvement projects across the patient journey. Eight were selected for detailed discussion at a provincial consensus conference, which provided input on priorities for action. A report on the priorities for action was prepared and widely circulated, and regional roadshows were held in all 14 regions of the province of Ontario. Region-specific data on incidence, stage, treatment compliance, and wait times among other issues relevant to LC, were shared with the regional care providers at these roadshows. Funding was provided by CCO to address opportunities for regional improvement based on the data and the priorities identified. RESULTS:: The LC disease pathways were refined through substantial multidisciplinary discussion, and the diagnostic
pathway was posted on CCO’s Web site in February 2012. The treatment pathways for small-cell LC and non-small-cell LC were posted in November 2012. LC Diagnostic Assessment Units/Programs have been initiated in 14 regions, and educational materials on dyspnea management, including a patient video, are available on CCO’s Web site. An audit has been undertaken to better understand the barriers to the uniform uptake of specific evidence-based practices across the province, and the results will be reported shortly. The proportion of LC patients, whose symptoms are assessed at least once a month, using a standardized symptom assessment instrument (Edmonton Symptom Assessment System), has improved through the DPM.

CONCLUSION:: Through CCO’s LC DPM initiative, Regional Cancer Programs have become aware of their performance on a range of LC-specific performance and quality metrics and have been motivated to undertake quality-improvement initiatives. Standardized diagnostic and treatment pathways have been developed. Ongoing measurement of a broad range of metrics, including stage-specific survival, guideline concordance, and measures of the patient experience will help determine the benefit of this major initiative.

[182]

TÍTULO / TITLE: - Genome-wide identification of genes with amplification and/or fusion in small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Iwakawa R; Takenaka M; Kohno T; Shimada Y; Totoki Y; Shibata T; Tsuta K; Nishikawa R; Noguchi M; Sato-Otsubo A; Ogawa S; Yokota J

INSTITUCIÓN / INSTITUTION: - Division of Multistep Carcinogenesis, National Cancer Center Research Institute, Tokyo, Japan.

RESUMEN / SUMMARY: - To obtain a landscape of gross genetic alterations in small cell lung cancer (SCLC), genome-wide copy number analysis and whole-transcriptome sequencing were performed in 58 and 42 SCLCs, respectively. Focal amplification of known oncogene loci, MYCL1 (1p34.2), MYCN (2p24.3), and MYC (8q24.21), was frequently and mutually exclusively detected. MYCL1 and MYC were co-amplified with other regions on either the same or the different chromosome in several cases. In addition, the 9p24.1 region was identified as being amplified in SCLCs without amplification of MYC family oncogenes. Notably, expression of the KIAA1432 gene in this region was significantly higher in KIAA1432 amplified cells than in non-amplified cells, and its mRNA expression showed strong correlations with the copy numbers. Thus, KIAA1432 is a novel gene activated by amplification in SCLCs. By whole-
transcriptome sequencing, a total of 60 fusion transcripts, transcribed from 95 different genes, were identified as being expressed in SCLC cells. However, no in-frame fusion transcripts were recurrently detected in > = 2 SCLCs, and genes in the amplified regions, such as PVT1 neighboring MYC and RLF in MYCL1 amplicons, were recurrently fused with genes in the same amplicons or with those in different amplicons on either the same or different chromosome. Thus, it was indicated that amplification and fusion of several genes on chromosomes 1 and 8 occur simultaneously but not sequentially through chromothripsis in the development of SCLC, and amplification rather than fusion of genes plays an important role in its development. © 2013 Wiley Periodicals, Inc.

[183]

TÍTULO / TITLE: - 1,25-Dihydroxyvitamin D3 up-regulates expression of hsa-let-7a-2 through the interaction of VDR/VDRE in human lung cancer A549 cells.

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


AUTORES / AUTHORS: - Guan H; Liu C; Chen Z; Wang L; Li C; Zhao J; Yu Y; Zhang P; Chen W; Jiang A

INSTITUCIÓN / INSTITUTION: - Institution of Biochemistry and Molecular Biology, Medical School of Shandong University, Jinan, 250012, China; Jinan Municipal Center For Disease Control and Prevention, Jinan, 250013, China.

RESUMEN / SUMMARY: - AIMS: We aim to investigate the relationship between 1,25-(OH)2VD3 and hsa-let-7a in lung cancer A549 cells. METHODS: Real-time PCR and luciferase reporter assays were used to detect the influence of 1,25-(OH)2VD3 on the expression of hsa-let-7a-2 after A549 cells were treated with 1,25-(OH)2VD3 (10(-8)-10(-6)mol/L). Analysis of the 5.0Kb upstream sequence of the pre-let-7a-2 showed that one vitamin D response element (VDRE) is located in -2066/-2042bp of pre-let-7a-2. Electrophoretic mobility shift assays (EMSA), chromatin immunoprecipitation (ChIP) and luciferase reporter assays were performed to determine whether 1,25-(OH)2VD3 activating vitamin D receptor (VDR) could bind to this VDRE to promote hsa-let-7a-2 expression. RESULTS: We found that 1,25-(OH)2VD3 could up-regulate the expression of hsa-let-7a-2 in a dose-dependent manner. The results of EMSA and ChIP demonstrated that 1,25-(OH)2VD3/VDR could interact with the VDRE in the upstream of pre-let-7a-2. Luciferase reporter assay showed that this VDRE is a functional cis-element mediating the up-regulation of hsa-let-7a-2 expression induced by 1,25-(OH)2VD3. CONCLUSIONS: Our data indicated that 1,25-(OH)2VD3 could up-regulate the transcription of hsa-let-7a-2 in lung cancer cells, and the up-regulation of hsa-let-7a-2 expression induced by 1,25-
(OH)2VD3 might mediate the anti-proliferation effects of 1,25-(OH)2VD3 in lung cancer cells.

[184] TÍTULO / TITLE: Mesenchymal stem cells as vectors for lung cancer therapy.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Kolluri KK; Laurent GJ; Janes SM
INSTITUCIÓN / INSTITUTION: Lungs for Living Research Centre, University College London, London, UK.
RESUMEN / SUMMARY: Despite recent advances in treatment, lung cancer accounts for one third of all cancer-related deaths, underlining the need of development of new therapies. Mesenchymal stem cells (MSCs) possess the ability to specifically home into tumours and their metastases. This property of MSCs could be exploited for the delivery of various anti-tumour agents directly into tumours. However, MSCs are not simple delivery vehicles but cells with active physiological process. This review outlines various agents which can be delivered by MSCs with substantial emphasis on TRAIL (tumour necrosis factor-related apoptosis-inducing ligand).

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Govaerts E; Vansteenkiste J
INSTITUCIÓN / INSTITUTION: Respiratory Oncology Unit, Department of Pulmonology, and Leuven Lung Cancer Group, University Hospital KU Leuven, Leuven, Belgium.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
An association between common variants in the 15q25 nicotinic acetylcholine receptor (nAChR) gene cluster CHRNA5-A3-B4 (responsible for encoding nAChR subunits) and lung cancer risk has recently been reported in both Caucasian and Chinese population. Cigarette smoking is one of the major risk factors for both lung and gastric cancer. Moreover, nAChR plays an important role in cigarette smoke-related lung carcinogenesis as well as gastric cancer. Nevertheless, no study has evaluated the association between CHRNA5-A3-B4 gene cluster variants (rs667282 and rs3743073, two variants modifying lung cancer risk) and risk of gastric cancer. We genotyped these two single nucleotide polymorphisms (SNPs) and analyzed their associations with risk of gastric cancer in a case-control study of 637 gastric cancer patients and 855 healthy individuals matched by age and sex in a Chinese Han population. The differences in genotype distribution of the two SNPs (rs667282, rs3743073) between the cases and controls were not statistically significant (p = 0.468 and p = 0.495, respectively). Overall, we did not observe a significant association of each genotype of the two SNPs with risk of gastric cancer (TT/CT vs. CC: adjusted OR = 1.12, 95% CI = 0.86-1.45; p = 0.401 for rs667282 and GG/TG vs. TT: adjusted OR = 1.13, 95% CI = 0.90-1.43; p = 0.300 for rs3743073). The results of our study indicated that these two SNPs at the 15q25 locus did not modify gastric cancer risk and the reported risk SNP at 15q25 may be specific to lung cancer. Additional larger studies are needed to further confirm our findings.

[187]

- mTOR inhibitors radiosensitize PTEN-deficient non-small-cell lung cancer cells harboring an EGFR activating mutation by inducing autophagy.

- Division of Radiation Effects, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea.
**RESUMEN / SUMMARY:** Clinical resistance to gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), in patients with lung cancer has been linked to acquisition of the T790M resistance mutation in activated EGFR or amplification of MET. Phosphatase and tensin homolog (PTEN) loss has been recently reported as a gefitinib resistance mechanism in lung cancer. The aim of this study was to evaluate the efficacy of radiotherapy in non-small-cell lung cancer (NSCLC) with acquired gefitinib resistance caused by PTEN deficiency to suggest radiotherapy as an alternative to EGFR TKIs. PTEN deficient-mediated gefitinib resistance was generated in HCC827 cells, an EGFR TKI sensitive NSCLC cell line, by PTEN knockdown with a lentiviral vector expressing short hairpin RNA-targeting PTEN. The impact of PTEN knockdown on sensitivity to radiation in the presence or absence of PTEN downstream signaling inhibitors was investigated. PTEN knockdown conferred acquired resistance not only to gefitinib but also to radiation on HCC827 cells. mTOR inhibitors alone failed to reduce HCC827 cell viability, regardless of PTEN expression, but ameliorated PTEN knockdown-induced radioresistance. PTEN knockdown-mediated radioresistance was accompanied by repression of radiation-induced cytotoxic autophagy, and treatment with mTOR inhibitors released the repression of cytotoxic autophagy to overcome PTEN knockdown-induced radioresistance in HCC827 cells. These results suggest that inhibiting mTOR signaling could be an effective strategy to radiosensitize NSCLC harboring the EGFR activating mutation that acquires resistance to both TKIs and radiotherapy due to PTEN loss or inactivation mutations.

[188] **TÍTULO / TITLE:** miR-194 suppresses metastasis of non-small cell lung cancer through regulating expression of BMP1 and p27

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

**REVISTA / JOURNAL:** Oncogene. 2013 Apr 15. doi: 10.1038/onc.2013.108.

**AUTORES / AUTHORS:** Wu X; Liu T; Fang O; Leach LJ; Hu X; Luo Z

**INSTITUCIÓN / INSTITUTION:** The State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China.

**RESUMEN / SUMMARY:** MicroRNAs (miRNAs) are increasingly implicated in regulating tumor malignance through their capacity to coordinately repress expression of tumor-related genes. Here, we show that overexpression of miR-194 in lung cancer cell lines, results in suppressing metastasis of lung cancer cells, while inhibiting its expression through ‘miRNA sponge’ promotes the cancer cells to metastasize. miR-194 expression is also found to be in strongly negative association with metastasis in clinical specimens of non-small cell lung cancer. We demonstrate that miR-194 directly targets both BMP1 and p27kip1.
The resulting downregulation of BMP1 leads to suppression of TGFbeta activity and, thus, to downregulation of the expression of key oncogenic genes (matrix metalloproteinases MMP2 and MMP9). This leads, in turn, to decreased tumor invasion. In addition, the miRNA-194-induced suppression of p27kip1 activates the RhoA pathway, producing enhanced development of actin stress fibers and impaired migration of cancer cells. These findings reveal two structurally independent but functionally linked branches of the regulatory and signaling pathway that together provide a bridge between the metastasis-depressing miRNA and the key genes that govern the malignancy of lung cancers. Oncogene advance online publication, 15 April 2013; doi:10.1038/onc.2013.108.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
- Enlace al texto completo (gratuito o de pago)
1177/0192623313491169
AUTORES / AUTHORS: - Bhusari S; Malarkey DE; Hong HH; Wang Y; Masinde T; Nolan M; Hooth MJ; Lea IA; Vasconcelos D; Sills RC; Hoenerhoff MJ
INSTITUCIÓN / INSTITUTION: - 1Cellular and Molecular Pathology Branch, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA.
RESUMEN / SUMMARY: - 3,3',4,4'-tetrachloroazobenzene (TCAB) is a contaminant formed during manufacture of various herbicide compounds. A recent National Toxicology Program study showed B6C3F1 mice exposed to TCAB developed a treatment-related increase in lung carcinomas in the high-dose group, and urethral carcinomas, an extremely rare lesion in rodents, in all dose groups. As the potential for environmental exposure to TCAB is widespread, and the mechanisms of urethral carcinogenesis are unknown, TCAB-induced urethral and pulmonary tumors were evaluated for alterations in critical human cancer genes, Kras and Tp53. Uroplakin III, CK20, and CK7 immunohistochemistry was performed to confirm the urothelial origin of urethral tumors. TCAB-induced urethral carcinomas harbored transforming point mutations in K-ras (38%) and Tp53 (63%), and 71% displayed nuclear TP53 expression, consistent with formation of mutant protein. Transition mutations accounted for 88% of Tp53 mutations in urethral carcinomas, suggesting that TCAB or its metabolites target guanine or cytosine bases and that these mutations are involved in urethral carcinogenesis. Pulmonary carcinomas in TCAB-exposed animals harbored similar rates of Tp53 (55%) and Kras (36%) mutations as urethral carcinomas, suggesting that TCAB may induce mutations
at multiple sites by a common mechanism. In conclusion, TCAB is carcinogenic at multiple sites in male and female B6C3F1 mice through mechanisms involving Tp53 and Kras mutation.

References:
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - El-Zein M; Parent ME; Nicolau B; Koushik A; Siemiatycki J; Rousseau MC
INSTITUCIÓN / INSTITUTION: - INRS-Institut Armand-Frappier, Universite du Quebec, Laval, Quebec, Canada.
RESUMEN / SUMMARY: - There is as yet no generally accepted explanation for the common finding that low body mass index (BMI) is associated with an increased risk of lung cancer. We investigated this association in a Canadian population-based case-control study (1996-2002) with a particular view to assessing the hypothesis that the observed association was due to residual confounding by smoking. Analyses were based on 1,076 cases and 1,439 controls who provided their height at enrollment and their weight at two points in time, at age 20 and 2 years before enrollment. BMI, in kg/m2, was classified into underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (>/=30). Smoking history was synthesized into a comprehensive smoking index (CSI) that integrated duration, intensity and time since quitting. Odds ratios (ORs) and 95% confidence intervals (CIs) for BMI-lung cancer associations were estimated, adjusting for CSI as well as several sociodemographic, lifestyle and occupational factors. The normal BMI category was used as the reference. Among those who were underweight at age 20, there was a lower risk of lung cancer (OR = 0.69, 95% CI: 0.50-0.95). Conversely, lung cancer risk was increased among those who were underweight 2 years before enrollment (OR = 2.30, 95% CI: 1.30-4.10). The results were almost identical when stratifying analyses based on smoking history into never/lighter and heavier smokers. The inverse association between recent BMI and lung cancer is unlikely to be largely attributable to residual confounding by smoking. Reverse causality or a true relationship between BMI and lung cancer remain plausible.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ● Enlace al texto completo (gratuito o de pago) 1016/j.ctrv.2013.03.007
AUTORES / AUTHORS: - Jahangeer S; Forde P; Soden D; Hinchion J
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, Cork University Hospital, Wilton, Cork, Ireland; Cork Cancer Research Centre, Bioscience Institute, University College Cork, Cork, Ireland. Electronic address: salj2008@yahoo.com.
RESUMEN / SUMMARY: - Lung cancer remains the most common cancer diagnosed worldwide and has one of the lowest survival rates of all cancers. Surgery remains the only curative treatment option but because most patients are either diagnosed at advanced stages or are unfit for surgery, less than a third of all lung cancer patients will undergo a surgical resection. Thermal ablation has emerged as an alternative option in patients who are unfit to undergo surgery. Thermal ablative therapies used in clinical practice to date include Radiofrequency Ablation (RFA), Microwave Ablation (MWA) and Cryoablation. This article will focus on the advantages and limitations of thermal ablative therapy and investigates the potential of a relatively new treatment modality, Electrochemotherapy (ECT), as a novel treatment for lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ● Enlace al texto completo (gratuito o de pago) 1002/mc.22039
AUTORES / AUTHORS: - Xie C; Yang L; Yang X; Yang R; Li Y; Qiu F; Chen M; Fang W; Bin X; Deng J; Huang D; Liu B; Zhou Y; Lu J
INSTITUCIÓN / INSTITUTION: - The Institute for Chemical Carcinogenesis, The State Key Lab of Respiratory Disease, Guangzhou Medical University, Guangzhou, P.R., China; Dongguan Taiping People Hospital, Dongguan, P.R., China.
RESUMEN / SUMMARY: - Signal-induced proliferation associated gene 1 (Sipa1) is a signal transducer to activate the Ras-related proteins and modulate cell progression, differentiation, adhesion and cancer metastasis. In this study, we tested the hypothesis that single nucleotide polymorphisms (SNPs) in Sipa1 are associated with lung cancer risk and metastasis. Three common SNPs (rs931127A > G, rs2448490G > A, and rs3741379G > T) were genotyped in a discovery set of southern Chinese population and then validated the promising SNPs in a validation set of an eastern Chinese population in a total of 1559 lung cancer patients and 1679 cancer-free controls. The results from the two sets
were consistent, the rs931127GG variant genotype had an increased risk of lung cancer compared to the rs931127AA/GA genotypes (OR = 1.27; 95% CI = 1.09-1.49) after combination of the two populations, and the rs931127GG interacted with pack-year smoked on increasing lung cancer risk (P = 0.037); this SNP also had an effect on patients' clinical stages (P = 0.012) that those patients with the rs931127GG genotype had a significant higher metastasis rate and been advanced N, M stages at diagnosis. However, these associations were not observed for rs2448490G > A and rs3741379G > T in the discovery set. Our data suggest that the SNP rs931127A > G in the promoter of Sipa1 was significantly associated with lung cancer risk and metastasis, which may be a biomarker to predict the risk and metastasis of lung cancer. © 2013 Wiley Periodicals, Inc.
size was significantly correlated with DFS (\(<\leq 0.5\) cm/ > 0.5 cm, \(<\leq 1\) cm/ >1 cm, \(<\leq 2\) cm/ >2 cm, \(<\leq 3\) cm/ >3 cm, 100%/91.5%/85.9%/80.8%/66.7% in 5-year DFS) \(p = 0.006\), overall). A multivariate analysis showed solid-predominant and invasive tumor size were independent predictors of increased risk of recurrence (solid versus nonsolid: hazard ratio = 4.08, 95% confidence interval:1.59-10.5, \(p = 0.003\); invasive tumor size: hazard ratio = 2.04, 95% confidence interval:1.14-3.63, \(p = 0.016\)). CONCLUSION: : The new International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society ADC classification and invasive tumor size are very useful predictors of recurrence of stage I ADCs in Japanese patients.

[194]
TITULO / TITLE: - Cell-cycle changes and oxidative stress response to magnetite in a549 human lung cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Konczol M; Weiss A; Stangenberg E; Gminski R; Garcia-Kaufer M; Giere R; Merfort I; Mersch-Sundermann V
INSTITUCIÓN / INSTITUTION: - Department of Environmental Health Sciences, University Medical Center Freiburg, Freiburg, Germany.
RESUMEN / SUMMARY: - In a recent study, magnetite was investigated for its potential to induce toxic effects and influence signaling pathways. It was clearly demonstrated that ROS formation leads to mitochondrial damage and genotoxic effects in A549 cells. On the basis of these findings, we wanted to elucidate the origin of magnetite-mediated ROS formation and its influence on the cell cycle of A549 and H1299 human lung epithelial cells. Concentration- and size-dependent superoxide formation, measured by electron paramagnetic resonance (EPR), was observed. Furthermore, we could show that the GSH level decreased significantly after exposure to magnetite particles, while catalase (CAT) activity was increased. These effects were also dependent on particle size, albeit less pronounced than those observed with EPR. We were able to show that incubation of A549 cells prior to particle treatment with diphenyleneiodonium (DPI), a NADPH-oxidase (NOX) inhibitor, leads to decreased ROS formation, but this effect was not observed for the NOX inhibitor apocynin. Soluble iron does not contribute considerably to ROS production. Analysis of cell-cycle distribution revealed a pronounced sub-G1 peak, which cannot be linked to increased cell death. Western blot analysis did not show activation of p53 but upregulation of p21 in A549. Here, we were unexpectedly able to demonstrate that exposure to magnetite leads to p21-
mediated G1-like arrest. This has been reported previously only for low concentrations of microtubule stabilization drugs. Importantly, the arrested sub-G1 cells were viable and showed no caspase 3/7 activation.

[195]

TÍTULO / TITLE: - The mutations of the EGFR and K-ras genes in resected stage I lung adenocarcinoma and their clinical significance.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s00595-013-0589-2
AUTORES / AUTHORS: - Ohba T; Toyokawa G; Kometani T; Nosaki K; Hirai F; Yamaguchi M; Hamatake M; Seto T; Ichinose Y; Sugio K
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka, 811-1395, Japan, taro.oba@gmail.com.
RESUMEN / SUMMARY: - PURPOSE: This study retrospectively assessed the mutations of the epidermal growth factor receptor (EGFR) and K-ras genes and their clinical significance in patients with resected stage I adenocarcinomas. METHODS: A total of 354 patients with resected lung adenocarcinomas were included, and 256 patients with stage I disease were analyzed for the prognostic and predictive value of these mutations. RESULTS: Mutations of EGFR and K-ras genes were detected in 149 (41.1 %) and 23 (6.4 %) of all tumors, and in 122 (47.6 %) and 14 (5.5 %) of stage I tumors, respectively. There were no significant differences in the disease-free survival (DFS) and overall survival (OS) between the EGFR-mutant and wild-type groups. However, the DFS and OS were significantly shorter in patients with K-ras mutations than in those without (5-year DFS: 50.8 vs. 76.9 %, 5-year OS: 70.0 vs. 86.6 %, p < 0.01). A multivariate analysis showed that K-ras mutations were an independent poor prognostic factor. Twenty-four of the 41 patients with recurrent disease after surgery were treated with an EGFR-TKI. Fifteen EGFR-mutant patients treated with an EGFR-TKI had a better prognosis than did the nine EGFR-wild-type patients. CONCLUSION: The presence of an EGFR gene mutation was a predictive factor for the response to EGFR-TKI treatment in patients with resected stage I adenocarcinoma, but was not a prognostic factor. The presence of a K-ras gene mutation was a poor prognostic factor.

[196]

TÍTULO / TITLE: - Autophagic cell death induced by resveratrol depends on the Ca/AMPK/mTOR pathway in A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
RESUMEN / SUMMARY: - Resveratrol has many biological effects, including antitumor, antiviral activities, and vascular protection. Recent studies have suggested that resveratrol exert its antitumor effects through induction of autophagy by an unknown mechanism. In this study, we investigated the involvement of autophagy in resveratrol-induced cell death and its potential molecular mechanisms in A549 human lung adenocarcinoma cells. Resveratrol-induced growth inhibition and cell death was assessed by MTT and clonogenic assays. Activation of autophagy was characterized by monodansylcadaverine, transmission electron microscopy, and expression of autophagy marker protein LC3. Western blot analysis was used to study the cell signals involved in the mechanisms of autophagic death. Intracellular free calcium was detected with Fura2-AM staining. Our results indicated that resveratrol induced A549 cell death was mediated by autophagy. 3-methyladenine, an inhibitor of autophagy, suppressed resveratrol-induced autophagic cell death, and knockdown of autophagy-related genes Atg5 and Beclin-1 with siRNAs reversed RSV-induced cell death. Intracellular free calcium accumulated immediately following resveratrol addition, which led to the activation of phospho-AMPK and phospho-Raptor, and a reduction in the amount of phospho-p70S6K. These effects could be reversed by the AMPK inhibitor compound C, and the calcium ion-chelating agent EGTA. In conclusion, we demonstrate that resveratrol-induced A549 cell death was mediated by the process of autophagic cell death via Ca2+/AMPK-mTOR signaling pathway.

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[197]
TÍTULO / TITLE: - FDG Uptake in the Chest Wall of a Patient with Small-Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Stigt JA; Boomsma MF; van Bemmel BC
INSTITUCIÓN / INSTITUTION: - Departments of *Pulmonology, daggerRadiology, and double daggerPathology Isala Klinieken, Zwolle, The Netherlands.
TÍTULO / TITLE: - Risk factors for recurrence after lung cancer resection as estimated using the survival tree method.

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

- ●●Enlace al texto completo (gratuito o de pago) 1378/chest.12-3034

AUTORES / AUTHORS: - Sawada S; Yamashita N; Suehisa H; Yamashita M

RESUMEN / SUMMARY: - ABSTRACT BACKGROUND: Patients with lung cancer often present with recurrence, even after resection. The identification of risk factors for recurrence after resection is useful. METHODS: Among 1338 patients with lung cancer who underwent a complete resection, 277 developed recurrences post-surgery. Data regarding the TNM factors, histological subtype and the presence/absence of vessel invasion were analyzed retrospectively using the survival tree method to identify groups with a high risk of recurrence after resection. RESULTS: The results revealed that the T factor, the N factor, and lymphatic (ly) and blood (v) vessel invasion were related to the risk of recurrence and six combinations of these factors were identified using the survival tree method; Group A: v = 0, T &lt;= 1b, ly = 0; Group B: v = 0, T &lt;= 1b, ly &gt;= 1; Group C: v = 0, T &gt;= 2; Group D: v &lt;= 1, N &lt;= 1, T &lt;= 2b; Group E: v &lt;= 1, N &lt;= 1, T &gt;= 3; and Group F: v &gt;= 1, N &gt;= 2. The six groups were then further classified into three groups: a low-risk group (Group A), a moderate-risk group (Groups B, C and D), and a high-risk group (Groups E and F). The 5-year recurrence-free survival rate was approximately 98% for the low-risk group, 75% for the moderate-risk group, and 30 % for the high-risk group. CONCLUSIONS: Combining the T, N, v and ly factors allowed the precise identification of a group with a high risk of recurrence after resection.

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TÍTULO / TITLE: - CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study.

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

- ●●Enlace al texto completo (gratuito o de pago) 1016/S1470-2045(13)70142-6

AUTORES / AUTHORS: - Seto T; Kiura K; Nishio M; Nakagawa K; Maemondo M; Inoue A; Hida T; Yamamoto N; Yoshioka H; Harada M; Ohe Y; Nogami N; Takeuchi K; Shimada T; Tanaka T; Tamura T
BACKGROUND: Currently, crizotinib is the only drug that has been approved for treatment of ALK-rearranged non-small-cell lung cancer (NSCLC). We aimed to study the activity and safety of CH5424802, a potent, selective, and orally available ALK inhibitor. METHODS: In this multicentre, single-arm, open-label, phase 1-2 study of CH5424802, we recruited ALK inhibitor-naive patients with ALK-rearranged advanced NSCLC from 13 hospitals in Japan. In the phase 1 portion of the study, patients received CH5424802 orally twice daily by dose escalation. The primary endpoints of the phase 1 were dose limiting toxicity (DLT), maximum tolerated dose (MTD), and pharmacokinetic parameters. In the phase 2 portion of the study, patients received CH5424802 at the recommended dose identified in the phase 1 portion of the study orally twice a day. The primary endpoint of the phase 2 was the proportion of patients who had an objective response. Treatment was continued in 21-day cycles until disease progression, intolerable adverse events, or withdrawal of consent. The analysis was done by intent to treat. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264. FINDINGS: Patients were enrolled between Sept 10, 2010, and April 18, 2012. The data cutoff date was July 31, 2012. In the phase 1 portion, 24 patients were treated at doses of 20-300 mg twice daily. No DLTs or adverse events of grade 4 were noted up to the highest dose; thus 300 mg twice daily was the recommended phase 2 dose. In the phase 2 portion of the study, 46 patients were treated with the recommended dose, of whom 43 achieved an objective response (93.5%, 95% CI 82.1-98.6) including two complete responses (4.3%, 0.5-14.8) and 41 partial responses (89.1%, 76.4-96.4). Treatment-related adverse events of grade 3 were recorded in 12 (26%) of 46 patients, including two patients each experiencing decreased neutrophil count and increased blood creatine phosphokinase. Serious adverse events occurred in five patients (11%). No grade 4 adverse events or deaths were reported. The study is still ongoing, since 40 of the 46 patients in the phase 2 portion remain on treatment. INTERPRETATION: CH5424802 is well tolerated and highly active in patients with advanced ALK-rearranged NSCLC. FUNDING: Chugai Pharmaceutical Co, Ltd.

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

●●Enlace al texto completo (gratuito o de pago) 1002/mc.22006
Lung cancer causes more deaths worldwide than any other cancer. In addition to cigarette smoking, dietary factors may contribute to lung carcinogenesis. Epidemiologic studies, including the environment and genetics in lung cancer etiology (EAGLE), have reported increased consumption of red/processed meats to be associated with higher risk of lung cancer. Heme-iron toxicity may link meat intake with cancer. We investigated this hypothesis in meat-related lung carcinogenesis using whole genome expression. We measured genome-wide expression (HG-U133A) in 49 tumor and 42 non-involved fresh frozen lung tissues of 64 adenocarcinoma EAGLE patients. We studied gene expression profiles by high-versus-low meat consumption, with and without adjustment by sex, age, and smoking. Threshold for significance was a false discovery rate (FDR) ≤ 0.15. We studied whether the identified genes played a role in heme-iron related processes by means of manually curated literature search and gene ontology-based pathway analysis. We found that gene expression of 232 annotated genes in tumor tissue significantly distinguished lung adenocarcinoma cases who consumed above/below the median intake of fresh red meats (FDR = 0.12). Sixty-three (approximately 28%) of the 232 identified genes (12 expected by chance, P-value < 0.001) were involved in heme binding, absorption, transport, and Wnt signaling pathway (e.g., CYPs, TPO, HPX, HFE, SLCs, and WNTs). We also identified several genes involved in lipid metabolism (e.g., NCR1, TNF, and UCP3) and oxidative stress (e.g., TPO, SGK2, and MTHFR) that may be indirectly related to heme-toxicity. The study’s results provide preliminary evidence that heme-iron toxicity might be one underlying mechanism linking fresh red meat intake and lung cancer. © 2013 Wiley Periodicals, Inc.
RESUMEN / SUMMARY: Lung adenocarcinoma (ADC) is one of the major histological types of lung cancer. Genetic polymorphism in DNA repair genes and lung ADC susceptibility is well documented. In this case-control study, the association between the polymorphic sites of DNA repair genes XPD-751, XRCC1-399, and OGG1-326, and lung ADC susceptibility in ethnic Han Chinese population has been investigated. Genomic DNA was isolated from the peripheral blood of 201 healthy controls and 82 lung ADC patients from the people of Hunan Province, China. Polymorphisms of the investigated genes were analyzed by using polymerase chain reaction restriction fragment length polymorphism. There was no significant difference between the samples from lung ADC patients and healthy controls about the genotype frequencies of XPD-751, XRCC1-399, and OGG1-326 sites. However, multifactor dimensionality reduction analysis showed that the genetic polymorphisms of the three-loci models of DNA repair genes (XPD-751/XRCC1-399/OGG1-326) are associated with lung ADC. Thus, this study reveals that a three-order interaction among the polymorphic sites of XPD-751, XRCC1-399, and OGG1-326 is associated with lung ADC risk in the studied population, although polymorphism in individual gene was not associated.

[202]

TÍTULO / TITLE: Identification of recurrent FGFR3 fusion genes in lung cancer through kinome-centered RNA sequencing.


AUTORES / AUTHORS: Majewski IJ; Mittempergher L; Davidson NM; Bosma A; Willems SM; Horlings HM; de Rink I; Greger L; Hooijer GK; Peters D; Nederlof PM; Hofland I; de Jong J; Wesseling J; Kluij R; Brugman W; Kerkhoven R; Nieboer F; Roepman P; Broeks A; Muley TR; Jassem J; Niklinski J; van Zandwijk N; Brazma A; Oshlack A; van den Heuvel M; Bernards R

INSTITUCIÓN / INSTITUTION: Division of Molecular Carcinogenesis, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands; Division of Cancer and Haematology, The Walter and Eliza Hall Institute, 1G Royal Parade, Parkville, Victoria, 3052, Australia.

RESUMEN / SUMMARY: Oncogenic fusion genes that involve kinases have proven to be effective targets for therapy in a wide range of cancers. Unfortunately, the diagnostic approaches required to identify these events are struggling to keep pace with the diverse array of genetic alterations that occur in
cancer. Diagnostic screening in solid tumours is particularly challenging, as many fusion genes occur with a low frequency. To overcome these limitations, we developed a capture enrichment strategy to enable high throughput transcript sequencing of the human kinome. This approach provides a global overview of kinase fusion events, irrespective of the identity of the fusion partner. To demonstrate the utility of this system we profiled one hundred non-small cell lung cancers and identified numerous genetic alterations impacting Fibroblast Growth Factor Receptor 3 (FGFR3) in lung squamous cell carcinoma and a novel ALK fusion partner in lung adenocarcinoma.

[203]

**TITULO / TITLE:** - Asbestos, Asbestosis, Smoking and Lung Cancer: New Findings from the North American Insulator Cohort.

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

**REVISTA / JOURNAL:** - Am J Respir Crit Care Med. 2013 Apr 13.

●●Enlace al texto completo (gratuito o de pago) [1164/rcrm.201302-0257OC]

**AUTORES / AUTHORS:** - Markowitz SB; Levin SM; Miller A; Morabia A

**INSTITUCIÓN / INSTITUTION:** - Center for the Biology of Natural Systems, Queens College-CUNY, Queens, New York, United States ; smarkowitz@qc.cuny.edu.

**RESUMEN / SUMMARY:** - Abstract Rationale Asbestos, smoking, and asbestosis increase lung cancer risk in incompletely elucidated ways. Smoking cessation among asbestos-exposed cohorts has been little studied. Objectives To measure the contributions of asbestos exposure, asbestosis, smoking and their interactions to lung cancer risk in an asbestos-exposed cohort, and to describe their reduction in lung cancer risk when they stop smoking. Methods We examined lung cancer mortality obtained through the National Death Index for 1981-2008 for 2,377 male North American insulators for whom chest x-ray, spirometric, occupational and smoking data were collected in 1981-1983 and for 54,243 non-asbestos exposed blue collar male workers from Cancer Prevention Study II for whom occupational and smoking data were collected in 1982. Measurements and Main Results Lung cancer caused 339 (19%) insulator deaths. Lung cancer mortality was increased by asbestos exposure among non-smokers [rate ratio = 3.6 (95% CI: 1.7-7.6)], by asbestosis among non-smokers [rate ratio = 7.40 (95% CI, 4.0-13.7], and by smoking without asbestos exposure [rate ratio = 10.3 (95% CI, 8.8-12.2)]. The joint effect of smoking and asbestos alone was additive [rate ratio = 14.4 (95% CI, 10.7-19.4)] and with asbestosis, supra-additive [rate ratio = 36.8 (95% CI, 30.1-46.0)]. Insulator lung cancer mortality halved within 10 years of smoking cessation and converged with that of never-smokers 30 years following smoking cessation. Conclusions Asbestos increases lung cancer mortality among non-smokers. Asbestosis further increases the lung cancer risk and,
considered jointly with smoking, has a supra-additive effect. Insulators benefit greatly by quitting smoking. Abstract word count: 246 words Key words: interaction, smoking cessation.

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[204]

**TÍTULO / TITLE:** - Mutation analysis of the EGFR gene and downstream signalling pathway in histologic samples of malignant pleural mesothelioma.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Mezzapelle R; Miglio U; Rena O; Paganotti A; Allegrini S; Antona J; Molinari F; Frattini M; Monga G; Alabiso O; Boldorini R

**INSTITUCIÓN / INSTITUTION:** - 1] Unit of Pathology, Department of Health Sciences, University of Eastern Piedmont ‘Amedeo Avogadro’, Via Solaroli 17, Novara 28100, Italy [2] Division of Cancer Genomics, ‘Edo ed Elvo Tempia Valenta’ Foundation, Via Malta 2, Biella 13900, Italy.

**RESUMEN / SUMMARY:** - Background: As epidermal growth factor receptor (EGFR) is involved in the pathogenesis of malignant pleural mesotheliomas (MPMs), the anti-EGFR drugs may be effective in treating MPM patients. Mutations of the EGFR gene or its downstream effectors may cause constitutive activation leading to cell proliferation, and the inhibition of apoptosis and metastases. Consequently, molecular profiling is essential for select patients with MPM who may respond to anti-EGFR therapies.

**MÉTODOS / METHODS:** - After manual macrodissection, genomic DNA was extracted from 77 histological samples of MPM: 59 epithelioid, 10 biphasic, and 8 sarcomatoid. Epidermal growth factor receptor gene mutations were sought by means of real-time polymerase chain reaction (PCR) and direct sequencing, KRAS gene mutations by mutant-enriched PCR, and PIK3CA and BRAF gene mutations by direct sequencing.

**RESULTADOS / RESULTS:** - Gene mutations were identified in nine cases (12%): five KRAS, three BRAF, and one PI3KCA mutation; no EGFR gene mutations were detected. There was no difference in disease-specific survival between the patients with or without gene mutations (P=0.552).

**CONCLUSIONES / CONCLUSIONS:** - Mutations in EGFR downstream pathways are not rare in MPM. Although none of those found in this study seemed to be prognostically significant, they may support a more specific selection of patients for future trials.

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[205]

**TÍTULO / TITLE:** - Regulation of membrane-type 1 matrix metalloproteinase expression by zonula occludens-2 in human lung cancer cells.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
During tumor invasion, tumor epithelial cells acquire migratory and invasive properties involving important phenotypic alterations. Among these changes, one can observe reorganization or a loss of cell-cell adhesion complexes such as tight junctions (TJs). TJs are composed of transmembrane proteins (occludin, claudins) linked to the actin cytoskeleton through cytoplasmic adaptor molecules including those of the zonula occludens family (ZO-1, -2, -3). We here evaluated the potential role of ZO-2 in the acquisition of invasive properties by tumor cells. In vivo, we showed a decrease of ZO-2 expression in bronchopulmonary cancers, with a preferential localization in the cytoplasm. In addition, in vitro, the localization of ZO-2 varied according to invasive properties of tumor cells, with a cytoplasmic localization correlating with invasion. In addition, we demonstrated that ZO-2 inhibition increases invasive and migrative capacities of invasive tumor cells. This was associated with an increase of MT1-MMP. These results suggest that ZO-2, besides its structural role in tight junction assembly, can act also as a repressor of tumor progression through its ability to reduce the expression of tumor-promoting genes in invasive tumor cells.
extracellular-signal-regulated kinases (ERK) and AKT (protein kinase B) was examined by western blot. Flow cytometry was used for analyzing cell-cycle status and apoptosis detection. RESULTS: In H23 cells, 20 μM erlotinib suppressed growth, while gefitinib did not suppress proliferation after 48 h of treatment. Neither gefitinib nor erlotinib affected the phosphorylation of ERK and AKT in H23 cells. Erlotinib augmented the sub-G1 population of H23 cells, while gefitinib reduced it. CONCLUSION: In H23 cells, erlotinib accelerated apoptosis, while gefitinib induced G1 arrest.

[207]
TÍTULO / TITLE: - Does bilobectomy offer satisfactory long-term survival outcome for non-small cell lung cancer?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Icard P; Heyndrickx M; Galateau-Salle F; Rosat P; Lerochais JP; Gervais R; Zalcman G; Hanouz JL
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, University Hospital of Caen, Caen, France. Electronic address: icard-p@chu-caen.fr
RESUMEN / SUMMARY: - BACKGROUND: Results of bilobectomy for non-small cell lung cancer have rarely been studied. METHODS: Retrospective analysis was conducted on patients with non-small cell lung cancer having undergone bilobectomy from January 1999 to June 2012 at our institution. Analysis aimed at determining perioperative mortality and morbidity, and at studying prognostic factors for long-term survival using the 7th TNM classification. RESULTS: A total of 103 patients (85 males; mean age 62 years) underwent upper-middle bilobectomy (n = 54) or lower-middle bilobectomy (n = 49). Histologic examination revealed 51 adenocarcinomas, 43 squamous cell carcinomas and 9 other cell carcinomas. Perioperative mortality was 0.97%. The overall morbidity rate was 71%, whereas the rate of life-threatening complications was 9.6%. Complications were more frequent in men (p = 0.032), in patients with chronic pulmonary obstructive diseases (p = 0.030) and after lower-middle bilobectomy (p = 0.0016). The overall 5-year Kaplan-Meier survival rate was 57.8%. In univariate analysis, factors associated with increased survival were the following: pathologic stage (stage I 74.9%, stage II 64.1%, stage III 28.8%, p = 0.0018); nodal status (N0 vs N1, p = 0.011; N0 vs N2, p = 0.0015; N0 vs N+, p = 0.0008); R status (R0 vs R1, p = 0.0032), and smoking status (past smoker or nonsmoker vs active smoker, p = 0.00054). Multivariate analysis revealed that active smokers (RR = 3.87, CI 95% [1.83 to 8.21]; p = 0.00042) and increasing stage (stage 0: RR=1; stage I: RR = 1.98, CI 95% [1.38 to 2.83];
stage II: RR = 3.90, CI 95% [1.90 to 8.02]; stage III: RR=7.72, CI 95% [2.62 to 22.73]; stage IV: RR = 15.25, CI 95% [3.61 to 64.40]; p = 0.0042) were significantly associated with poorer survival. CONCLUSIONS: Bilobectomy can be performed with low mortality, acceptable morbidity and long term survival in accordance with TNM staging.

[208]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Zhang J; Yin Y; Niu XM; Liu Y; Garfield D; Chen SF; Wang R; Wang L; Chen HQ
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Shanghai Cancer Hospital, Fudan University, Shanghai, China.
RESUMEN / SUMMARY: - OBJECTIVES: To investigate the association between polymorphisms of aromatase (encoded by the CYP19A1 gene and a key enzyme in biosynthesis of oestradiol) and the risk of lung cancer, and whether there were differences stratified by sex and smoking history. METHODS: This case-control study included consecutive, nonselected and pathologically-confirmed lung cancer patients and healthy people. Participants were classed as nonsmokers or smokers by questionnaire. Peripheral blood samples from all participants were genotyped for three single-nucleotide polymorphism (SNPs; rs727479, rs730154 and rs10046); allelic frequencies were compared across genotype and clinical records. RESULTS: A total of 529 patients with lung cancer and 567 age- and sex-matched controls were included. After adjustment for age, sex and smoking history, rs727479 was significantly associated with the incidence of lung cancer (for alleles AC vs AA). There was also a significant difference between patients and controls in haplotype CCA, while haplotype ACA was only significantly associated with nonsmokers and female nonsmokers. CONCLUSIONS: Polymorphisms of CYP19A1 may be related to the increased risk of lung cancer; in particular, haplotype ACA may contribute to lung-cancer progression in nonsmokers. Further validation with larger populations is required.

[209]
TÍTULO / TITLE: - Lung cancer in never-smokers. Does smoking history matter in the era of molecular diagnostics and targeted therapy?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Lung cancer in never-smokers was recognised as a distinct clinical entity around the mid-2000s because these patients tended to be Asian women and diagnosed at a younger age with a preponderance of adenocarcinoma and better survival outcome despite a more advanced stage of presentation. It was soon discovered that lung cancer in never-smokers had a higher prevalence of activating EGFR mutations and we tend to classify lung cancer by smoking status for screening purpose. With the discoveries of many actionable driver mutations such as activating EGFR mutations and ALK rearrangement in adenocarcinoma of the lung we have switched to classifying non-small cell lung cancer into different individual molecular subgroups based on the presence of a dominant driver mutation. Although many actionable driver mutations are found in never-smokers with adenocarcinoma, this review will summarise that a substantial proportion of patients with these actionable driver mutations had a previous smoking history. Alternatively among the driver mutations that are associated with smoking history, a fair amount of these patients were never-smokers. Thus smoking status should not be used as a screen strategy for identifying driver mutations in clinical practice. Finally smoking history may have predictive and/or prognostic significance within individual molecular subgroups and identifying the difference according to smoking history may help optimise future targeted therapy.

[210]
TÍTULO / TITLE: First assessment of whole-brain radiation therapy combined with pemetrexed-based chemotherapy in non-small-cell lung carcinoma: data on safety and efficacy.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
1097/CAD.0b013e328360974d
AUTORES / AUTHORS: Chargari C; Pacaut C; Le Moulec S; Moriceau G; Moussaid Y; Rivoirard R; Dulou R; Jacob J; Guy JB; Bauduceau O; Ceccaldi B; Vedrine L; Fournel P; Magne N
INSTITUCIÓN / INSTITUTION: Departments of aMedical and Radiation Therapy bNeurosurgery, Hopital d'Instruction des Armees du Val-de-Grace, Paris Departments of cRadiation Therapy dMedical Oncology, Institut de Cancerologie Lucien Neuwirth, Saint Priest en Jarez, France eDepartment of Medical Oncology, Institut National d'Oncologie, Rabat, Morocco.
RESUMEN / SUMMARY: The folate antimetabolite pemetrexed was approved for the treatment of patients with metastatic nonsquamous non-small-cell lung
carcinoma. Its activity on brain metastases makes pemetrexed attractive in combination with whole-brain radiation therapy (WBRT), but it could also potentially increase toxicity. We examined the medical records of 43 consecutive patients with brain metastases from non-small-cell lung carcinoma. Patients received pemetrexed-based chemotherapy at a dose of 500 mg/m. The median total number of pemetrexed-based chemotherapy cycles was 4 (range: 1-28). During the course of chemotherapy, patients received WBRT delivering 30 Gy in 10 fractions (n=34) or 20 Gy in five fractions (n=9). The median follow-up time was 30.5 weeks (range: 1-79 weeks). Intracranial progression was a cause of death in nine patients (20.9%). Clinical benefit of WBRT was reported in 30 patients (69.8%). The best radiological response was a complete response in eight patients (18.6%), a partial response in 16 patients (37.2%), stable disease in 11 patients (25.6%), and progression in four patients (9.3%). A stable intracranial disease until the last follow-up was observed in 26 patients (60.5%). The median estimated overall survival was 31 weeks (95% CI: 24-37 weeks). Most WBRT-related toxicities were low and 21 patients (48.9%) had no reported acute neurological toxicity. One patient developed unexplained encephalopathy 5 weeks after WBRT completion in the context of progressive diffuse brain metastases. The combination of pemetrexed with WBRT led to considerable clinical improvement and tumor responses in most patients. Overall neurological toxicity was rather low. A clinical trial is essential for better analysis of the potential synergistic effects of a drug with radiation and evaluation of neurological toxicity.

[211]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kesanakurti D; Maddirela DR; Chittivelu S; Rao JS; Chetty C
INSTITUCIÓN / INSTITUTION: - Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine at Peoria, One Illini Drive, Peoria, IL 61605, United States.
RESUMEN / SUMMARY: - MicroRNAs are a novel family of small non-codingRNAs that regulate the expression of several genes involved in normal development as well as human disorders including cancer. Here we show that miR-874 plays a tumor suppressor role in non-small cell lung cancer (NSCLC) in vitro and in vivo. In silico target prediction analysis revealed numerous genes associated with tumor progression including MMP-2 and uPA as the putative
target genes of miR-874. Our preliminary in situ hybridization experiments demonstrated the diminution of miR-874 expression in lung cancer tissues compared to their normal counterparts. Overexpression of miR-874 in CD133-positive cancer stem cell (CSC) population led to a significant loss in CSC-phenotype and enhanced sphere de-differentiation into epithelial-like cells. Restoration of miR-874 expression drastically reduced cell invading ability in comparison to mock and control-miR-treated cells by suppressing the protein levels of MMP-2 and uPA. In in vivo experiments, miR-874 treatment decreased orthotopic tumor growth in nude mice compared to mock and control-miR treatments. Further, the immunoreactivity of human anti-MMP-2 and anti-uPA was significantly reduced in tumor sections from mice that received miR-874 treatment. In conclusion, our study highlights the possible tumor suppressor role of miR-874 in NSCLC-initiating cells and suggests miR-874 as a potential target in the treatment of NSCLC.

[212]

**TÍTULO / TITLE:** - X-ray repair cross-complementing group 1 Arg194Trp polymorphism is associated with increased risk of lung cancer in Chinese Han population.

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


**AUTORES / AUTHORS:** - Wu T; Xu YH; Ye XL

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiology, The First Affiliated Hospital, College of Medicine, Zhejiang University, No. 79, Qing-Chun Road, Hangzhou, 310003, People's Republic of China, docjackwu@yahoo.com.cn.

**RESUMEN / SUMMARY:** - There were many studies performed to assess the association between X-ray repair cross-complementing group 1 (XRCC1) Arg194Trp polymorphism and lung cancer risk in Chinese Han population, but contradictory results were reported. To provide a comprehensive and objective assessment of the association, a meta-analysis of all eligible case-control studies was carried out. After searching the databases and reading the abstracts, 12 case-control studies on the association between XRCC1 Arg194Trp polymorphism and lung cancer risk were finally included into this meta-analysis. Those 12 studies included a total of 4,385 cases and 4,545 controls. XRCC1 Arg194Trp polymorphism was associated with increased risk of lung cancer in Chinese Han population under three main models (allele contrast model, odds ratio (OR) = 1.12, 95 % confidence interval (CI) 1.00-1.26, P = 0.049; homozygote model, OR = 1.27, 95 % CI 1.09-1.48, P = 0.003; recessive model, OR = 1.26, 95 % CI 1.09-1.46, P = 0.003). However, there was no obvious association between XRCC1 Arg194Trp polymorphism and
lung cancer risk under the dominant model (OR = 1.06, 95% CI 0.98-1.16, P = 0.146). Sensitivity analysis suggested the stability and liability of this meta-analysis. Therefore, this meta-analysis suggests that XRCC1 Arg194Trp polymorphism is associated with increased risk of lung cancer in Chinese Han population.

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[213]

TÍTULO / TITLE: - Lymphatic Endothelial Differentiation in Pulmonary Lymphangioleiomyomatosis Cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Davis JM; Hyjek E; Husain AN; Shen L; Jones J; Schuger LA

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Biological Sciences Division, University of Chicago, Chicago, Illinois (JEH, ANH, LS, JJ, LAS).
RESUMEN / SUMMARY: - Pulmonary lymphangioleiomyomatosis (LAM) is a rare, low-grade neoplasm affecting almost exclusively women of childbearing age. LAM belongs to the family of perivascular epithelioid cell tumors, characterized by spindle and epithelioid cells with smooth muscle and melanocytic differentiation. LAM cells infiltrate the lungs, producing multiple, bilateral lesions rich in lymphatic channels and forming cysts, leading to respiratory insufficiency. Here we used antibodies against four lymphatic endothelial markers-podoplanin (detected by D2-40), prospero homeobox 1 (PROX1), vascular endothelial growth factor receptor 3 (VEGFR-3), and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1)-to determine whether LAM cells show lymphatic differentiation. Twelve of 12 diagnostic biopsy specimens (early-stage LAM) and 19 of 19 explants (late-stage LAM) showed immunopositivity for D2-40 in most neoplastic cells. PROX1, VEGFR-3, and LYVE1 immunoreactivity varied from scarce in the early stage to abundant in the late stage. Lymphatic endothelial, smooth muscle, and melanocytic markers were partially co-localized. These findings indicate that lymphatic endothelial differentiation is a feature of LAM and provide evidence of a previously unidentified third lineage of differentiation in this neoplasm. This study has implications for the histological diagnosis of LAM, the origin of the neoplastic cells, and potential future treatment with drugs targeting lymphangiogenesis.

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[214]
Novel Hybrids of (Phenylsulfonyl)furoxan and Anilinopyrimidine as Potent and Selective Epidermal Growth Factor Receptor Inhibitors for Intervention of Non-Small-Cell Lung Cancer.

A series of hybrids (12ª-k) from (phenylsulfonyl)furoxan and anilinopyrimidine were synthesized and biologically evaluated as epidermal growth factor receptor (EGFR) inhibitors for intervention of non-small-cell lung cancer (NSCLC). Compound 12k exhibited strong and selective EGFR L858R/T790M inhibitory activity (IC50 = 0.047 μM) and displayed antiproliferative effects on EGFR mutation NSCLC cell lines HCC827 (del E746_A750) and H1975 (L858R/T790M) with IC50 values of 0.007 and 0.029 μM, respectively. Additionally, 12k released high levels of NO in H1975 cells but not in normal human cells, and its activity was diminished by pretreatment with a NO scavenger. Furthermore, 12k induced apoptosis of H1975 and HCC827 cells more strongly than WZ4002 (1), inhibited EGFR downstream signaling in H1975 cells, and suppressed the nuclear factor-kappaB activation in H1975 cells, while 1 had no significant effects under the same conditions. Finally, 12k substantially inhibited tumor growth in an H1975 xenograft mouse model. Overall, 12k might be a promising candidate for the treatment of NSCLC.

Current clinical immunotherapy targets in advanced nonsmall cell lung cancer (NSCLC).

NSCLC remains one of the most challenging malignancies to treat. Despite the introduction of innovative therapies over the last decade, the 5-year survival of NSCLC is still <20%. Clearly, novel, therapeutic approaches are required. Targeting the immune system to derive
meaningful clinical benefit has proved successful in various malignancies in recent years. As a result, there is renewed focus on the use of immunotherapy in lung cancer. In this review, we provide an overview of current immune-modulatory approaches in the treatment of NSCLC.

[216]

TÍTULO / TITLE: - Smoking-induced CXCL14 Expression in the Human Airway Epithelium Links COPD to Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Shaykhiev R; Sackrowitz R; Fukui T; Zuo WL; Chao I; Strulovici-Barel Y; Downey RJ; Crystal RG
INSTITUCIÓN / INSTITUTION: - Weill Cornell Medical College, Department of Genetic Medicine, New York, New York, United States.

RESUMEN / SUMMARY: - CXCL14, a recently described epithelial cytokine, has multiple putative roles in inflammation and carcinogenesis. In the context that chronic obstructive pulmonary disease (COPD) and lung cancer are both smoking-related disorders associated with airway epithelial disorder and inflammation, we hypothesized that the airway epithelium responds to cigarette smoking with altered CXCL14 gene expression contributing to the disease-relevant phenotype. Using genome-wide microarrays with subsequent immunohistochemistry analysis, the data demonstrates that the expression of CXCL14 is up-regulated in the airway epithelium of healthy smokers and further increased in COPD smokers, especially within hyperplastic/metaplastic lesions, in association with multiple genes relevant to epithelial structural integrity and cancer. In vitro studies revealed that expression of CXCL14 is induced in the differentiated airway epithelium by cigarette smoke extract in an epidermal growth factor (EGF) receptor-dependent manner, and EGF mediates CXCL14 up-regulation in the differentiated airway epithelium through its effect on basal stem/progenitor cell population. Analysis of two independent lung cancer cohorts revealed dramatic up-regulation of CXCL14 expression in adenocarcinoma and squamous cell carcinoma. High expression of the COPD-associated CXCL14-correlating cluster of genes correlated in lung adenocarcinoma with poor survival. These data suggest that smoking-induced expression of CXCL14 in the airway epithelium represents a novel potential molecular link between smoking-associated airway epithelial injury, COPD and lung cancer.

[217]
TÍTULO / TITLE: - Advanced imaging (positron emission tomography and magnetic resonance imaging) and image-guided biopsy in initial staging and monitoring of therapy of lung cancer.

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


AUTORES / AUTHORS: - Islam S; Walker RC

INSTITUCIÓN / INSTITUTION: - From the *Interventional Pulmonology, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Wexner Medical Center, Ohio State University, Columbus, OH; and daggerDepartment of Medical Imaging, VA Tennessee Valley Healthcare System; Vanderbilt University Medical Center; and Vanderbilt-Ingram Cancer Center, Nashville, TN.

RESUMEN / SUMMARY: - The results of the National Lung Screening Trial strongly support early detection and definitive treatment to reduce lung cancer mortality. Once lung cancer is discovered, accurate staging at baseline is imperative to maximize patient benefit and cost-effective use of health care resources. Although computed tomography (CT) remains a powerful tool for staging of lung cancer, advances in other imaging modalities, specifically positron emission tomography/CT and magnetic resonance imaging, can improve baseline staging over CT alone and can allow a more rapid and accurate assessment of response to treatment. Although noninvasive imaging is extremely useful, tissue diagnosis remains the criterion standard for staging lung cancer and monitoring treatment response. Accordingly, tissue sampling using advanced bronchoscopic imaging guidance, such as ultrasound or electromagnetic navigation, allows precise tissue location and sampling of mediastinal nodes or lung nodules in the least invasive manner. In the future, bronchoscopy may allow real-time microscopic analysis.

[218]

TÍTULO / TITLE: - Synergistic induction of apoptosis by sulindac and simvastatin in A549 human lung cancer cells via reactive oxygen species-dependent mitochondrial dysfunction.

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


AUTORES / AUTHORS: - Hwang KE; Park C; Kwon SJ; Kim YS; Park DS; Lee MK; Kim BR; Park SH; Yoon KH; Jeong ET; Kim HR
RESUMEN / SUMMARY: - Prevention of lung cancer is more feasible and holds greater promise when different agents are used in combination to target multiple processes during carcinogenesis. The mechanisms by which non-steroidal anti-inflammatory drugs and statins inhibit cancer cell growth and induce apoptosis are not fully understood. This study was designed to investigate lung cancer chemoprevention through a mechanism-based approach using sulindac at low doses in combination with simvastatin. We found that sulindac-induced cytotoxicity was significantly enhanced in the presence of simvastatin. The combination of sulindac and simvastatin induced more extensive caspase-dependent apoptosis in A549 cells compared to that induced with either drug alone. The combination of sulindac and simvastatin also increased the loss of mitochondrial transmembrane potential (Psim) and the cytosolic release of cytochrome c. In addition, ROS generation in cells treated with both sulindac and simvastatin was markedly increased compared to cells treated with either sulindac or simvastatin alone. The enhancement of ROS generation by sulindac and simvastatin was abrogated by pretreatment with NAC, which also prevented apoptosis and mitochondrial dysfunction induced by sulindac and simvastatin. These results suggest that sulindac and simvastatin-induced ROS generation in A549 lung cancer cells causes their accumulation in mitochondria, triggering the release of apoptogenic molecules from the mitochondria to the cytosol, and thus leading to caspase activation and cell death.

[219] TÍTULO / TITLE: - Regulation of pro-angiogenic tissue factor expression in hypoxia-induced human lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Eisenreich A; Zakrzewicz A; Huber K; Thierbach H; Pepke W; Goldin-Lang P; Schultheiss HP; Pries A; Rauch U

INSTITUCIÓN / INSTITUTION: - Charite-Universitätsmedizin Berlin, Campus Benjamin Franklin, Centrum fur Herz- und Kreislaufmedizin, D-12200 Berlin, Germany.
RESUMEN / SUMMARY: - Alternative splicing is a key regulatory mechanism for cellular metabolism controlling cell proliferation and angiogenesis, both of which are crucial processes for tumorigenesis under hypoxia. Human cells express two tissue factor (TF) isoforms, alternatively spliced TF (asTF) and 'full length' TF (flTF). flTF is the major source of thrombogenicity whereas, the function of
soluble asTF, particularly in cancer, is widely unknown. In the present study, we examined the impact of alternative splicing on the pro-angiogenic potential and the TF expression pattern of A549 cells under hypoxia. We focused our efforts toward alternative splicing factors, such as Clk1, and pro-angiogenic proliferation-regulating factors, such as Cyr61. We further examined the influence of asTF overexpression on the expression of MCP-1, Cyr61 and VEGF, as well as on cell number and pro-angiogenic properties of A549 cells. Notably, we found hypoxia to induce the expression of alternative splicing factors (Clk1 and Clk4) as well as proliferation- and angiogenesis-promoting factors (Cyr61 and flTF). asTF overexpression in A549 cells also increased both cell number and tube formation. These effects were mediated by the induction of Cyr61, MCP-1 and VEGF, as well as by integrin alphavbeta3. Taken together, our results suggest that the pro-angiogenic potential of A549 lung cancer cells is modulated under hypoxic conditions via modulation of TF isoform expression which in turn is controlled by alternative splicing.

[220]

TÍTULO / TITLE: - Imputation-based association analyses identify new lung cancer susceptibility variants in CDK6 and SH3RF1 and their interactions with smoking in Chinese populations.

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


AUTORES / AUTHORS: - Deng Q; Guo H; Dai J; Yang L; Wu C; Wang Q; Hu Z; Yang M; Liu L; Yu D; Hu D; Hong X; Qiu F; Yang H; Wang T; Tan W; Chu M; Feng J; Teng K; Gong J; Sun C; Hu X; Zhang K; Lu J; Lin D; Shen H; Wu T

INSTITUCIÓN / INSTITUTION: - Institute of Occupational Medicine and Ministry of Education (MOE) Key Laboratory for Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

RESUMEN / SUMMARY: - Cell cycle regulation, apoptosis, oxidative stress, and inflammation response play critical roles in the development of smoking-induced lung cancer. However, it is still not well known whether their genetic variants are associated with lung cancer susceptibility. Here we performed imputation-based association analyses to investigate the influence of common genetic variants in these pathways and their interactions with smoking on lung cancer susceptibility. We first selected 24 042 unvalidated genetic variants in 798 genes from the imputed dataset of the previous lung cancer genome-wide association study (GWAS) in 2331 cases and 3077 controls, and then conducted additional two-stage validations in 4133 cases and 4522 controls. We found a genome-wide significant (P < 5.0x10^-8) association for rs2282987 in CDK6 at 7q21.2 [odds ratio (OR) = 1.18, combined Padd = 2.27x10^-9] and a
consistent association for rs2706748 in SH3RF1 at 4q32.3 (OR = 1.17, combined Padd = 5.10x10^-6). Interaction analyses showed that rs2282987 and rs2706748 interacted with both smoking status (Pinteraction were 1.04x10^-2 and 3.03x10^-2, respectively) and smoking dose (Pinteraction were 1.21x10^-2 and 5.21x10^-2, respectively) to contribute to lung cancer susceptibility in subjects aged 50 to 60 years. These results further underscore the contribution of genetic variants involved in pathways of cell cycle regulation and apoptosis to lung cancer susceptibility, and highlight gene-environment interactions in lung cancer etiology, especially in subjects aged 50 to 60 years.

[221]
TITULO / TITLE: Lung adenocarcinoma subtypes based on expression of human airway basal cell genes.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: Eur Respir J. 2013 May 3.
●●Enlace al texto completo (gratuito o de pago) 1183/09031936.00144012
AUTORES / AUTHORS: Fukui T; Shaykhiev R; Agosto-Perez F; Mezey JG; Downey RJ; Travis WD; Crystal RG
INSTITUCIÓN / INSTITUTION: Weill Cornell Medical College, New York, New York.
RESUMEN / SUMMARY: Lung cancer, including lung adenocarcinoma (adenoCa), is a heterogeneous disease, which evolves from molecular alterations in the airway epithelium. The study explores whether a subtype of lung adenoCa expresses the unique molecular features of human airway basal cell (BC), and how expression of the airway BC features correlates with the molecular, pathologic and clinical phenotype of lung adenoCa. Three independent lung adenoCa data sets were analysed for expression of genes that constitute the airway BC signature. Expression of the BC signature in lung adenoCa was then correlated to clinical and biologic parameters. Remarkable enrichment of airway BC signature genes was found in lung adenoCa. A subset of lung adenoCa (“BC-high adenoCa”) exhibited high expression of BC signature genes in association with poorer tumor grade, higher frequency of vascular invasion, and shorter survival than adenoCa with lower expression of these genes. At the molecular level, “BC-high adenoCa” displayed higher frequency of KRAS mutations, activation of transcriptional networks and pathways related to cell cycle, extracellular matrix organization, and a distinct differentiation pattern with suppression of ciliated- and exocrine bronchiolar cell (Clara cell)-related genes. Activation of the airway BC program is a molecular feature of a distinct, aggressive subtype of lung adenoCa.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ● Enlace al texto completo (gratuito o de pago) 3109/09553002.2013.784425
AUTORES / AUTHORS: - Leonard BE

[223]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ● Enlace al texto completo (gratuito o de pago) 3892/ijo.2013.1895
AUTORES / AUTHORS: - Zou M; Xia S; Zhuang L; Han N; Chu Q; Chao T; Peng P; Chen Y; Gui Q; Yu S
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, P.R. China.
RESUMEN / SUMMARY: - Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are being widely used as targeted therapy in non-small cell lung cancer (NSCLC), but most cases acquire drug-resistance in 9 months. However, the mechanisms of resistance are still not fully understood. Since it has been demonstrated that EGFR-TKI-mediated repression of downstream signaling cascades and apoptosis induction is a key mechanism through which EGFR-TKIs exert their cytotoxic effects, we reasoned that activation of downstream signaling pathways and changes in the expression of apoptosis-related proteins contribute to the acquired resistance to EGFR-TKIs. We analyzed the protein levels of p-Akt, Bcl-2, Bax between gefitinib-sensitive and gefitinib-resistant lung cancer cell lines and evaluated whether targeting the anti-apoptotic protein Bcl-2 induces cell apoptosis and further sensitizes resistant H1975 cells to gefitinib. The data showed that p-Akt was activated and accompanied by substantial Bcl-2 in the H1975 lung cancer cell line, whereas no evidence was observed in HCC827 cells. Using small interfering RNA (siRNA) to silence Bcl-2 in H1975 cells led to significant downregulation of Bcl-2 protein expression, decreased cell viability in vitro and induced intrinsic apoptosis confirmed by flow cytometry and PARP cleavage. In Bcl-2 siRNA-transfected cells, adding gefitinib further reduced the number of viable cells, induced apoptosis to a greater extent compared to either treatment alone.
These preclinical data suggested that downregulation of Bcl-2 by RNAi in the gefitinib-resistant H1975 lung cancer cell line with T790M mutation enhanced the effects of gefitinib and may offer a novel therapeutic strategy for the treatment of NSCLC.

[224]
**TITULO / TITLE:** - Miliary pulmonary lymphangioleiomyomatosis.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1164/rccm.201203-0427IM)
  ●●Enlace al texto completo (gratuito o de pago) [1164/rccm.201203-0427IM](https://doi.org/10.1164/rccm.201203-0427IM)
**AUTORES / AUTHORS:** - Xu KF; Zhang W; Liu H
**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China.

[225]
**TITULO / TITLE:** - Does Pneumonectomy Have a Role in the Treatment of Stage IIIA Non-Small Cell Lung Cancer?
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1016/j.athoracsur.2013.02.044)
  ●●Enlace al texto completo (gratuito o de pago) [1016/j.athoracsur.2013.02.044](https://doi.org/10.1016/j.athoracsur.2013.02.044)
**AUTORES / AUTHORS:** - Shah AA; Worni M; Kelsey CR; Onaitis MW; D'Amico TA; Berry MF
**INSTITUCIÓN / INSTITUTION:** - Division of Cardiovascular and Thoracic Surgery, Duke University Medical Center, Durham, North Carolina.
**RESUMEN / SUMMARY:** - BACKGROUND: The role of surgical resection for stage IIIA non-small cell lung cancer (NSCLC) is unclear. We sought to examine outcomes after pneumonectomy for patients with stage IIIA disease. METHODS: All patients with stage IIIA NSCLC who had pneumonectomy at a single institution between 1999 and 2010 were reviewed. The Kaplan-Meier method was used to estimate long-term survival and multivariable Cox proportional hazards regression was used to identify clinical characteristics associated with survival. RESULTS: During the study period, 324 patients had surgical resection of stage IIIA NSCLC. Pneumonectomy was performed in 55 patients, 23 (42%) of whom had N2 disease. Induction treatment was used in 17 patients (31%) overall and in 11 of the patients (48%) with N2 disease. Perioperative mortality was 9% (n = 5) overall and 18% (n = 3) in patients that
had received induction therapy (p = 0.17). Complications occurred in 32 patients (58%). Three-year survival was 36% and 5-year survival was 29% for all patients. Three-year survival was 40% for N0-1 patients and 29% for N2 patients (p = 0.59). In multivariable analysis, age over 60 years (hazard ratio [HR] 3.65, p = 0.001), renal insufficiency (HR 5.80, p = 0.007), and induction therapy (HR 2.17, p = 0.05) predicted worse survival, and adjuvant therapy (HR 0.35, p = 0.007) predicted improved survival. CONCLUSIONS: Long-term survival after pneumonectomy for stage IIIA NSCLC is within an acceptable range, but pneumonectomy may not be appropriate after induction therapy or in patients with renal insufficiency. Patient selection and operative technique that limit perioperative morbidity and facilitate the use of adjuvant chemotherapy are critical to optimizing outcomes.

[226]


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


Enlace al texto completo (gratuito o de pago) 1080/01635581.2013.785003

AUTORES / AUTHORS: - Tyagi A; Raina K; Gangar S; Kaur M; Agarwal R; Agarwal C

INSTITUCIÓN / INSTITUTION: - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA.

RESUMEN / SUMMARY: - The present study examines grape seed extract (GSE) efficacy against a series of non-small-cell lung cancer (NSCLC) cell lines that differ in their Kras and p53 status to establish GSE potential as a cytotoxic agent against a wide range of lung cancer cells. GSE suppressed growth and induced apoptotic death in NSCLC cells irrespective of their k-Ras status, with more sensitivity toward H460 and H322 (wt k-Ras) than A549 and H1299 cells (mutated k-Ras). Mechanistic studies in A549 and H460 cells, selected, based on comparative efficacy of GSE at higher and lower doses, respectively, showed that apoptotic death involves cytochrome c release associated caspases 9 and 3 activation, and poly (ADP-ribosyl) polymerase cleavage, strong phosphorylation of ERK1/2 and JNK1/2, downregulation of cell survival proteins, and upregulated proapoptotic Bak expression. Importantly, GSE treatment caused a strong superoxide radical-associated oxidative stress, significantly decreased intracellular reduced glutathione levels, suggesting, for the first time, the involvement of GSE-caused oxidative stress in its apoptotic
inducing activity in these cells. Because GSE is a widely-consumed dietary agent with no known untoward effects, our results support future studies to establish GSE efficacy and usefulness against NSCLC control.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1080/01635581.2013.785007
AUTORES / AUTHORS: - Singh N; Nambiar D; Kale RK; Singh RP
INSTITUCIÓN / INSTITUTION: - a School of Life Sciences, Central University of Gujarat, Gandhinagar, India.
RESUMEN / SUMMARY: - Usnic acid (UA) is a secondary metabolite abundantly found in lichens. Some studies have shown the anticancer potential of UA; however, its efficacy and associated mechanisms are yet to be fully explored. Herein, we assessed the anticancer potency and associated molecular alterations by UA in human lung carcinoma A549 cells. UA treatment (25-100 μM) for 24 and 48 h decreased total cell number by 39-67% (P < 0.01) and 68-89% (P < 0.001), respectively, and enhanced cell death by up to twofold and eightfold (P < 0.001), respectively. UA (1-10 μM) also significantly (P < 0.001) suppressed colony formation of A549 cells. The cell growth inhibition was associated with cell cycle arrest at G0/ G1 phase. UA decreased the expression of cyclin-dependent kinase (CDK)4, CDK6, and cyclin D1 and increased the expression of CDK inhibitor (CDKI) p21/cip1 protein. While examining the cell death associated molecular changes, we observed that UA induces mitochondrial membrane depolarization and led to more than twofold increase (P < 0.01) in apoptotic cells. The apoptotic effect of UA was accompanied by enhanced poly(ADP-ribose) polymerase cleavage. This study shows that UA inhibits cell growth involving G0/G1 phase cell cycle arrest and induces cell death via mitochondrial membrane depolarization and induction of apoptosis in human lung carcinoma cells.

[228] TÍTULO / TITLE: - ERK2 but not ERK1 mediates HGF-induced motility in non small cell lung carcinoma cell lines.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1242/jcs.115832
Aberrant signalling of receptor tyrosine kinases (RTKs), such as c-Met, the receptor for hepatocyte growth factor (HGF), has been implicated in the oncogenesis of various tumours including non-small cell lung carcinoma (NSCLC). Through its pro-migratory properties, c-Met has been implicated specifically in the process of tumour metastasis demanding a better understanding of the underlying signalling pathways. Various players downstream of c-Met have been well characterised, including the extracellular-signal-regulated kinases (ERKs) \(^2\). In a small interfering (si) RNA based high throughput wound healing screen performed in A549 lung carcinoma cells, we identified ERK2 but not ERK1 as a strong mediator of HGF-induced motility. This finding was confirmed in several NSCLC cell lines as well as HeLa cells. One known substrate for ERK kinases in cell migration, the focal adhesion protein paxillin, was also one of the hits identified in the screen. We demonstrate that HGF stimulation results in a time dependent phosphorylation of paxillin on serine 126, a process which can be blocked by inhibition of the ERK1/2 upstream kinase Mitogen-Activated Protein Kinase/ERK Kinase 1 (MEK1) or inhibition of glycogen synthase kinase (GSK) 3. Further we show that paxillin turnover at focal adhesions is increased upon HGF-stimulation, an effect that is dependent on serines 126 (GSK3 site) and 130 (ERK site) within paxillin. In line with the isoform specific requirement of ERK2 for HGF-mediated migration in lung tumour cell models, ERK2 but not ERK1 is shown to be responsible for paxillin S126 phosphorylation and its increased turnover at focal adhesions.

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Analysis of Occupational Asbestos Exposure and Lung Cancer Mortality Using the G Formula.

We employed the parametric G formula to analyze lung cancer mortality in a cohort of textile manufacturing workers who were occupationally exposed to asbestos in South Carolina. A total of 3,002 adults with a median age of 24 years at enrollment (58% male, 81% Caucasian) were followed for 117,471 person-years between 1940 and 2001, and 195 lung cancer deaths were observed. Chrysotile asbestos exposure was measured in fiber-years per milliliter of air, and annual occupational exposures were estimated on the basis of detailed work histories. Sixteen percent of person-years involved exposure to asbestos, with a median exposure of 3.30 fiber-
years/mL among those exposed. Lung cancer mortality by age 90 years under the observed asbestos exposure was 9.44%. In comparison with observed asbestos exposure, if the facility had operated under the current Occupational Safety and Health Administration asbestos exposure standard of <0.1 fibers/mL, we estimate that the cohort would have experienced 24% less lung cancer mortality by age 90 years (mortality ratio = 0.76, 95% confidence interval: 0.62, 0.94). A further reduction in asbestos exposure to a standard of <0.05 fibers/mL was estimated to have resulted in a minimal additional reduction in lung cancer mortality by age 90 years (mortality ratio = 0.75, 95% confidence interval: 0.61, 0.92).
dose level +1, approximately 40% lower gefitinib plasma concentrations were noted on day 29 compared with day 15 along with a mean 44% reduction in area under the plasma concentration-time curve from 0 to 24 h (AUC0-24). Bexarotene appears to lower the Cmax and AUC0-24 of gefitinib through cytochrome P450 CYP3A4. Our results have pharmacokinetic implications for ongoing trials that combine bexarotene with other small molecules in the era of personalized cancer therapy.

[231]

**TÍTULO / TITLE:** CHEK2*1100delC homozygosity in the Netherlands - prevalence and risk of breast and lung cancer.

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


**AUTORES / AUTHORS:** Huijts PE; Hollestelle A; Balliu B; Houwing-Duistermaat JJ; Meiijers CM; Blom JC; Ozturk B; Krol-Warmerdam EM; Wijnen J; Berns EM; Martens JW; Seynaeve C; Kiemeney LA; van der Heijden HF; Tollenaar RA; Devilee P; van Asperen CJ

**INSTITUCIÓN / INSTITUTION:** Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands.

**RESUMEN / SUMMARY:** The 1100delC mutation in the CHEK2 gene has a carrier frequency of up to 1.5% in individuals from North-West Europe. Women heterozygous for 1100delC have an increased breast cancer risk (odds ratio 2.7). To explore the prevalence and clinical consequences of 1100delC homozygosity in the Netherlands, we genotyped a sporadic breast cancer hospital-based cohort, a group of non-BRCA1/2 breast cancer families, and breast tumors from a tumor tissue bank. Three 1100delC homozygous patients were found in the cohort of 1434 sporadic breast cancer patients, suggesting an increased breast cancer risk for 1100delC homozygotes (odds ratio 3.4, 95% confidence interval 0.4-32.6, P=0.3). Another 1100delC homozygote was found in 592 individuals from 108 non-BRCA1/2 breast cancer families, and two more were found after testing 1706 breast tumors and confirming homozygosity on their wild-type DNA. Follow-up data was available for five homozygous patients, and remarkably, three of them had developed contralateral breast cancer. A possible relationship between 1100delC and lung cancer risk was investigated in 457 unrelated lung cancer patients but could not be confirmed. Due to the small number of 1100delC homozygotes identified, the breast cancer risk estimate associated with this genotype had limited accuracy but is probably higher than the risk in heterozygous females. Screening for CHEK2 1100delC could be beneficial in countries with a relatively high allele frequency.

European
Enlace al texto completo (gratuito o de pago) 1007/s40265-013-0032-4

AUTORES / AUTHORS: - Berge EM; Doebele RC

INSTITUCIÓN / INSTITUTION: - Division of Medical Oncology, Department of Medicine, University of Colorado, Mail Stop 8117, 12801 E. 17th Avenue, Room 8105, Aurora, CO, 80045, USA, Eamon.Berge@ucdenver.edu.

RESUMEN / SUMMARY: - Metastatic non-small cell lung cancer remains a disease with a high annual incidence and annual mortality worldwide, with limitations in first-line treatment past a fixed amount of platinum doublet chemotherapy for patients that do not harbor a targetable genetic abnormality such as an EGFR mutation or ALK gene rearrangement. Previous attempts to extend first-line treatment past 4-6 cycles of conventional cytotoxic chemotherapy have been disappointing, resulting in diminished quality of life and increased toxicity without improvement of progression-free or overall survival. Several advances in third-generation chemotherapy and targeted agents have generated a renewed interest in maintenance therapy, with several randomized phase III trials reporting a significant improvement in progression-free and overall survival with manageable toxicity profiles. The availability of new chemotherapy agents, tyrosine kinase inhibitors, and immunotherapy agents with a more tolerable or nonoverlapping toxicity profile have resulted in improvements in progression-free survival and median overall survival in maintenance settings with specific agents such as pemetrexed and erlotinib. Patients who are responding to first-line therapy, have not suffered a detrimental decrease in quality of life or performance status, and understand the risks and benefits of further immediate chemotherapy should be considered for maintenance treatment.
Lung cancer is one of the commonest cancers detected worldwide with a high mortality rate. The responsible factors affecting survival include delayed prognosis, and lack of effective treatments. To help improve the disease management, there is a need for better screening and development of specific markers that help in the early diagnosis. Analysis of differentially expressed proteins in cancer cells in comparison to their normal counterparts using proteome profiling revealed identification of new biomarkers as therapeutic targets. Therefore, an animal model for lung cancer was developed and monitored by histopathological evaluation. Lung tissue proteins were isolated, solubilized and resolved on 2D gel electrophoresis using broad pH range IPG strips (pH 3-10). Liquid chromatography and mass spectrometry (LC-MS/MS) revealed 66 proteins to be differentially expressed in cancer tissue as compared to normal. The study identified and characterized three of these proteins, namely peroxiredoxin-6, beta-actin and collagen alpha-1 (VI) as potentially prospective biomarkers for early detection of lung cancer.
Radiotherapy is routinely used for the treatment of lung cancer. However, the mechanisms underlying ionizing radiation (IR)-induced senescence and its role in lung cancer treatment are poorly understood. Here, we show that IR suppresses the proliferation of human non-small cell lung cancer (NSCLC) cells via an apoptosis-independent mechanism. Further investigations reveal that the anticancer effect of irradiation correlates well with IR-induced premature senescence, as evidenced by increased senescence-associated beta-glactosidase (SA-beta-gal) staining, decreased BrdU incorporation and elevated expression of p16INK4a (p16) in irradiated NSCLC cells. Mechanistic studies indicate that the induction of senescence is associated with activation of the p53-p21 pathway, and that inhibition of p53 transcriptional activity by PFT-alpha attenuates IR-induced tumor cell killing and senescence. Gain-of-function assays demonstrate that restoration of p53 expression sensitizes H1299 cells to irradiation, whereas knockdown of p53 expression by siRNA inhibits IR-induced senescence in H460 cells. Furthermore, treatment with Nutlin-3\â, a small molecule inhibitor of MDM2, enhances IR-induced tumor cell killing and senescence by stabilizing the activation of the p53-p21 signaling pathway. Taken together, these findings demonstrate for the first time that pharmacological activation of p53 by Nutlin-3\â can sensitize lung cancer cells to radiation therapy via promoting IR-induced premature senescence.
in various nonsmall cell lung cancer cells. Further study showed that HDMC elevated cellular reactive oxygen species (ROS) levels, thus inducing expressions of ATF4 and C/EBP homologous protein (CHOP). Then, death receptor 5 (DR5) was upregulated through ATF4-CHOP axis and eventually resulted in apoptosis. We also found that downregulation of c-FLIPL contributed to HDMC-induced apoptosis. In conclusion, HDMC induces apoptosis in human nonsmall cell lung cancer cells via activation of DR5 signaling pathway, and ROS-mediated ATF4-CHOP axis is involved in the process. Our results further supported the potential for HDMC to be developed as a new antitumor agent for cancer therapy or chemoprevention. © 2013 IUBMB Life, 2013.

[237]

TÍTULO / TITLE: - A National Study of Nodal Upstaging After Thoracoscopic Versus Open Lobectomy for Clinical Stage I Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago)
1016/j.athoracsur.2013.04.011
AUTORES / AUTHORS: - Licht PB; Jorgensen OD; Ladegaard L; Jakobsen E
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, Odense University Hospital, Odense, Denmark. Electronic address: plicht@health.sdu.dk.
RESUMEN / SUMMARY: - BACKGROUND: Nodal upstaging after surgical intervention for non-small cell lung cancer (NSCLC) occurs when unsuspected lymph node metastases are found during the final evaluation of surgical specimens. Recent data from The Society of Thoracic Surgery (STS) database demonstrated significantly lower nodal upstaging after thoracoscopic (VATS) lobectomy than after thoracotomy. STS data, however, may be biased from voluntary reporting, and survival was not investigated. We used a complete national registry to compare nodal upstaging and survival after lobectomy by VATS or thoracotomy. METHODS: The Danish Lung Cancer Registry was used to identify patients who underwent lobectomy for clinical stage I NSCLC from 2007 to 2011. Patient demographics, comorbidity, preoperative staging, surgical approach, number of lymph nodes harvested, final pathology, and survival were evaluated. Nodal upstaging was identified by comparing cT N M with pT N M. RESULTS: Lobectomy for clinical stage I NSCLC was performed in 1,513 patients: 717 (47%) by VATS and 796 (53%) by thoracotomy. Nodal upstaging occurred in 281 patients (18.6%) and was significantly higher after thoracotomy for N1 upstaging (13.1% vs 8.1%; p < 0.001) and N2 upstaging (11.5% vs 3.8%; p < 0.001). Overall unadjusted survival was significantly higher after VATS, but after adjusting for differences in sex, age, comorbidity, and pT N M
by Cox regression analysis, we found no difference between VATS and thoracotomy (hazard ratio, 0.98; 95% confidence interval, 0.80 to 1.22, p = 0.88). CONCLUSIONS: National data confirm that nodal upstaging was lower after VATS than after open lobectomy for clinical stage I NSCLC. Multivariate survival analysis, however, showed no difference in survival, indicating that differences in nodal upstaging result from patient selection for reasons not captured in our registry.

[238]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hartel PH; Hartel JV; Fanburg-Smith JC; Gilmore RW; Fleming D; Barnett S; Mudry R; Parker JE
INSTITUCIÓN / INSTITUTION: - 1Davis Health System, Davis Memorial Hospital, Elkins, WV, USA.
RESUMEN / SUMMARY: - We evaluated clinical parameters, histomorphology, and thyroid transcription factor 1 (TTF-1) immunoreactivity in 40 epidermal growth factor receptor (EGFR) mutation- and anaplastic lymphoma kinase (ALK) rearrangement-negative invasive pulmonary adenocarcinomas. Tumors were histomorphologically quantitated by a pulmonary pathologist and TTF-1 immunohistochemistry applied. EGFR mutation and ALK rearrangement status was determined with polymerase chain reaction/DNA sequencing and fluorescence in situ hybridization, respectively. Treatment response was related to type of treatment (P < .005) and clinical stage (P = .001). EGFR mutation- and ALK rearrangement-negative pulmonary adenocarcinomas containing papillary/micropapillary histology showed greater morphologic heterogeneity (P < .001), greater TTF-1 immunoreactivity (P = .004), and were more common in treatment responders (P < .05). These findings support that patients with pulmonary adenocarcinomas that are subject to nontargeted therapies may respond to treatment as a function of tumor cell differentiation with TTF-1 as a potential biomarker of this response.

[239]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

   ●●Enlace al texto completo (gratuito o de pago) 1007/s10552-013-0230-0

AUTORES / AUTHORS: - Farioli A; Violante FS; Mattioli S; Curti S; Kriebel D

INSTITUCIÓN / INSTITUTION: - Section of Occupational Medicine, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.

RESUMEN / SUMMARY: - PURPOSE: To investigate the association between external beam radiotherapy (EBRT) for prostate cancer and mesothelioma using data from the US Surveillance, Epidemiology, and End Results (SEER) cancer registries. METHODS: We analyzed data from the SEER database (1973-2009). We compared EBRT versus no radiotherapy. Incidence rate ratios (IRR) and 95 % confidence intervals (95 % CI) of mesothelioma among prostate cancer patients were estimated with multilevel Poisson models adjusted by race, age, and calendar year. Confounding by asbestos was investigated using relative risk of mesothelioma in each case’s county of residence as a proxy for asbestos exposure. RESULTS: Four hundred and seventy-one mesothelioma cases (93.6 % pleural) occurred in 3,985,991 person-years. The IRR of mesothelioma was increased for subjects exposed to EBRT (1.28; 95 % CI 1.05, 1.55) compared to non-irradiated patients, and a population attributable fraction of 0.49 % (95 % CI 0.11, 0.81) was estimated. The IRR increased with latency period: 0-4 years, IRR 1.08 (95 % CI 0.81, 1.44); 5-9 years, IRR 1.31 (95 % CI 0.93, 1.85); >/=10 years, IRR 1.59 (95 % CI 1.05, 2.42). Despite the fairly strong evidence of association with EBRT, the population attributable rate of mesothelioma was modest-3.3 cases per 100,000 person-years. The cumulative incidence of mesothelioma attributable to EBRT was 4.0/100,000 over 5 years, 24.5/100,000 over 10 years, and 65.0/100,000 over 15 years.

CONCLUSIONS: Our study provides evidence that EBRT for prostate cancer is a small but detectable risk factor for mesothelioma. Patients should be advised of risk of radiation-induced second malignancies.

[240]

TÍTULO / TITLE: - Immunohistochemical staining with EGFR mutation-specific antibodies: high specificity as a diagnostic marker for lung adenocarcinoma.

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

   ●●Enlace al texto completo (gratuito o de pago) 1038/modpathol.2013.53

AUTORES / AUTHORS: - Hannah Wen Y; Brogi E; Hasanovic A; Ladanyi M; Soslow RA; Chitale D; Shia J; Moreira AL

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA.
RESUMEN / SUMMARY: We previously demonstrated a high specificity of immunohistochemistry using epidermal growth factor receptor (EGFR) mutation-specific antibodies in lung adenocarcinoma and correlation with EGFR mutation analysis. In this study, we assessed EGFR mutation status by immunohistochemistry in a variety of extrapulmonary malignancies, especially those that frequently show EGFR overexpression. Tissue microarrays containing triplicate cores of breast carcinomas (n=300), colorectal carcinomas (n=65), pancreatic adenocarcinoma (n=145), and uterine carcinosarcoma or malignant mixed mullerian tumors (n=25) were included in the study. Tissue microarray of lung adenocarcinoma with known EGFR mutation status was used as reference. Immunohistochemistry was performed using antibodies specific for the E746-A750del and L858R mutations. In pulmonary adenocarcinoma, a staining intensity of 2+ or 3+ correlates with mutation status and is therefore considered as positive. Out of 300 breast carcinomas, 293 (98%) scored 0, 5 (2%) had 1+ staining, 2 (1%) were 2+ for the L858R antibody. All breast carcinomas scored 0 with the E746-A750 antibody. All the colorectal, pancreatic carcinomas and malignant mixed mullerian tumors were negative (0) for both antibodies. Molecular analysis of the breast carcinomas that scored 2+ for L858R showed no mutation. Our results show that EGFR mutation-specific antibodies could be an additional tool distinguishing primary versus metastatic carcinomas in the lung. False-positivity can be seen in breast carcinoma but is extremely rare (1%). Modern Pathology advance online publication, 19 April 2013; doi:10.1038/modpathol.2013.53.

[241]

[242]

TÍTULO / TITLE: - CT screening for lung cancer finds more cancers, after more investigations.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

TÍTULO / TITLE: - Basic mechanisms of therapeutic resistance to radiation and chemotherapy in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Willers H; Azzoli CG; Santivasi WL; Xia F

INSTITUCIÓN / INSTITUTION: - From the *Department of Radiation Oncology, and daggerDivision of Hematology/Oncology, Department of Medicine,
Massachusetts General Hospital Cancer Center, Harvard Medical School. Boston, MA; and double daggerDepartment of Radiation Oncology, College of Medicine, Ohio State University, Columbus, OH.

RESUMEN / SUMMARY: - In recent years, there have been multiple breakthroughs in our understanding of lung cancer biology. Despite significant advances in molecular targeted therapies, DNA-damaging cytotoxic therapies will remain the mainstay of lung cancer management for the near future. Similar to the concept of personalized targeted therapies, there is mounting evidence that perturbations in DNA repair pathways are common in lung cancers, altering the resistance of the affected tumors to many chemotherapeutics as well as radiation. Defects in DNA repair may be due to a multitude of mechanisms including gene mutations, epigenetic events, and alterations in signal transduction pathways such as epidermal growth factor receptor and phosphoinositide 3-kinase/AKT. Functional biomarkers that assess the subcellular localization of central repair proteins in response to DNA damage may prove useful for individualization of cytotoxic therapies including poly(adenosine diphosphate-ribose) polymerase inhibitors. A better mechanistic understanding of cellular sensitivity and resistance to DNA damaging agents should facilitate the development of novel, individualized treatment approaches. Absolute resistance to radiation therapy, however, does not exist. To some extent, radiation therapy will always have to remain unselective and indiscriminant to eradicate persistent, drug-resistant tumor stem cell pools.

[243] TÍTULO / TITLE: - Systemic treatment of advanced lung carcinoid tumors: show me the data!
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1378/chest.12-2455
AUTORES / AUTHORS: - Jett JR; Carr LL

[244] TÍTULO / TITLE: - Inhibition of cytoplasmic GSK-3beta increases cisplatin resistance through activation of Wnt/beta-catenin signaling in A549/DDP cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1016/j.canlet.2013.05.005
Cisplatin-based chemotherapy is recommended as the first-line therapy for advanced non-small cell lung cancer (NSCLC). However, acquired cisplatin resistance is ubiquitous in patients with NSCLC, but the molecular mechanism of such resistance remains ambiguous. The present study sought to examine the role of the Wnt/beta-catenin signaling pathway in cisplatin resistance by assessing the phosphorylation and subcellular distribution of GSK-3beta in a human lung adenocarcinoma cell line, A549, and its cisplatin-resistant subline, A549/DDP. Total GSK-3beta, phosphorylated GSK-3betaser9 and phosphorylated GSK-3betatyr216 in cytoplasmic and nuclear fractions of A549/DDP and A549 cells were examined by western blot analysis. The regulation of cisplatin resistance, apoptosis, beta-catenin and survivin protein expression by inhibition of cytoplasmic GSK-3beta were determined by MTT assay, flow cytometry analysis, immunofluorescence technique and western blot analysis. In the present study, cytoplasmic levels of p-GSK-3betaser9 were significantly increased in A549/DDP cells as compared with A549 cells (P<0.01), and these levels were further increased by cisplatin treatment in A549/DDP cells (P<0.01). In contrast, cytoplasmic levels of p-GSK-3betaser9 were reduced in A549 cells after treatment with cisplatin (P<0.01). However, cytoplasmic levels of p-GSK-3betatyr216 were significantly decreased in A549/DDP cells as compared with A549 cells (P<0.01), and these levels were further decreased by cisplatin treatment in A549/DDP cells (P<0.01). Conversely, cytoplasmic levels of p-GSK-3betatyr216 were raised in A549 cells after treatment with cisplatin (P<0.01). Analysis of downstream effectors of the Wnt/beta-catenin signaling pathway revealed upregulation of beta-catenin and survivin expression in A549/DDP cells treated with cisplatin as compared to untreated cells. In A549 cells, cisplatin treatment decreased the expression of beta-catenin and survivin. Furthermore, phosphorylation of GSK-3beta at serine 9 by LiCl and transient interference of GSK-3beta by siRNA increased beta-catenin and survivin protein expression in A549/DDP cells. Low exogenous and endogenous cytoplasmic GSK-3beta expression enhanced the IC50 and inhibited apoptosis. In conclusion, activation of the Wnt/beta-catenin signaling pathway and upregulated survivin expression due to cytoplasmic GSK-3beta inhibition might lead to cisplatin resistance in NSCLC.
**Título / Title:** Autocrine IL-8 and VEGF mediate epithelial-mesenchymal transition and invasiveness via p38/JNK-ATF-2 signalling in A549 lung cancer cells.

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


**Autores / Authors:** Desai S; Laskar S; Pandey BN

**Institución / Institution:** Radiation Biology and Health Sciences Division, Bhabha Atomic Research Centre, Mumbai 400085, India.

**Resumen / Summary:** Soluble factors in tumour microenvironment play a major role in modulating the metastatic potential of cancer cells. Herein, we investigated the effect of autocrine cytokines and growth factors in the form of self-conditioned medium (CM) on A549 lung carcinoma cells. We demonstrated that CM induced morphological and molecular changes associated with epithelial-mesenchymal transition viz change in shape from cuboidal to spindle, actin cytoskeleton remodelling, upregulation of vimentin and downregulation of E-cadherin etc. These changes were accompanied with enhanced motility, invasion, anchorage-independent growth and anoikis-resistance. Amongst the different factors of CM, IL-8 and VEGF were found to play a major role in the CM-induced motility and invasion. In the intracellular signalling cascade, CM triggered phosphorylation of JNK and p38 which was associated with the CM-enhanced invasiveness. In CM-treated cells, activated p38 and JNK further activated ATF-2 (Activating Transcription Factor-2) and knock-down of ATF-2 abrogated the CM-induced invasiveness, suggesting the signal transduction along the p38/JNK-ATF-2 axis. Furthermore, neutralising IL-8 and VEGF in CM, significantly abrogated CM-induced phosphorylation of ATF-2. Conversely, exogenous addition of these individual cytokines in plain medium, increased the activation of ATF-2 and invasiveness marginally. However, when added in combination these cytokines (IL-8 and VEGF) resulted in drastic increase in ATF-2 phosphorylation and subsequent invasiveness suggesting their synergetic interplay in the observed phenomenon. Taken together, our results identify IL-8/VEGF induced JNK/p38-ATF-2 as a novel pro-invasive pathway, which may be explored as potential therapeutic target to circumvent the invasiveness of lung malignancies.

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**Título / Title:** Slow-growing lung cancer: an emerging entity from screening to clinical management.

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

[245]
REVISTA / JOURNAL: - Eur Respir J. 2013 May 16.
AUTORES / AUTHORS: - Infante M; Berghmans T; Heuvelmans MA; Hillerdal G; Oudkerk M
INSTITUCIÓN / INSTITUTION: - IRCCS Istituto Clinico Humanitas, Milan, Italy.
RESUMEN / SUMMARY: - The current paradigm is that untreated lung cancer is invariably and rapidly fatal, therefore the medical community normally dismisses the idea that a patient could live with such a disease for years without any therapy. Yet, evidence from lung cancer screening research and from recent clinical series suggests that, although rarely recognized in routine practice, slow-growing lung cancers do exist and are more common than previously thought. Current evidence is reviewed and clinical cases are illustrated to show that slow-growing lung cancer is a real clinical entity, and the reasons why management protocols developed in the screening setting may also be useful in clinical practice are discussed. Features suggesting that a lung cancer may be slow-growing are described and appraised, areas of uncertainty are examined, modern management options for early-stage disease are appraised, and the influence that all this knowledge might have on our clinical decision-making is weighed. Further research directed at developing appropriate guidelines for these peculiar but increasingly common patients is warranted.

TÍTULO / TITLE: - Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Bodelon C; Polley MY; Kemp TJ; Pesatori AC; McShane LM; Caporaso NE; Hildesheim A; Pinto LA; Landi MT
INSTITUCIÓN / INSTITUTION: - Division of Cancer Epidemiology and Genetics.
RESUMEN / SUMMARY: - BACKGROUND: Some patients diagnosed with early-stage lung cancer and treated according to standard care survive for only a short period of time, while others survive for years for reasons that are not well understood. Associations between markers of inflammation and survival from lung cancer have been observed. MATERIALS AND METHODS: Here, we investigate whether circulating levels of 77 inflammatory markers are associated with long versus short survival in stage I and II lung cancer. Patients who had survived either <79 weeks (approximately 1.5 years) (short survivors, SS) or >156 weeks (3 years) (long survivors, LS) were selected from a retrospective population-based study. Logistic regression was used to calculate adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The false
discovery rate was calculated to adjust for multiple testing. RESULTS: A total of 157 LS and 84 SS were included in this analysis. Thirteen markers had adjusted OR on the order of 2- to 5-fold when comparing the upper and lower quartiles with regard to the odds of short survival versus long. Chemokine CCL15 [chemokine (C-C motif) ligand 15] was the most significant marker associated with increased odds of short survival (ORs = 4.93; 95% CI 1.90-12.8; q-value: 0.042). Smoking and chronic obstructive pulmonary disease were not associated with marker levels. CONCLUSIONS: Our results provide some evidence that deregulation of inflammatory responses may play a role in the survival of early-stage lung cancer. These findings will require confirmation in future studies.

[248]

TITULO / TITLE: - Reproductive factors and risk of lung cancer in female textile workers in Shanghai, China.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gallagher LG; Rosenblatt KA; Ray RM; Li W; Gao DL; Applebaum KM; Checkoway H; Thomas DB
INSTITUCIÓN / INSTITUTION: - Department of Environmental and Occupational Health Sciences, University of Washington, Box 357234, Seattle, WA, 98195, USA, lgallag@u.washington.edu.
RESUMEN / SUMMARY: - PURPOSE: Hormonal factors may play a role in the development of lung cancer in women. This study examined the relationship between lung cancer and reproductive factors in a large cohort of women, most of whom never smoked (97 %). METHODS: A cohort of 267,400 female textile workers in Shanghai, China, enrolled in a trial of breast self-examination provided information on reproductive history, demographical factors, and cigarette smoking at enrollment in 1989-91. The cohort was followed until July of 2000 for incidence of lung cancer; 824 cases were identified. Hazard ratios (HR) and 95 % confidence intervals (CI) associated with selected reproductive factors were calculated using Cox proportional hazards modeling, adjusting for smoking, age, and also parity when relevant. RESULTS: Nulliparous women were at increased risk compared to parous women (HR = 1.33, 95 % CI 1.00-1.77). Women who had gone through menopause at baseline were at increased risk compared to women of the same age who were still menstruating. Risk was higher in women with a surgical menopause (HR = 1.64, 95 % CI 0.96-2.79) than in those with a natural menopause (HR = 1.35, 95 % CI 0.84-2.18), and risk was highest in those postmenopausal women with a hysterectomy and bilateral oophorectomy at baseline (HR = 1.39, 95 % CI 0.96-2.00), although the
risk estimates were not statistically significant. CONCLUSIONS: These results support experimental data that demonstrate a biological role for hormones in lung carcinogenesis.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1007/s11010-013-1682-7
AUTORES / AUTHORS: - Li J; Song Y; Wang Y; Luo J; Yu W
INSTITUCIÓN / INSTITUTION: - Department of Clinical Laboratory, Yinzhou People’s Hospital, Ningbo, 315040, China.
RESUMEN / SUMMARY: - Recent studies have implied that miRNAs act as crucial modulators for epithelial-to-mesenchymal transition (EMT). We found that miR-148ª is significantly downregulated in non-small cell lung cancer (NSCLC) compared to adjacent non-cancerous lung tissues, and the downregulated miR-148ª was significantly associated with lymph-node metastasis. Functional assays demonstrated that miR-148ª inhibited EMT in NSCLC cells. Moreover, miR-148ª decreased 3’-untranslated region luciferase activity of ROCK1 and ROCK1 protein expression. Knockdown of ROCK1 reversed EMT resembling that of miR-148ª overexpression. Furthermore, ROCK1 was widely upregulated in NSCLC, and its mRNA levels were inversely correlated with miR-148ª expression. These findings suggest that miR-148ª acts as a novel EMT suppressor in NSCLC cells, at least in part by modulation of ROCK1.

[250] TÍTULO / TITLE: - Bone mass density, fracture history, self-reported osteoporosis as proxy variables for estrogen and the risk of non-small-cell lung cancer-A population based cohort study, the HUNT study: Are proxy variables friends or faults?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.04.001
AUTORES / AUTHORS: - Hatlen P; Langhammer A; Forsmo S; Carlsen SM; Amundsen T
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Medicine, St. Olavs Hospital HF, 7006 Trondheim, Norway; Department of Circulation and Medical
RESUMEN / SUMMARY: - Lung cancer has the highest mortality of all cancers. Patients with early stage disease have the best cure rates and that emphasizes the importance of early detection. About half of all non-small cell lung cancers (NSCLC) are estrogen receptor positive. The impact of estrogen and its receptors for NSCLC carcinogenesis has been studied but is still unclear. Low estrogen levels are associated with osteoporosis. We hypothesize that low bone mineral density (BMD), a positive history of fracture or self-reported osteoporosis, used as a proxy variable for life time estrogen exposure, are associated with a low incidence of NSCLC. We analyzed data from a cohort study, the Nord-Trondelag Health Study 2 (1995-1997) linked to the Norwegian Cancer Registry. Using the logistic regression model we calculated the odds ratio (OR) with a 95% confidence interval (CI) for the risk of NSCLC for the three proxy variables, stratified by sex. Participants older than 50 years of age, having measured bone density (N=18,156), having answered the questions on self-reported fracture (N=37,883) and osteoporosis (N=25,701) and known body mass index (BMI) (N=29,291), were evaluated for inclusion. In 6996 participants all these information was available in addition to tobacco use, and in women also hormonal replacement therapy (HRT). Lung function (FEV1 percent of predicted) was included in a sensitivity analysis. We identified 132 (1.9%) cases of NSCLC, 59 (1.2%) and 73 (3.3%) cases in women and men, respectively. Low BMD was associated with a higher risk of NSCLC, OR: 2.38, 95% CI: 1.09-5.18 and OR: 2.67, 95% CI: 1.39-5.16 in women and men, respectively. No association was found between the two other proxy variables and the risk of NSCLC. Inclusion of lung function in the model did not change the results.

Contrary to our hypothesis, women and men with low BMD had a higher risk for NSCLC. In addition the study demonstrates that the risk depends on which proxy variable was chosen, and we may ask: are proxy variables reliable?

[251]

TÍTULO / TITLE: - CYP2D6 T188C variant is associated with lung cancer risk in the Chinese population.

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


AUTORES / AUTHORS: - Huang Y; Liu X; Kuang X; Liao D

INSTITUCIÓN / INSTITUTION: - University of South China, Hengyang, China.

RESUMEN / SUMMARY: - The CYP2D6 gene has been suggested to play an important role in the pathogenesis of lung cancer. However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the
association of CYP2D6 T188C variant with lung cancer. Published literature from PubMed, Embase, Chinese National Knowledge Infrastructure and Wanfang data were retrieved. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using fixed- or random-effects model. A total of nine studies (1,516 lung cancer cases and 1,950 controls) for CYP2D6 T188C variant were included in the meta-analysis. The meta-analysis indicated that compared with CYP2D6 TT genotype, non-TT genotype (CC or CT) was significantly associated with lung cancer in the Chinese (OR = 1.61, 95% CI = 1.38-1.87, p < 0.001), with no evidence of between-study heterogeneity (I² = 0.0%, p = 0.991). The sensitivity analysis indicated that the association was stable and no publication bias was detected. The present meta-analysis supported the positive association of CYP2D6 T188C variant with lung cancer in the Chinese. Further large-scale studies with the consideration for gene-gene/gene-environment interactions should be conducted to investigate the association.

[252]

**TÍTULO / TITLE:** - Harmonizing SUVs in multicentre trials when using different generation PET systems: prospective validation in non-small cell lung cancer patients.

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


●●Enlace al texto completo (gratuito o de pago) 1007/s00259-013-2391-1

**AUTORES / AUTHORS:** - Lasnon C; Desmonts C; Quak E; Gervais R; Do P; Dubos-Arvis C; Aide N

**INSTITUCIÓN / INSTITUTION:** - Nuclear Medicine Department, Francois Baclesse Cancer Centre, Caen, France.

**RESUMEN / SUMMARY:** - PURPOSE: We prospectively evaluated whether a strategy using point spread function (PSF) reconstruction for both diagnostic and quantitative analysis in non-small cell lung cancer (NSCLC) patients meets the European Association of Nuclear Medicine (EANM) guidelines for harmonization of quantitative values. METHODS: The NEMA NU-2 phantom was used to determine the optimal filter to apply to PSF-reconstructed images in order to obtain recovery coefficients (RCs) fulfilling the EANM guidelines for tumour positron emission tomography (PET) imaging (PSFEANM). PET data of 52 consecutive NSCLC patients were reconstructed with unfiltered PSF reconstruction (PSFallpass), PSFEANM and with a conventional ordered subset expectation maximization (OSEM) algorithm known to meet EANM guidelines. To mimic a situation in which a patient would undergo pre- and post-therapy PET scans on different generation PET systems, standardized uptake values (SUVs) for OSEM reconstruction were compared to SUVs for PSFEANM
and PSFallpass reconstruction. RESULTS: Overall, in 195 lesions, Bland-Altman analysis demonstrated that the mean ratio between PSFEANM and OSEM data was 1.03 [95% confidence interval (CI) 0.94-1.12] and 1.02 (95% CI 0.90-1.14) for SUVmax and SUVmean, respectively. No difference was noticed when analysing lesions based on their size and location or on patient body habitus and image noise. Ten patients (84 lesions) underwent two PET scans for response monitoring. Using the European Organization for Research and Treatment of Cancer (EORTC) criteria, there was an almost perfect agreement between OSEMPET1/OSEMPET2 (current standard) and OSEMPET1/PSFEANM-PET2 or PSFEANM-PET1/OSEMPET2 with kappa values of 0.95 (95% CI 0.91-1.00) and 0.99 (95% CI 0.96-1.00), respectively. The use of PSFallpass either for pre- or post-treatment (i.e. OSEMPET1/PSFallpass-PET2 or PSFallpass-PET1/OSEMPET2) showed considerably less agreement with kappa values of 0.75 (95% CI 0.67-0.83) and 0.86 (95% CI 0.78-0.94), respectively. CONCLUSION: Protocol-optimized images and compliance with EANM guidelines allowed for a reliable pre-and post-therapy evaluation when using different generation PET systems. These data obtained in NSCLC patients could be extrapolated to other solid tumours.

[253]
TÍTULO / TITLE: Knockdown of copper chaperone antioxidant-1 by RNA interference inhibits copper-stimulated proliferation of non-small cell lung carcinoma cells.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Cai H; Peng F
INSTITUCIÓN / INSTITUTION: Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX 75390-8542, USA.
RESUMEN / SUMMARY: Copper is required for cell proliferation and tumor angiogenesis. Cellular copper metabolism is regulated by a network of copper transporters and chaperones. Antioxidant-1 (ATOX1) is a cytosolic copper chaperone important for intracellular copper transport, which plays a role in the regulation of cell proliferation by functioning as a transcription factor in cell growth signal-transduction pathways. The present study aimed to explore the role of ATOX1 in the copper-related regulation of lung cancer cell proliferation by immunohistochemical (IHC) analysis of ATOX1 expression in non-small cell lung cancer (NSCLC) tissue samples and by assessing the effects of RNA interference (RNAi)-mediated knockdown of ATOX1 on copper-stimulated proliferation of NSCLC cells. Overexpression of ATOX1 was detected in NSCLC by IHC analysis of the tissue samples from patients diagnosed with NSCLC.
when compared with expression of ATOX1 in non-malignant lung tissue samples. Knockdown of ATOX1 in the NSCLC cells transduced by a lentiviral vector encoding short hairpin RNA (shRNA) specific for ATOX1 was associated with reduction in copper-stimulated cell proliferation. These findings suggest that ATOX1 plays an important role in copper-stimulated proliferation of NSCLC cells and ATOX1 holds potential as a therapeutic target for lung cancer therapy targeting copper metabolism.

[254]

**TITULO / TITLE:** - Comparison of EGFR-TKI and chemotherapy in the first-line treatment of advanced EGFR mutation-positive NSCLC.

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


**ENlace al texto completo (gratis o de pago) 4149/neo_2013_055**

**AUTORES / AUTHORS:** - Fiala O; Pesek M; Finek J; Benesova L; Bortlicek Z; Minarik M

**RESUMEN / SUMMARY:** - Molecular targeted therapy based on EGFR tyrosine kinase inhibitors (EGFR-TKI) is currently a state of the art option for management of advanced stage NSCLC. Activating EGFR mutations are preferable for a good treatment response to EGFR-TKI. The presented retrospective study evaluated a clinical observation of EGFR-TKI aiming at its efficacy and safety in comparison to a standard chemotherapy in the first-line treatment of advanced stage NSCLC. Total number of patients with advanced stage (IIIB, IV) EGFR mutation-positive NSCLC was 54 of which 23 were treated with EGFR-TKI and 31 patients with various chemotherapy regimens in the first line. The treatment efficacy was characterized in terms of disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). The comparison of DCR was performed using Fisher’s exact test and the differences in survival were tested using log-rank test. DCR for EGFR-TKI treatment was 95.6% vs. 70.9% for chemotherapy (p=0.032). Median of PFS in patients treated with EGFR-TKI was 7.2 months vs. 2.5 months in patients treated with chemotherapy (p<0.001). Median of OS was 14.5 months vs. 21.4 months (p=0.729). EGFR-TKI was associated with higher incidence of skin rash and diarrhoea; chemotherapy was associated with higher incidence of haematologic adverse events and nausea or vomiting. The analysis results showed a favourable DCR and PFS in patients treated with EGFR-TKI in the first line. The non-significant difference in OS could be attributed to across-over during the patient follow-up as well as the differences in performance status and age between both groups. EGFR-TKI is the optimal choice for the first-line treatment of EGFR mutation-positive NSCLC. Keywords: EGFR-TKI, first-line treatment, NSCLC, erlotinib, gefitinib, targeted treatment of NSCLC.
TÍTULO / TITLE: - EGFR and KRAS mutational profiling in fresh non-small cell lung cancer (NSCLC) cells.

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


AUTORES / AUTHORS: - Stella GM; Scabini R; Inghilleri S; Cemmi F; Corso S; Pozzi E; Morbini P; Valentini A; Dore R; Ferrari S; Luisetti M; Zorzetto M

INSTITUCIÓN / INSTITUTION: - Laboratory of Biochemistry and Genetics, Division of Pneumology, Department of Molecular Medicine, University and Fondazione IRCCS Policlinico San Matteo, 27100, Pavia, Italy.

RESUMEN / SUMMARY: - PURPOSE: Knowledge of tumor mutational status has become a priority for effective NSCLC-tailored treatment. NSCLC diagnosis is more often reached through biopsy; thus, there is a clear need to implement for routine tumor molecular profiling on small cytological samples. This work aims to screen and compare the EGFR and KRAS mutational prevalence in fresh tumor cells and in corresponding routinely processed samples derived from trans-thoracic fine-needle aspiration. The latter currently represents the most appropriate diagnostic procedure in case of peripheral lesions, such as adenocarcinomas, which account for almost 40 % of all NSCLCs and for the highest EGFR mutational rates. METHODS: Two hundred and forty-four patients carrying peripheral lung masses underwent CT-guided aspiration. The obtained material was split, and a part was addressed to conventional histopathological analysis while the remaining one was stored at -20 degrees C. In case of confirmation of adenocarcinoma, tumor genomic DNA was extracted from both fresh and fixed material, and EGFR and KRAS sequencing was performed. RESULTS: We identified 136 adenocarcinomas; from 134, we could recover enough material for the study. A full match was demonstrated between EGFR/KRAS mutational prevalences through the two approaches tested. We found EGFR mutations in 13 patients (9.7 %); 7 were females and 11 never or former smokers. KRAS mutations occurred in 20 (14.9 %) patients. EGFR and KRAS mutations were mutually exclusive. CONCLUSIONS: Mutational screening on fresh cancer cells is an achievable, safe and cost-effective procedure which might allow routinely tumor molecular profiling as powerful integration of conventional histopathological analysis.

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TÍTULO / TITLE: - Characterization of a Novel Long Non-Coding RNA, SCAL1, Induced by Cigarette Smoke and Elevated in Lung Cancer Cell Lines.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●●Enlace al texto completo (gratuito o de pago) 1165/rcmb.2013-0159RC

AUTORES / AUTHORS: - Thai P; Statt S; Chen CH; Liang E; Campbell C; Wu R

INSTITUCIÓN / INSTITUTION: - University of California, Davis, School of Medicine, Center for Comparative Respiratory Biology and Medicine, and Division of Pulmonary and Critical Care Medicine, Davis, California, United States; ptil@yahoo.com.

RESUMEN / SUMMARY: - The incidence of lung diseases and cancer caused by cigarette smoke is increasing. The molecular mechanism(s) of gene regulation induced by cigarette smoke that ultimately lead to cancer remains unclear. This report describes a novel long non-coding RNA (LncRNA) that is induced by cigarette smoke extract (CSE) both in vitro and in vivo and is elevated in numerous lung cancer cell lines. We have termed this IncRNA, SCAL1 (Smoke and Cancer Associated LncRNA 1). This IncRNA is located in chromosome 5 and initial sequencing analysis reveals a transcript with 4 exons and three introns. Expression of SCAL1 is regulated transcriptionally by NRF2 as determined by siRNA knockdown of NRF2 and KEAP1. An NF-E2 motif is identified in the promoter region that shows binding to NRF2 following its activation. Functionally, siRNA knockdown of SCAL1 in HBE1 cells shows significant potentiation of cytotoxicity induced by CSE in vitro. Altogether, these results identify a novel and intriguing new non-coding RNA that may act downstream of NRF2 to regulate gene expression and mediate oxidative stress protection in airway epithelial cells.

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TÍTULO / TITLE: - Estrogen and insulin-like growth factor synergistically promote the development of lung adenocarcinoma in mice.

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


●●Enlace al texto completo (gratuito o de pago) 1002/ijc.28262

AUTORES / AUTHORS: - Tang H; Liao Y; Xu L; Zhang C; Liu Z; Deng Y; Jiang Z; Fu S; Chen Z; Zhou S

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Thoracic Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China.

RESUMEN / SUMMARY: - Objective: Estrogen receptor (ER) and insulin-like growth factor-1 receptor (IGF-1R) signaling are implicated in lung cancer progression. Based on our previous findings, we sought to investigate whether estrogen and IGF-1 act synergistically to promote lung adenocarcinoma (LADE)
development in mice. Methods: LADE was induced with urethane in ovariectomized Kunming mice. Tumor-bearing mice were divided into seven groups: 17beta-estradiol (E2), E2+fulvestrant (Ful; estrogen inhibitor), IGF-1, IGF-1+AG1024 (IGF-1 inhibitor), E2+IGF-1, E2+IGF-1+Ful+AG1024, and control groups. After 14 weeks, the mice were sacrificed and tumor growth was determined. The expression of ERalpha/ERbeta, IGF-1, IGF-1R, and Ki67 was examined using tissue-microarray-immunohistochemistry, and IGF-1, p-ERbeta, p-IGF-1R, p-MAPK, and p-AKT levels were determined based on Western blot analysis. Fluorescence-quantitative PCR was used to detect the mRNA expression of ERbeta, ERbeta2, and IGF-1R. Results: Tumors were found in 93.88% (46/49) of urethane-treated mice, and pathologically proven LADE was noted in 75.51% (37/49). In the E2+IGF-1 group, tumor growth was significantly higher than in the E2 group (P <0.05), the IGF-1 group (P <0.05), and control group (P <0.05). Similarly, the expression of ERbeta, p-ERbeta, ERbeta2, IGF-1, IGF-1R, p-IGF-1R, p-MAPK, p-AKT, and Ki67 at the protein and/or mRNA levels were markedly higher in the ligand group than in the ligand + inhibitor groups (all P <0.05). Conclusion: The present study demonstrated for the first time that estrogen and IGF-1 act to synergistically promote the development of LADE in mice, and this may be related to the activation of the MAPK and AKT signaling pathways in which ERbeta1, ERbeta2, and IGF-1R play important roles. © 2013 Wiley Periodicals, Inc.
chemotherapy vs chemoradiotherapy) in a consecutive series of patients with sleeve lobectomy for NSCLC. RESULTS: Ninety-nine patients underwent sleeve resection, 28 of them after induction therapy. Twelve patients received chemotherapy alone, and 16 patients had radiochemotherapy. There were no significant differences in postoperative 90-day mortality (3.6% vs 2.8%) and morbidity (54% vs 49%) for patients with and without induction therapy. Bronchial anastomosis complications occurred in 3 patients (10.8%) with neoadjuvant therapy and in 2 (2.8%) without (p = 0.3). In the induction therapy group, two bronchial stenoses occurred after radiochemotherapy and one bronchopleural fistula after chemotherapy alone. In patients without induction therapy, one bronchial stenosis and one bronchopleural fistula were observed. All bronchial stenoses were successfully treated by dilatation, and both bronchopleural fistulas occurring after right lower lobectomy were successfully treated by reoperation and completion sleeve bilobectomy with preservation of the upper lobe. CONCLUSIONS: Sleeve lobectomy for NSCLC can be safely performed after induction chemotherapy and radiochemotherapy with mortality and incidence of airway complications similar to that observed in nonpretreated patients. The treatment of airway complications does not differ for patients with and without induction therapy.

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[259] TÍTULO / TITLE: - Moderate hypothermia attenuates oxidative stress injuries in alveolar epithelial A549 cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chiou SY; Lee YS; Jeng MJ; Tsao PC; Soong WJ
INSTITUCIÓN / INSTITUTION: - 1Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC.
RESUMEN / SUMMARY: - ABSTRACT Reactive oxygen species (ROS) are generally involved in lung inflammation and acute lung injury. We investigated the effects of hypothermia on ROS-induced cell damage in human alveolar type II cells. A549 cells were exposed to H2O2 and cultured at different temperatures, namely, normothermia (37 degrees C), mild hypothermia (34 degrees C), or moderate hypothermia (32 degrees C). Cell damage was measured using various assays. The biochemical studies demonstrated a significant increase in apoptosis and intracellular ROS at 32 degrees C in uninjured A549 cells. After exposure to H2O2, a marked decrease in cell viability (<50%) was demonstrated, and this was significantly ameliorated upon culture at 32 degrees C. Significantly intracellular damage was found to affect
the 24-hour H2O2-exposed cells in 37 degrees C (P < .05), including an increase in apoptosis and necrosis, intracellular ROS, caspase-3 activity, HMGB1 protein expression, and some alterations to the cell cycle. On hypothermic treatment, the 24-hour H2O2-induced caspase-3 activation was significantly suppressed in cells cultured at both 32 degrees C and 34 degrees C (P < .05 versus 37 degrees C). The cell cycle changes in 24-hour H2O2-exposed cells were significantly diminished when the cells were cultured in 32 degrees C (P < .05 versus 37 degrees C). However, these intracellular alterations were not seen in 6-hour H2O2-exposed cells. We concluded that moderate hypothermia (32 degrees C) of alveolar epithelial A549 cells seems to provide protection against H2O2-induced 24-hour oxidative stress by attenuating cell death and intracellular damage. However, moderate hypothermia might cause minor damage to uninjured cells, so the use of hypothermic treatment needs to be judiciously applied.

[260]

**TITULO / TITLE:** - P53 codon 72 polymorphism and lung cancer risk: evidence from 27,958 subjects.

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


- Enlace al texto completo (gratuito o de pago) 1007/s13277-013-0859-z

**AUTORES / AUTHORS:** - Zhou C; Chen H; Wang A

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Zhou Pu Hospital, 135 Guanyue Road, Pudong new District, Shanghai, 201318, China, zhou2000sh@163.com.

**RESUMEN / SUMMARY:** - The role of p53 codon 72 polymorphism in the development of lung cancer remains obscure due to inconsistent findings of individual case-control studies published to date. A meta-analysis was conducted to better estimate the association between the p53 codon 72 variant and lung cancer risk. All relevant publications from the PubMed, Embase, Web of Science, and Wanfang databases were retrieved. Based on the inclusion criteria, 39 publications involving 44 independent case-control studies were finally included into this meta-analysis. Data were extracted and the pooled odds ratio (OR) with the corresponding 95 % confidence interval (95 % CI) was calculated. The overall pooled ORs showed no significant relationship of the p53 codon 72 polymorphism with increased or decreased risk of lung cancer in all gene contrast models (OR Pro vs. Arg = 1.04, 95 % CI = 0.96-1.13, P OR < 0.001; OR Pro/Pro vs. Arg/Arg = 1.07, 95 % CI = 0.91-1.25, P OR < 0.001; OR Arg/Pro vs. Arg/Arg = 1.04, 95 % CI = 0.94-1.15, P OR < 0.001; OR Pro/Pro + Arg/Pro vs. Arg/Arg = 1.04, 95 % CI = 0.94-1.16, P OR < 0.001; OR Pro/Pro vs. Arg/Arg + Arg/Pro = 1.07, 95 % CI = 0.93-1.23, P OR < 0.001). According to the
ethnicity, no significant association was observed in subgroup analyses of the Asians, Caucasians, Africans and the mixed population. Similar finding was found in subgroup analyses of hospital-based and population-based studies. Concerning the histological types of lung cancer, the p53 codon 72 variant exerts risk effect on the lung carcinogenesis in patients with adenocarcinoma (OR Arg/Pro vs. Arg/Arg = 1.10, 95 % CI = 1.00-1.22, P OR = 0.048).

Additionally, subgroup analysis by the smoking status demonstrated that the p53 codon 72 variant seemed to play a protective role in lung carcinogenesis among the non-smokers but not the smokers in the contrast model of Arg/Pro vs. Arg/Arg (OR Arg/Pro vs. Arg/Arg = 0.71, 95 % CI = 0.50-1.00, P OR = 0.049). The present meta-analysis suggests the p53 codon 72 polymorphism may weakly modify the risk for lung cancer among the adenocarcinoma patients and non-smokers. Nevertheless, this association needs further confirmation in future studies with high quality.
transcription of nEGFR target genes. We showed that PMLIV is recruited by nEGFR to the target promoters and reduces the promoter histone acetylation level via HDAC1. Together, our results suggest that PMLIV interacts with nEGFR upon EGFR activation and represses the transcription of nEGFR target genes such as CCND1 and thus leading to inhibition of the lung cancer cell growth.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
••Enlace al texto completo (gratuito o de pago) 1016/j.athoracsur.2013.01.088
AUTORES / AUTHORS: - Spaggiari L; Tessitore A; Casiraghi M; Guarize J; Solli P; Borri A; Gasparri R; Petrella F; Maisonneuve P; Galetta D
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, European Institute of Oncology, Milan, Italy; University School of Milan, Milan, Italy. Electronic address: lorenzo.spaggiari@ieo.it.
RESUMEN / SUMMARY: - BACKGROUND: Extended resections (ER) for lung cancer may improve survival in selected patients. However, analysis on large series is still lacking. We reviewed our experience to identify prognostic factors useful for patient selection. METHODS: Between 1998 and 2010, 167 patients with involvement of one or more mediastinal organs underwent operations with the intent to perform ER. At thoracotomy, 42 patients (25%) were considered unresectable (explorative thoracotomy [ET]), and 125 (75%) underwent ER. The types of ER were superior vena cava in 43 patients (34.4%), carina in 33 (26.4%), combined with superior vena cava in 18 (14.4%), with the left atrium in 35 (28%), and with the aorta in 14 (11.2%). We excluded Pancoast tumors and vertebral resections. The minimum follow-up was 6 months. Kaplan-Meier method and log-rank test were used for statistical analysis of survival.
RESULTS: There were 136 men (81.4%), with mean age of 63 years (range, 36 to 81 years). Of the 167 patients, induction chemotherapy was administered in 119 (71.3%), including 34 ET patients (81%) and 85 ER patients (68%). Complete resection was achieved in 106 patients (84.8%). The overall 5-year survival was 23% (27% in ER and 13% in ET, p = 0.41). Overall 30-day mortality was 4.8% and morbidity was 34.1%. Factors affecting survival were complete resection (p < 0.01), pStage 0-I-II disease (p < 0.0007), and age younger than 60 years (p < 0.01). CONCLUSIONS: ER for lung cancer invading mediastinal organs could improve long-term survival (46% at 5-years in pN0). The best surgical candidates are young patients without lymph nodes.
involvement who undergo radical resection. Multimodality treatment is suggested in case of mediastinal lymph node involvement.

[263]
TÍTULO / TITLE: - The Matricellular Protein CCN1 Suppresses Lung Cancer Cell Growth by Inducing Senescence via the p53/p21 Pathway.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Leu SJ; Sung JS; Chen MY; Chen CW; Cheng JY; Wang TY; Wang JJ
INSTITUCIÓN / INSTITUTION: - Department of Biotechnology and Laboratory Science in Medicine, National Yang-Ming University, Taipei, 112, Taiwan; Department of Education and Research, Taipei City Hospital, Taipei, 111, Taiwan.
RESUMEN / SUMMARY: - CCN1, a secreted matrix-associated molecule, is involved in multiple cellular processes. Previous studies have indicated that expression of CCN1 correlates inversely with the aggressiveness of non-small-cell lung carcinoma (NSCLC); however, the underlying mechanisms remain elusive. Using three NSCLC cell line systems, here we show that long-term treatment of cells with the recombinant CCN1 protein led to a permanent cell cycle arrest in G1 phase; cells remained viable as judged by apoptotic assays. CCN1-treated NSCLC cells acquired a phenotype characteristic of senescent cells, including an enlarged and flattened cell shape and expression of the senescence-associated beta-galactosidase. Immunoblot analysis showed that addition of CCN1 increased the abundance of hypo-phosphorylated Rb, as well as accumulation of p53 and p21. Silencing the expression of p53 or p21 by lentivirus-mediated shRNA production in cells blocked the CCN1-induced senescence. Furthermore, a CCN1 mutant defective for binding integrin alpha6beta1 and co-receptor heparin sulfate proteoglycans was incapable of senescence induction. Our finding that direct addition of CCN1 induces senescence in NSCLC cells provides a potential novel strategy for therapeutic intervention of lung cancers. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[264]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
RESUMEN / SUMMARY: - BACKGROUND: The healthy worker survivor bias is well-recognized in occupational epidemiology. Three component associations are necessary for this bias to occur: i) prior exposure and employment status; ii) employment status and subsequent exposure; and iii) employment status and mortality. Together, these associations result in time-varying confounding affected by prior exposure. We illustrate how these associations can be assessed using standard regression methods. METHODS: We use data from 2975 asbestos textile factory workers hired between January 1940 and December 1965 and followed for lung cancer mortality through December 2001. RESULTS: At entry, median age was 24 years, with 42% female and 19% non-Caucasian. Over follow-up, 21% and 17% of person-years were classified as at work and exposed to any asbestos, respectively. For a 100 fiber-year/mL increase in cumulative asbestos, the covariate-adjusted hazard of leaving work decreased by 52% (95% confidence interval [CI], 46-58). The association between employment status and subsequent asbestos exposure was strong due to nonpositivity: 88.3% of person-years at work (95% CI, 87.0-89.5) were classified as exposed to any asbestos; no person-years were classified as exposed to asbestos after leaving work. Finally, leaving active employment was associated with a 48% (95% CI, 9-71) decrease in the covariate-adjusted hazard of lung cancer mortality. CONCLUSIONS: We found strong associations for the components of the healthy worker survivor bias in these data. Standard methods, which fail to properly account for time-varying confounding affected by prior exposure, may provide biased estimates of the effect of asbestos on lung cancer mortality under these conditions.


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


AUTORES / AUTHORS: - Kratz JR; Tham PT; Mulvihill MS; Ziaei F; Ray MR; Hurst JW; Segal MR; Berryman DM; Chu W; He B; Jablons DM; Mann MJ
RESUMEN / SUMMARY: A molecular assay prognostic of survival in resected nonsquamous non-small cell lung cancer designed to meet the need for improved risk stratification in early-stage disease has recently been described. This assay measures the expression levels of 14 genes using RNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissues. The assay underwent blinded clinical validation in 2 large international cohorts involving approximately 1500 patients; the analytical precision and reproducibility of this assay, however, have not yet been reported. For each of the 14 TaqMan quantitative polymerase chain reaction (PCR) primer and probe sets used in the molecular prognostic assay, the linear range, PCR efficiency, limits of blank, limits of quantitation, and quantitative bias were determined using serial dilutions of pooled RNA extracted from FFPE samples. The reproducibility of the entire molecular assay was determined by performing repeat testing of FFPE samples over multiple days. The linear range of individual quantitative TaqMan PCR primer and probe sets was between 2- and 2-fold input RNA. The median CT of the quantitative PCR primer and probe sets at 10 ng of input RNA was 24.3; the median efficiency was 91.2%. The median quantitative bias across all quantitative PCR primer and probe sets was 0.75% (range, 0.32% to 1.32%). In repeat testing, the mean SD of the risk score (scaled from 1 to 100) was 2.18, with a mean coefficient of variation of 0.08. The molecular prognostic assay presented in this study demonstrates high precision and reproducibility, validating its clinical utility as a reliable prognostic tool that can contribute to the management of patients with early-stage disease.


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


AUTORES / AUTHORS: Bak Y; Ham S; Baatartsogt O; Jung SH; Choi KD; Han TY; Han IY; Yoon DY

INSTITUCIÓN / INSTITUTION: Department of Bioscience and Biotechnology, Bio/Molecular Informatics Center, Konkuk University, Hwayang-dong 1, Gwangjin-gu, Seoul, 143-701, Republic of Korea.

RESUMEN / SUMMARY: It has been reported that extracts from Asian traditional/medical herbs possess therapeutic agents against cancers, metabolic
diseases, inflammatory diseases, and other intractable diseases. In this study, we assessed the molecular mechanisms involved in the anticancer effects of A1E, the extract of Korean medicinal herbs. We examined the role of the cytotoxic and apoptotic pathways in the cancer chemopreventive activity in non-small-cell lung cancer (NSCLC) cell lines NCI-H460 and NCI-H1299. A1E inhibited the proliferation of NCI-H460 more efficiently than NCI-H1299 (p53-/−) cells. The apoptosis was detected by nuclear morphological changes, annexin V-FITC/PI staining, cell cycle analysis, western blot, RT-PCR, and measurement of mitochondrial membrane potential. A1E induced cellular morphological changes and nuclear condensation at 24 h in a dose-dependent manner. A1E also perturbed cell cycle progression at the sub-G1 stage and altered cell cycle regulatory factors in NCI-H460 cells. Furthermore, A1E inhibited the PI3K/Akt and NF-kappaB survival pathways, and it activated apoptotic intrinsic and extrinsic pathways. A1E increased the expression levels of members of the extrinsic death receptor complex FasL and FADD. In addition, A1E treatment induced cleavage of caspase-8, caspase-9, caspase-3, and poly ADP-ribose polymerase (PARP), whereas the expression levels of Bcl-2 and Bcl-xl were downregulated. A1E induced mitochondrial membrane potential collapse and cytochrome C release. Our results suggest that A1E induces apoptosis via activation of both extrinsic and intrinsic pathways and inhibition of PI3K/Akt survival signaling pathways in NCI-H460 cells. In conclusion, these data demonstrate the potential of A1E as a novel chemotherapeutic agent in NSCLC.
by simultaneous application of fenofibrate and budesonide, agonists for PPARalpha and glucocorticoid receptor, respectively. We observed differential effects on cell proliferation in A549 and SK-MES-1 lung cancer cells by budesonide and fenofibrate. Fenofibrate inhibited cell proliferation in both TP53 wild type and deficient lung cancer cells. The anti-proliferation effect of budesonide in TP53 wild type A549 cells was abolished in SK-MES-1 cells that do not have wild type TP53 protein. An additive effect against cell proliferation by budesonide and fenofibrate combination was observed only in TP53 wild type A549 cancer cells. Analysis of cell cycle distribution and cyclin profile indicated that the inhibition of cell proliferation was associated with G1 cell cycle arrest. The suppression of NF-kappaB activity and ERK signaling may contribute to the inhibition of cell proliferation by budesonide and/or fenofibrate. The additive inhibitory effect on cell proliferation by budesonide and fenofibrate combination suggests that the same or greater therapeutic effect could be achieved with reduced dosage and side effects when the two compounds are applied simultaneously. © 2013 Wiley Periodicals, Inc.

[268] TÍTULO / TITLE: - Amiodarone is a cost-neutral way of preventing atrial fibrillation after surgery for lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
    ●●Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt169
AUTORES / AUTHORS: - Riber LP; Christensen TD; Pilegaard HK
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic and Vascular Surgery & Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark.
RESUMEN / SUMMARY: - OBJECTIVES: Our aim was to estimate the costs and health benefits of routinely administered postoperative amiodarone as a prophylactic agent in reducing the risk of atrial fibrillation in patients undergoing surgery for lung cancer. METHODS: This was a cost-effectiveness study, based on the randomized, controlled, double-blinded PASCART study, using avoidance of atrial fibrillation as the measure of benefit. Two hundred and fifty-four eligible, consecutively enrolled patients, undergoing surgery for lung cancer at the department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark, were included and randomized to receive either 300 mg of amiodarone or placebo (5% aqueous dextrose solution), administered intravenously over 20 min immediately after surgery, followed by 600 mg of amiodarone/placebo orally twice per day (8 a.m. and 6 p.m.) for the first five postoperative days. RESULTS: In the amiodarone group there were 11 cases of atrial fibrillation, compared with 38 in the control group (P < 0.001). There were no differences in the length of hospital stay or resources used. The mean total
costs per patient were equal and amounted to euro7288 per patient (P = 0.23). There were no signs of adverse developments referable to amiodarone in this prophylactic regime. CONCLUSIONS: For patients undergoing surgery for lung cancer, routine use of postoperative prophylactic intravenous bolus and five subsequent days of oral amiodarone therapy reduces the risk of atrial fibrillation in a cost-neutral manner.

[269]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
    ●●Enlace al texto completo (gratuito o de pago) 1016/j.canlet.2013.03.028
AUTORES / AUTHORS: - Chen MC; Chen CH; Liu YN; Wang HP; Pan SL; Teng CM
INSTITUCIÓN / INSTITUTION: - Pharmacological Institute, College of Medicine, National Taiwan University, Taipei, Taiwan.
RESUMEN / SUMMARY: - Here, we report that TW01001, a novel piperazinedione compound, could be a new mitotic inhibitor for the treatment of non-small cell lung cancer by the following observations in A549 cells: (1) induction of cells to accumulate at G2/M phase, which ultimately led to cell apoptotic death, (2) accumulation of p53 and inhibition of survival signalings, and (3) induction of p53-independent autophagy. Taken together, our data suggested that TW01001 induces autophagy-p53-signaling pathway to cause mitotic arrest and cell growth inhibition in A549 cells and provides the framework for further development as a novel therapeutic agent for lung cancer treatment.

[270]
TÍTULO / TITLE: - Long-term survival with surgery as part of a multimodality approach for N3 lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
    ●●Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt171
AUTORES / AUTHORS: - Riquet M; Mordant P; Fabre-Guillemin E; Arame A; Foucault C; Dujon A; Le Pimpec Barthes F
INSTITUCIÓN / INSTITUTION: - Department of General Thoracic Surgery, Georges Pompidou European Hospital, Paris-Descartes University, Paris, France.
RESUMEN / SUMMARY: - OBJECTIVES: The extension of non-small-cell lung cancer (NSCLC) to supraclavicular (SC) and contralateral (CL) mediastinal
lymph nodes is termed N3 and usually forbids surgical resection. However, scarce surgical series have reported encouraging results, and we sought to analyse our experience with this particular subgroup of patients. METHODS: We retrospectively reviewed the charts of 5857 patients undergoing surgery for NSCLC during the last 30 years in two French centres. Eleven patients presenting with pathological-N3 were found, and more closely analysed concerning lymphatic spread, surgical indication and prognosis. RESULTS: N3 consisted of tumoural extension to the SC (n = 5), CL mediastinal (n = 5) or both (SC + CL, n = 1) stations. Patients underwent induction treatment with chemotherapy alone (n = 4), chemoradiotherapy (n = 3) or first-line surgery (n = 4). All patients underwent a complete surgical resection of the tumour associated with ipsilateral systematic mediastinal lymph node dissection. Additional resection of N3 lymph nodes was performed in 8 cases. Adjuvant treatment included chemoradiotherapy (n = 6), chemotherapy alone (n = 1) or radiation therapy alone (n = 1). All 5 patients with SC-N3 presented with ipsilateral disease; 3 of them survived 5 years. Four patients with CL-N3 presented with left-sided tumour and nodal extension to the 4R station, and none of them survived. CONCLUSIONS: Some N3-patients with specific anatomical location may benefit from multimodality treatment including surgery. These results support further prospective studies for selected N3-patients.

[271] 
TÍTULO / TITLE: - Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. 
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary 
AUTORES / AUTHORS: - Sheng L; Luo M; Sun X; Lin N; Mao W; Su D 
INSTITUCIÓN / INSTITUTION: - Department of Radiation Therapy, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China; Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Zhejiang, China. 
RESUMEN / SUMMARY: - Serum fibrinogen converted to insoluble fibrin by activated thrombin, plays an important role in the coagulation system. Increased fibrinogen considerably influences cancer cell growth, progression and metastasis. In nonsmall cell lung cancer (NSCLC), however, the association between serum fibrinogen concentration and prognosis has not been fully examined. We enlisted 567 operable NSCLC patients in this study. Preoperative serum fibrinogen was measured by the Clauss method. The association of serum fibrinogen concentration with clinical pathological factors and patient outcome was evaluated. Survival analysis indicated that serum fibrinogen was an independent prognostic factor in operable NSCLC. Patients with hyperfibrinogenemia had an elevated risk of disease progression and death.
compared with patients with normal fibrinogen levels. The hazard ratio was 1.49 (95% confidence interval [CI] 1.07-2.05) for disease progression and 1.64 (95% CI 1.06-2.53) for death. The trend linking increasing fibrinogen levels with risk was also statistically significant for both outcomes (p < 0.05). These analyses were adjusted for patient age, sex, smoking behavior, disease stage, tumor grade and histology. Kaplan-Meier survival curves showed similar results. Preoperative serum fibrinogen is a novel independent prognostic biomarker in operable NSCLC. © 2013 Wiley Periodicals, Inc.

[272]

TÍTULO / TITLE: - Molecular pathogenesis of malignant mesothelioma.

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


AUTORES / AUTHORS: - Sekido Y

INSTITUCIÓN / INSTITUTION: - Division of Molecular Oncology, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.

RESUMEN / SUMMARY: - Malignant mesothelioma (MM) is an aggressive tumor arising primarily from the pleural or peritoneal cavities. It develops by asbestos exposure after a long latency, which is characterized by insidious growth and clinical presentation at an advanced stage of disease. MM is highly refractory to conventional therapies even with a combination of aggressive surgical intervention and multimodality strategies, with cure remaining elusive. Molecular genetic analysis has revealed several key genetic alterations which are responsible for the development and progression of MM. The CDKN2A/ARF, NF2, and BAP1 genes are the most frequently mutated tumor suppressor genes detected in MM cells; the alterations of the latter two are relatively characteristic of MM. Merlin, which is encoded by NF2, regulates multiple cell signaling cascades including the Hippo and mTOR pathways which regulate cell proliferation and growth. BAP1 is involved in histone modification and its inactivation induces the disturbance of global gene expression profiling. The discovery of a new familial cancer syndrome with germline mutation of BAP1 also indicates the importance of genetic factors in MM susceptibility. Meanwhile, although frequent expression and functional activations of oncogene products such as receptor tyrosine kinases are observed in MM cells, activating mutations of these genes are rare. With further comprehensive genome analyses, new genetic and epigenetic alterations in MM cells are expected to be revealed more precisely, and the new knowledge based on them will be applied for developing new diagnostic tools and new target therapies against MMs.
[273] **TÍTULO / TITLE:** - Survival in untreated stage I lung cancer.  
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](http://example.com)  
●●Enlace al texto completo (gratuito o de pago) [10.1378/chest.13-0087](http://example.com)  
**AUTORES / AUTHORS:** - Reich JM; Kim JS; Asaph JW

[274] **TÍTULO / TITLE:** - Feruloyl-l-arabinose attenuates migration, invasion and production of reactive oxygen species in H1299 lung cancer cells.  
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](http://example.com)  
●●Enlace al texto completo (gratuito o de pago) [10.1016/j.fct.2013.05.019](http://example.com)  
**AUTORES / AUTHORS:** - Fang HY; Wang HM; Chang KF; Hu HT; Hwang LJ; Fu TF; Lin YC; Chang WC; Chiu TP; Wen ZH; Fong Y; Chiu CC; Chen BH  
**INSTITUCIÓN / INSTITUTION:** - Department of Food Nutrition, Chung-Hwa University of Medical Technology, Tainan  701, Taiwan.  
**RESUMEN / SUMMARY:** - Ferulic acid (FA), a phenolic compound, is an abundant dietary antioxidant and exerts the mitogenic effect on cells. Recently, we isolated an active FA derivative, namely feruloyl-l-arabinose (FAA), from coba husk. The aim of this study was to investigate the effects of FAA on the proliferation, migration and invasion of H1299 human lung cancer cells. Our results showed a strong antioxidant potential of FAA. Additionally, FAA inhibited the migration and invasion ability, while causing a significant accumulation of G2/M-population, of H1299 tumor cells in a dose-dependent manner, whereas no significant change on cell proliferation was observed. Results from the wound healing assay revealed that cell migration ability was markedly inhibited by FAA treatments. Similarly, results of gelatin zymography study showed that FAA treatments significantly decreased the activities of matrix metalloproteinase (MMP)-2 and MMP-9, suggesting that FAA-mediated inhibition on migration and invasion of lung cancer cells may be achieved by the down-regulation of the MMPs activities. Taken together, our present work provides a new insight into the novel inhibitory function of FAA on cell migration in H1299 cells, suggesting its promising role in the chemoprevention of lung cancer.

PURPOSE: The ETS2 transcription factor is an evolutionarily conserved gene that is deregulated in cancer. We analyzed the transcriptome of lung adenocarcinomas and normal lung tissue by expression profiling and found that ETS2 was significantly down-regulated in adenocarcinomas. In this study, we probed the yet unknown functional role of ETS2 in lung cancer pathogenesis. EXPERIMENTAL DESIGN: Lung adenocarcinomas (n=80) and normal lung tissues (n=30) were profiled using the Affymetrix Human Gene 1.0 ST platform. Immunohistochemical (IHC) analysis was performed to determine ETS2 protein expression in NSCLC histological tissue specimens (n=201). Patient clinical outcome, based on ETS2 IHC expression, was statistically assessed using the log-rank and Kaplan-Meier tests. RNA interference and over-expression strategies were employed to assess effects of ETS2 expression on the transcriptome and on various malignant phenotypes. RESULTS: ETS2 expression was significantly reduced in lung adenocarcinomas compared to normal lung (p<0.001). Low ETS2 IHC expression was a significant predictor of shorter time to recurrence in NSCLC (p=0.009, HR=1.89) and adenocarcinoma (p=0.03, HR=1.86). Moreover, ETS2 was found to significantly inhibit lung cancer cell growth, migration and invasion (p<0.05), and microarray and pathways analysis revealed significant (p<0.001) activation of the HGF pathway following ETS2 knockdown. In addition, ETS2 was found to suppress MET phosphorylation and knockdown of MET expression significantly attenuated (p<0.05) cell invasion mediated by ETS2-specific siRNA. Furthermore, knockdown of ETS2 augmented HGF-induced MET phosphorylation, cell migration and invasion. CONCLUSIONS: Our findings point to a tumor suppressor role for ETS2 in human NSCLC pathogenesis through inhibition of the MET proto-oncogene.

The ubiquitin-CXCR4 axis plays an important role in acute lung-infection-enhanced lung tumor metastasis.
PURPOSE: Our goals are to test the effect of acute lung infection on tumor metastasis and to investigate the underlying mechanisms. EXPERIMENTAL DESIGN: We combined bacteria- and lipopolysaccharide (LPS)-induced acute lung injury/inflammation (ALI) mouse models with mouse metastatic models to study the effect of acute inflammation on lung metastasis in mice. The mechanisms were invested in ex vivo, in vitro, and in vivo studies. RESULTS: Both bacteria- and LPS-induced acute lung injury/inflammation significantly enhanced lung metastasis of four tail vein-injected mouse tumor cell lines. Bacteria also enhanced lung metastasis when 4T1 cells orthotopically injected. The bronchoalveolar lavage fluid (BALF) from LPS- or bacteria-injected mice stimulated migration of tumor cells. In vivo tracking of metastatic RM-9 cells showed that bacterial injection enhanced early dissemination of tumor cells to the lung. The majority of the BALF migratory activity could be blocked by AMD3100, a CXCR4 inhibitor. All tested cell lines expressed CXCR4. The levels of extracellular ubiquitin (Ub), but not SDF-1, in BALF were significantly increased by LPS. Ub was able to induce AMD3100-sensitive migration of tumor cells. Finally, the anti-bacterial amoxicillin and AMD3100 blocked the enhancement effect of bacterial infection on tumor metastasis. CONCLUSIONS: Acute lung infection dramatically increased cancer cell homing to the lung and lung metastasis. This may be due to an alteration of the lung microenvironment and preparation of a favorable metastatic “niche”. This effect was seen in multiple cancer types and thus may have broad applications for cancer patients in prevention and/or treatment of metastasis.
family. Previous studies have demonstrated that overexpression of TOB1 significantly enhances the radiosensitivity of breast and cervical cancer cells. However, the potential mechanisms of TOB1 are still debated. In the present study, we evaluated the effects of infrared (IR) radiation on TOB1 expression in the human lung cancer cell lines NCI-H1975 and A549 via western blot analysis. NCI-H1975 cells were transfected with TOB1 recombinant plasmid, and A549 cells were treated with TOB1-small interfering RNA (siRNA) to establish gain-of-function and loss-offunction cell models. The effects of radiation and TOB1 overexpression and silencing on clonogenic survival, cell cycle distribution and DNA repair were assessed. Western blot analysis was performed to determine the related mechanisms. The expression levels of TOB1 were significantly induced by IR radiation. Overexpression of TOB1 abrogated radiation-induced G2/M arrest, reduced clonogenic cell survival and enhanced gamma-H2AX foci in NCI-H1975 cells exposed to irradiation. TOB1-siRNA demonstrated opposite effects in A549 cells. TOB1 regulated the activation of mitogen-activated protein kinase (MAPK) and modulated the phosphorylation of p53 via activation of the MAPK/extracellular signal-regulated kinase (ERK) pathway. The findings suggest that TOB1 may be a novel molecular target of irradiation. TOB1 modulated the radiosensitivity of lung cancer cells via the MAPK/ERK signaling pathway.

[278]

TÍTULO / TITLE: - High expression of JMJD6 predicts unfavorable survival in lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1007/s13277-013-0789-9
AUORES / AUTHORS: - Zhang J; Ni SS; Zhao WL; Dong XC; Wang JL
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Changzheng Hospital, Second Military Medical University, No. 415, Fengyang Road, Shanghai, 200003, China.
RESUMEN / SUMMARY: - The upregulated expression of JMJD6 was observed in various human cancers. However, little was known about JMJD6 expression and its clinicopathological significance in lung adenocarcinoma. The aim of this study was to investigate the expression and significance of JMJD6 in lung adenocarcinoma progression and prognosis. The levels of JMJD6 mRNA and protein in lung adenocarcinoma specimens and corresponding non-tumorous lung tissues were evaluated by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) and Western blot. In order to investigate the correlations between JMJD6 and the clinicopathological features of lung adenocarcinoma, the expression of JMJD6 in 154 patients with lung
adenocarcinoma was detected by immunohistochemistry. By qRT-PCR and Western blot, the relative expression levels of JMJD6 mRNA and protein were significantly higher in lung adenocarcinoma tissues than in corresponding non-tumorous lung tissues (P < 0.001). Immunohistochemical staining revealed that high JMJD6 expression was closely correlated with tumor size (P = 0.005), pathological grade (P = 0.003), pT status (P = 0.012), pN status (P = 0.003), and pleural invasion (P < 0.001). Moreover, the results of Kaplan-Meier analysis indicated that a high expression level of JMJD6 resulted in a significantly poor prognosis of lung adenocarcinoma patients. Multivariate analysis showed that the status of JMJD6 expression was an independent prognostic factor for lung adenocarcinoma patients. Our results showed that JMJD6 plays a key role in lung adenocarcinoma and therefore may provide an opportunity for developing a novel therapeutic target as well as a prognostic marker in lung adenocarcinoma.

[279]

**TITULO / TITLE:** Inhalable magnetic nanoparticles for targeted hyperthermia in lung cancer therapy.

**RESUMEN / SUMMARY:** Inhalable magnetic nanoparticles for targeted hyperthermia in lung cancer therapy.


**AUTORES / AUTHORS:** Sadhukha T; Wiedmann TS; Panyam J

**INSTITUCION / INSTITUTION:** Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, United States.

**RESUMEN / SUMMARY:** Lung cancer (specifically, non-small cell lung cancer; NSCLC) is the leading cause of cancer-related deaths in the United States. Poor response rates and survival with current treatments clearly indicate the urgent need for developing an effective means to treat NSCLC. Magnetic hyperthermia is a non-invasive approach for tumor ablation, and is based on heat generation by magnetic materials, such as superparamagnetic iron oxide (SPIO) nanoparticles, when subjected to an alternating magnetic field. However, inadequate delivery of magnetic nanoparticles to tumor cells can result in sub-lethal temperature change and induce resistance while non-targeted delivery of these particles to the healthy tissues can result in toxicity. In our studies, we evaluated the effectiveness of tumor-targeted SPIO nanoparticles for magnetic hyperthermia of lung cancer. EGFR-targeted, inhalable SPIO nanoparticles were synthesized and characterized for targeting lung tumor cells as well as for magnetic hyperthermia-mediated antitumor efficacy in a mouse orthotopic model of NSCLC. Our results show that EGFR targeting enhances tumor retention of SPIO nanoparticles. Further, magnetic
hyperthermia treatment using targeted SPIO nanoparticles resulted in significant inhibition of in vivo lung tumor growth. Overall, this work demonstrates the potential for developing an effective anticancer treatment modality for the treatment of NSCLC based on targeted magnetic hyperthermia.

[280]

TÍTULO / TITLE: Novel FGFR inhibitor ponatinib suppresses the growth of non-small cell lung cancer cells overexpressing FGFR1.

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


AUTORES / AUTHORS: Ren M; Hong M; Liu G; Wang H; Patel V; Biddinger P; Silva J; Cowell J; Hao Z

INSTITUCIÓN / INSTITUTION: Cancer Center, Department of Medicine, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA 30912, USA.

RESUMEN / SUMMARY: Lung cancer is still the leading cause of cancer-related deaths worldwide. Identifying new oncogenic drivers and developing efficient inhibitors through molecular targeting approaches are crucial for improving therapies. The aim of this study was to investigate whether targeting fibroblast growth factor receptor 1 (FGFR1) with ponatinib inhibits the cell growth in both established and primary lung cancer cells overexpressing FGFR1. Eighty-eight non-small cell lung cancer (NSCLC) and paired normal tissue specimens were analyzed by real-time RT-PCR for FGFR1 gene expression. We identified four cell lines and two newly established primary lung cancer cultures that showed high FGFR1 expression levels, and evaluated the effect of the novel FGFR1 inhibitor ponatinib on cell growth. Approximately 50% (30 out of 59) NSCLC specimens expressed FGFR1>2-fold compared with their adjacent normal counterparts using quantitative RT-PCR. Ponatinib treatment of established NSCLC cell lines expressing higher levels of FGFR1 resulted in marked cell growth inhibition and suppression of clonogenicity. This growth inhibition was associated with inactivation of FGFR1 and its downstream targets. FGFR1 knockdown by shRNA achieved similar results when compared to treatment with ponatinib. Furthermore, ponatinib was able to significantly inhibit the growth of primary lung cancer cultures in vitro. Our data indicate that pharmacological inhibition of FGFR1 kinase activity with ponatinib may be effective for the treatment of lung cancer patients whose tumors overexpress FGFR1.

[281]
**TÍTULO / TITLE:** A novel imidazopyridine PI3K inhibitor with anticancer activity in non-small cell lung cancer cells.

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


**AUTORES / AUTHORS:** Lee H; Kim SJ; Jung KH; Son MK; Yan HH; Hong S; Hong SS

**INSTITUCION / INSTITUTION:** Department of Drug Development, College of Medicine, Inha University, Sinheungdong, Junggu, Incheon 400-712, Republic of Korea.

**RESUMEN / SUMMARY:** Lung cancer is the leading cause of cancer-related mortality in the world, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases. Since more than 60% of NSCLC cases express the epidermal growth factor receptor (EGFR), EGFR tyrosine kinase inhibitors are used to treat NSCLC. However, due to the acquired resistance associated with EGFR-targeted therapy, other strategies for the treatment of NSCLC are urgently needed. Therefore, we investigated the anticancer effects of a novel phosphatidylinositol 3-kinase alpha (PI3Kalpha) inhibitor, HS-173, in human NSCLC cell lines. HS-173 demonstrated anti-proliferative effects in NSCLC cells and effectively inhibited the PI3K signaling pathway in a dosedependent manner. In addition, it induced cell cycle arrest at G2/M phase as well as apoptosis. Taken together, our results demonstrate that HS-173 exhibits anticancer activities, including the induction of apoptosis, by blocking the PI3K/Akt/mTOR pathway in human NSCLC cell lines. We, therefore, suggest that this novel drug could potentially be used for targeted NSCLC therapy.

[282]

**TÍTULO / TITLE:** Suicide in lung cancer: Who is at risk?

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


**AUTORES / AUTHORS:** Urban D; Rao A; Bressel M; Neiger D; Solomon B; Mileshkin L

**RESUMEN / SUMMARY:** ABSTRACT BACKGROUND: Suicide rates among lung cancer patients are higher than the general population. This study aims to identify patient and disease characteristics associated with suicide in lung cancer patients. METHODS: We conducted an analysis of subjects with primary lung cancer diagnosed between 1973 - 2008 recorded in the Surveillance, Epidemiology and End Results (SEER) database. RESULTS: Of 871,230 persons diagnosed with lung cancer, 1184 suicides were identified. The rate of suicide did not change considerably over time, with 8.83 compared to 7.17 suicides per 10,000 persons-years in 1973-79 and 2000-09, respectively. The
standardized mortality ratio (SMR) of the entire cohort was 4.95, with an SMR of 13.4 within 3 months of a cancer diagnosis. Despite most subgroups having a higher SMR than the general population, a wide variation of suicide risk was seen amongst different subgroups, including histologic type (SMR 1.58 vs 7.28 in bronchoalveolar and small cell carcinoma, respectively). The highest SMR’s were found in: males; older age; higher grade tumour; metastatic disease, and patients who did not receive or refused treatment. Despite the higher SMR among metastatic patients, over 50% of suicides occurred in those with locoregional, and potentially curable disease. CONCLUSION(S): Lung cancer patients have a higher risk of suicide compared with the general US population, especially within 3 months of diagnosis. Despite the higher SMR among poorer prognosis patients, a concerning proportion of suicides occur in potentially curable patients, highlighting the need for effective screening strategies to avoid this preventable cause of death.
is the most important predictor of death within both of these early postoperative periods. We used the data in the NLCA to develop a predictive score, based on an English population and specific to lung cancer surgery, which estimates risk of death within 90 days; this score should be tested in future cohorts.

[284]

TÍTULO / TITLE: Is lobectomy really more effective than sublobar resection in the surgical treatment of second primary lung cancer?  
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary  
AUTORES / AUTHORS: Zuin A; Andriolo LG; Marulli G; Schiavon M; Nicotra S; Calabrese F; Romanello P; Rea F  
INSTITUCIÓN / INSTITUTION: Thoracic Surgery, Department of Cardio-Thoracic and Vascular Sciences, University of Padua, Padua, Italy.  
RESUMEN / SUMMARY: OBJECTIVES: Sublobar resection for early-stage lung cancer is still a controversial issue. We sought to compare sublobar resection (segmentectomy or wedge resection) with lobectomy in the treatment of patients with a second primary lung cancer. METHODS: From January 1995 to December 2010, 121 patients with second primary lung cancer, classified by the criteria proposed by Martini and Melamed, were treated at our Institution. We had 23 patients with a synchronous tumour and 98 with metachronous. As second treatment, we performed 61 lobectomies (17 of these were completion pneumonectomies), 38 atypical resections and 22 segmentectomies. Histology was adenocarcinoma in 49, squamous in 38, bronchoalveolar carcinomas in 14, adenosquamous in 8, large cells in 2, anaplastic in 5 and other histologies in 5. RESULTS: Overall 5-year survival from second surgery was 42%; overall operative mortality was 2.5% (3 patients), while morbidity was 19% (22 patients). Morbidity was comparable between the lobectomy group, sublobar resection and completion pneumonectomies (12.8, 27.7 and 30.8%, respectively, P = 0.21). Regarding the type of surgery, the lobectomy group showed a better 5-year survival than sublobar resection (57.5 and 36%, respectively, P = 0.016). Compared with lobectomies, completion pneumonectomies showed a significantly less-favourable survival (57.5 and 20%, respectively, P = 0.001). CONCLUSIONS: From our experience, lobectomy should still be considered as the treatment of choice in the management of second primary lung cancer, but sublobar resection remains a valid option in high-risk patients with limited pulmonary function. Completion pneumonectomy was a negative prognostic factor in long-term survival.

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[285]
TÍTULO / TITLE: - Lung cancer mortality highest for black individuals in the most segregated counties.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Printz C

[286]
TÍTULO / TITLE: - Proton magnetic resonance metabolomic characterization of ovarian serous carcinoma effusions: chemotherapy-related effects and comparison with malignant mesothelioma and breast carcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Vettukattil R; Hetland TE; Florenes VA; Kaern J; Davidson B; Bathen TF
INSTITUCIÓN / INSTITUTION: - Dept. of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Postbox 8905, 7491 Trondheim, Norway. Electronic address: muhammad.r.vettukattil@ntnu.no.
RESUMEN / SUMMARY: - Malignant serous effusions are a common manifestation of advanced cancer, associated with significant morbidity and mortality. The aim of this study was to identify the metabolic differences between ovarian serous carcinoma effusions obtained pre- and post-chemotherapy, as well as to compare ovarian carcinoma (OC) effusions with breast carcinoma and malignant mesothelioma specimens. The supernatants of 115 effusion samples were analyzed by high-resolution magnetic resonance spectroscopy in vitro and multivariate analysis. The samples comprised pleural and peritoneal effusions from 95 OC, 10 breast carcinomas, and 10 malignant mesotheliomas. Among the OC, 8 were paired peritoneal specimens obtained pre- and post-chemotherapy from the same patient. OC had elevated levels of ketones (aceto-acetate and beta-hydroxybutyrate) and lactate compared to malignant mesotheliomas and breast carcinomas, whereas the latter had more glucose, alanine, and pyruvate. Multivariate analysis of paired effusions in OC showed a significant increase in glucose and lipid levels in the post-treatment spectra (P = .039). Magnetic resonance spectroscopy is a promising technique for comprehensive and comparative studies of metabolites in malignant serous effusions, and our study shows that small metabolites associated with effusions
might improve our understanding of tumor biology and disease progression and has diagnostic potential in this differential diagnosis.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Hou YL; Chen JJ; Wu YF; Xue CJ; Li FZ; Zheng Q; Chen H
INSTITUCIÓN / INSTITUTION: Clinical Laboratories, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.
RESUMEN / SUMMARY: OBJECTIVES: The aim of the study was to investigate the clinical significance of serum mitochondrial DNA (mtDNA) in lung cancer. DESIGN AND METHODS: Serum mtDNA from 65 lung cancer patients, 20 patients with benign lung diseases and 55 healthy individuals was quantified using real-time fluorescent quantitative polymerase chain reaction (FQ-PCR). Data were analyzed using statistical software SPSS 13.0. RESULTS: Serum mtDNA levels in lung cancer patients were significantly higher, compared to those in patients with benign lung diseases and healthy individuals (u=108, p=0.000; u=293, p=0.000), and closely associated with TNM stage (p=0.01). The use of serum mtDNA facilitated detection of lung cancer at a cutoff value of 0.74x10^4 copies/μL with a sensitivity of 86.2% and specificity of 80.7%. However, serum mtDNA levels were not associated with patient age, gender, histological type, and lymph node metastasis (p>0.05). CONCLUSIONS: Quantification of serum mtDNA using FQ-PCR potentially serves as a novel complementary tool to improve the clinical screening and detection of lung cancer.

[288] TÍTULO / TITLE: MGr1-Ag promotes invasion and bone metastasis of small-cell lung cancer in vitro and in vivo.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Zhang F; Wang Y; Xu M; Dong H; Liu N; Zhou J; Pang H; Ma N; Zhang N; Pei Y; Zhang H; Liu L
OBJECTIVES:: Medically inoperable lung cancer patients often have comorbidities that preclude pathologic diagnosis from being attained. We perform a multi-institutional analysis to determine if unbiopsied early-stage lung carcinoma can be safely and effectively treated with stereotactic body radiation therapy (SBRT). MATERIALS AND METHODS:: Thirty-four patients with unbiopsied lung cancer were treated with SBRT at the University of Louisville or University of Virginia. Patients had computed tomography (CT) and positron emission tomography (PET) imaging clinically
consistent with lung malignancy. Median SBRT dose was 50 Gy (range, 30 to 55 Gy) in a median of 5 fractions (range, 3 to 10 fractions) with static field SBRT or volumetric modulated arc therapy. RESULTS:: Median follow-up is 16.7 months. Primary tumors had a median longest dimension on the original CT of 1.6 cm (range, 0.5 to 3.3 cm) and posttreatment CT scan of 1.25 cm (range, 0.0 to 4.5 cm) (P=0.025). Median pretreatment standard uptake value on initial PET scan is 4.6 mg/mL (range, 0.0 to 16.2 mg/mL), and at a median of 7.6 months after SBRT, decreased to 2.25 mg/mL (range, 0.0 to 10.9 mg/mL) on posttreatment PET (P=0.002). Crude local control is 97.1%. The estimated 2-year regional control is 80%, distant control 85%, and overall survival 85%. There were no grade 3 or greater acute toxicities and only 3 grade 3 chronic treatment-related toxicities. DISCUSSION:: In medically inoperable patients with unbiopsied lung cancer, local control can be achieved with minimal toxicity with the use of SBRT. The use of SBRT for unbiopsied early-stage lung cancer patients should be performed in a multidisciplinary setting and after detailed discussion with the patient about the risks and benefits of SBRT.
blockers (i.e., anticytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] antibodies) may be efficacious as single agents and in combination with standard-of-care regimens. Notably, in a phase II trial, ipilimumab—a fully human anti-CTLA-4 monoclonal antibody recently approved for treatment of unresectable or metastatic melanoma—demonstrated encouraging results when used as part of a chemoimmunotherapeutic regimen in patients with SCLC. Ipilimumab is undergoing further investigation in this population.

CONCLUSIONS: Treatment options for SCLC are limited and prognosis poor, emphasizing the need for novel treatments. Although current strategies successfully induce a response, the response is not durable. Evidence of an immune response in SCLC and a better understanding of the immunosuppressive tumor environment support the combinatorial use of immunomodulators, such as ipilimumab, with traditional chemotherapy regimens to improve patient outcomes and potentially sustain the effect from chemotherapeutic induction.

[291]

**TÍTULO / TITLE:** Human Lung Cancer-associated Fibroblasts Enhance Motility of Non-small Cell Lung Cancer Cells in Co-culture.

**RESUMEN / SUMMARY:** The metastatic potential of non-small cell lung cancer (NSCLC) cells has been shown to be associated with the tumor microenvironment. Cancer-associated fibroblasts (CAFs) are a major component of the tumor microenvironment, regulating tumor cell function by secreting growth factors, chemokines, and extracellular matrix (ECM). In this study, we examined the role of CAFs in the tumor progression of NSCLC. Firstly, we established primary cultures of CAFs and matched normal fibroblasts (NFs) from patients with resected NSCLC. CAFs exhibited greater expression of the pan-mesenchymal marker alpha-smooth muscle actin (alpha-SMA) than did NFs, although they displayed similar morphology. Furthermore, we employed a direct co-culture assay with human NSCLC A549 and H358 cells, and found that CAFs were more potent in inducing the epithelial-to-mesenchymal transition (EMT) phenotype than NFs, as indicated by an elongated and disseminated appearance. CAF-induced EMT led to an increase in motility and a decrease in proliferation of NSCLC cells through SMAD family number-3 (SMAD3)-dependent up-regulation of the growth inhibitory gene.
p21(CIP1) [cyclin-dependent kinase inhibitor-1\(^a\) (CDKN1A)] and alpha-SMA. Taken together, these findings provide evidence that lung CAFs have tumor-promoting capacity distinct from NFs and might play a significant role in the metastatic potential of NSCLC.

[292]
**Título / Title:** Comparison of Antitumor Effects of Native and Recombinant Human Interferon-alpha on Non-small Cell Lung Cancer Cells.
**Resumen / Summary:** Enlace al Resumen / Link to its Summary
**Autores / Authors:** Santak G; Santak M; Forcic D
**Institución / Institution:** Department of Surgery, County Hospital PoZega, Osjecka 107, HR-34 000 PoZega, Croatia. gsantak@hotmail.com.
**Resumen / Summary:** BACKGROUND: In the present work, we compared the antitumor effects of native human interferon-alpha (IFN-alpha) (nHuIFN-alpha) and recombinant human IFN-alpha (rHuIFN-alpha) on human lung adenocarcinoma A549 cells. MATERIALS AND METHODS: The antitumor activity was determined by measuring cell viability and apoptosis, while the abundance of mRNA, measured by polymerase chain reaction (PCR), determined the potential role of p21 and survivin in antitumor activity of nHuIFN-alpha. RESULTS: The results show that nHuIFN-alpha significantly reduced A549 cell viability, compared to rHuIFN-alpha. The most potent effect of nHuIFN-alpha was also observed when apoptosis was measured. A549 cells treated with nHuIFN-alpha expressed a significantly higher amount of p21 mRNA, while the amount of survivin mRNA was significantly reduced. CONCLUSION: Considering both the anti-proliferative and anti-apoptotic effects of each IFN-alpha, we conclude that further elucidation of the mechanisms of the antitumor activity of nHuIFN-alpha will help in producing more effective and less toxic therapeutic protocols and preparations.

[293]
**Título / Title:** Dioscorin Pre-treatment Protects A549 Human Airway Epithelial Cells from Hydrogen Peroxide-Induced Oxidative Stress.
**Resumen / Summary:** Enlace al Resumen / Link to its Summary
**Revista / Journal:** Inflammation. 2013 Apr 11.
**Autores / Authors:** Hsu JY; Chu JJ; Chou MC; Chen YW
**Institución / Institution:** Division of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.
Hydrogen peroxide (H2O2) is a highly reactive oxygen species involved in lung and bronchial epithelium injury. Increased H2O2 levels have been reported in expired breath condensates of patients with inflammatory airway diseases such as chronic obstructive pulmonary disease. Protecting airway epithelial cells from oxidative stress is an important task in the prevention and management of airway diseases. Previous studies demonstrate that yam (Dioscorea batatas Decne) has antioxidant and antitrypsin activities. This study evaluated the validity of dioscorin in vitro. The results showed that dioscorin attenuated the alteration of H2O2 on G2/M cell cycle arrest. This might be associated with the activation of IkappaB and subsequent inactivation of NF-kappaB. Furthermore, dioscorin suppressed IL-8 secretion and reduced changes of adhesion molecule expressions in H2O2-injured A549 cells. These results help in understanding the potential of traditional Chinese herbal medicine as treatment for airway inflammatory diseases.

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Prognostic parameters for acute esophagus toxicity in Intensity Modulated Radiotherapy and concurrent chemotherapy for locally advanced non-small cell lung cancer.

Background and Purpose: The aim of this study was to correlate clinical and dosimetric variables with acute esophageal toxicity (AET) following Intensity Modulated Radiotherapy (IMRT) with concurrent chemotherapy for locally advanced non-small cell lung cancer (NSCLC). In addition, timeline of AET was reported. Material and Methods: 153 patients with locally advanced NSCLC treated with 66Gy/2.75Gy/24 fractions of radiotherapy and concurrent daily low dose cisplatin were selected. Medical records and treatments of these patients were retrospectively reviewed. Maximum AET grade 2 and maximum grade 3 were the endpoints of this study. Dates for onset, maximum and recovery (to baseline) of AET were reported. Univariate and multivariate analysis were applied to correlate clinical, tumor, dosimetric and chemotherapy dose variables to AET grade 2 and grade 3. Results: AET grade 2 occurred in 37% and grade 3 in 20% of the patients.
The median onset of AET was around day 15 for all grades. The median onset of the maximum grade was day 30 for both grades 2 and 3. The median duration was 43 days for grade 1, 50 days for grade 2 and >80 days for grade 3. Of the grade 3 AET patients, 48% recovered within 3 months. Esophagus V50, ethnic background, and the number of cisplatin administrations were significantly correlated with grade 3 AET. CONCLUSIONS: For NSCLC patients treated with concurrent chemotherapy and IMRT A higher number of cisplatin administrations, non-Caucasian background and higher V50oes were associated with grade 3 AET. The median onset of AET grade 3 is 15 days after the start of treatment, maximized at day 30, with a median duration of >80 days.

[295]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fedor D; Johnson WR; Singhal S
INSTITUCIÓN / INSTITUTION: - Thoracic Surgery Research Laboratory, Department of Surgery, Perelman School of Medicine, 6 White Building 3400 Spruce Street, Philadelphia, PA, USA. Electronic address: dfedor@mail.med.upenn.edu.
RESUMEN / SUMMARY: - PURPOSE: To date, few large-scale original studies have focused specifically on local recurrence following curative lung cancer surgery. This review seeks to consolidate and analyze data from these studies regarding local recurrence incidence, risk factors, salvage treatments, and outcomes to increase awareness in the Oncology community and to spark new research in this area. METHODS: PubMed literature was searched for large-scale cohort studies involving recurrence following lung cancer surgery. Studies with a primary focus on local recurrence and studies that examined overall recurrence but provided relevant numerical data on local recurrence were included. Each chosen study’s methods were critically analyzed to reconcile as best as possible large differences in reported results across the studies. RESULTS: Up to 24% of patients recur locally following lung cancer surgery. Risk of local recurrence increases with the stage of the primary cancer, but even stage I patients experience local recurrence up to 19% of the time. Overall survival time following local recurrence varies widely across studies, from 7 to 26 months, and may be related to frequency of follow-up visits. Salvage therapy appears to increase survival time. However, estimates of this increase vary widely, and measurements of benefits of the various salvage options are
confounded by lack of control of subjects’ condition at the time of salvage therapy administration. CONCLUSIONS: Local recurrence following lung cancer surgery is a significant problem warranting additional research. At present, data on this topic is scarce. We recommend initiation of additional large-scale studies to clearly define the parameters of local recurrence in order to provide useful guidance to clinicians.

[296]


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


AUTORES / AUTHORS: Akamatsu H; Inoue A; Mitsudomi T; Kobayashi K; Nakagawa K; Mori K; Nukiwa T; Nakanishi Y; Yamamoto N

INSTITUCIÓN / INSTITUTION: *Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan. h.akamatsu@scchr.jp.

RESUMEN / SUMMARY: OBJECTIVE: Interstitial lung disease associated with gefitinib is a critical adverse reaction. When gefitinib was administered to EGFR-unknown patients, the interstitial lung disease incidence rate was approximately 3-4% in Japan, and usually occurs during the first 4 weeks of treatment. However, it has not been fully investigated in EGFR-mutated patients. METHODS: We collected clinical records of participants of two Phase III trials (WJTOG 3405 and NEJ 002), which compared gefitinib with platinum doublet chemotherapy. All patients were EGFR mutated, chemo-naive and had good performance status. RESULTS: A total of 402 patients were enrolled in this study. In the gefitinib arm, 10 (5.0%) of 201 patients developed interstitial lung disease, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed interstitial lung disease (Grade 1) in the chemotherapy arm. With regard to gefitinib, smoking history was significantly associated with developing interstitial lung disease (odds ratio 0.18; 95% confidence interval: 0.05-0.74; P = 0.01). The cumulative incidence rate of interstitial lung disease was similar in the 0-4, 5-8 and 9-12 week time periods. However, between smokers and never-smokers, cumulative incidence rates in the first 4 weeks were significantly different (4.7% versus 0%, P = 0.03). Three of 10 patients developed interstitial lung disease after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively). CONCLUSIONS: Among EGFR-mutated patients, the incidence of interstitial lung disease associated with gefitinib was not different from that in previous reports. Smoking history
was associated with developing interstitial lung disease, and smokers had a higher incidence rate of interstitial lung disease in the first 4 weeks.
[298]  
**TÍTULO / TITLE:** Recruitment and Phenotypic Characteristics of Interleukin 9-Producing CD4 T Cells in Malignant Pleural Effusion.

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

**REVISTA / JOURNAL:** Lung. 2013 May 23.

**AUTORES / AUTHORS:** Bu XN; Zhou Q; Zhang JC; Ye ZJ; Tong ZH; Shi HZ

**INSTITUCIÓN / INSTITUTION:** Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, 8 Gongren Tyuchang Nanlu, Chaoyang, 100020, Beijing, China.

**RESUMEN / SUMMARY:** BACKGROUND: Our previous data have demonstrated that the number of IL-9-producing CD4+ T cells (Th9 cells) in malignant pleural effusion (MPE) was significantly increased when compared with that in blood. The aim of the present study was to investigate the mechanism by which Th9 cells were recruited into MPE and the phenotypic characteristics of pleural Th9 cells. METHODS: The expression patterns of chemokine receptors (CCRs) on Th9 cells and the chemoattractant activity of chemokine CCL20 for Th9 cells in vitro were observed. The phenotypic features of Th9 cells in MPE were determined by flow cytometry. RESULTS: We found that Th9 cells in both MPE and blood expressed a high level of CCR6 on their surface. An in vitro migration assay confirmed that both MPE and supernatants of cultured pleural mesothelial cells could induce the migration of Th9 cells, and anti-CCL20 mAb significantly inhibited the ability of MPE or supernatants to stimulate Th9 cell chemotaxis. We also noted that pleural Th9 cells expressed high levels of CD45RO and very low levels of CD45RA and CD62L, displaying the phenotype of effector memory cells. CONCLUSIONS: Our data revealed that recruitment of Th9 cells into MPE could be induced by pleural CCL20 and that the majority of Th9 cells in MPE displayed the phenotype of effector memory cells.

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[299]  
**TÍTULO / TITLE:** In vitro cell tests of pancreatic malignant tumor cells by photothermotherapy based on DMSO porous silicon colloids.

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


**AUTORES / AUTHORS:** Hong C; Lee C

**INSTITUCIÓN / INSTITUTION:** Department of Materials Science and Engineering, Inha University, 253 Yonghyeon-dong, Incheon, 402-751, Republic of Korea.

**RESUMEN / SUMMARY:** Dimethyl sulfoxide porous silicon (DMSO-PSi) colloid in which DMSO was used as a surfactant suitable for inhibiting the agglomeration
of PSi nanoparticles was prepared for use in cancer photothermotherapy. The photothermal effect of the DMSO-PSi colloid was found to be high enough to destroy cancer cells (T = approximately 52 degrees C). The mean particle size of the PSi nanoparticles in the DMSO-PSi colloid was 67 nm, which is low enough to flow through blood vessels without causing a blockage. The DMSO-PSi colloid in combination with an NIR laser resulted in a cell viability of 5.70 %, which is a sufficiently high cytotoxic effect.

[300]
TÍTULO / TITLE: - Dosimetric impact of Acuros XB deterministic radiation transport algorithm for heterogeneous dose calculation in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Han T; Followill D; Mikell J; Repchak R; Molineu A; Howell R; Salehpour M; Mourtada F
INSTITUCIÓN / INSTITUTION: - Department of Radiation Physics, the University of Texas MD Anderson Cancer Center, Houston, Texas 77030.
RESUMEN / SUMMARY: - Purpose: The novel deterministic radiation transport algorithm, Acuros XB (AXB), has shown great potential for accurate heterogeneous dose calculation. However, the clinical impact between AXB and other currently used algorithms still needs to be elucidated for translation between these algorithms. The purpose of this study was to investigate the impact of AXB for heterogeneous dose calculation in lung cancer for intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT). Methods: The thorax phantom from the Radiological Physics Center (RPC) was used for this study. IMRT and VMAT plans were created for the phantom in the Eclipse 11.0 treatment planning system. Each plan was delivered to the phantom three times using a Varian Clinac iX linear accelerator to ensure reproducibility. Thermoluminescent dosimeters (TLDs) and Gafchromic EBT2 film were placed inside the phantom to measure delivered doses. The measurements were compared with dose calculations from AXB 11.0.21 and the anisotropic analytical algorithm (AAA) 11.0.21. Two dose reporting modes of AXB, dose-to-medium in medium (Db,m) and dose-to-water in medium (Dw,m), were studied. Point doses, dose profiles, and gamma analysis were used to quantify the agreement between measurements and calculations from both AXB and AAA. The computation times for AAA and AXB were also evaluated. Results: For the RPC lung phantom, AAA and AXB dose predictions were found in good agreement to TLD and film measurements for both IMRT and VMAT plans. TLD dose predictions were within 0.4%-4.4% to AXB doses (both Dm,m and Dw,m); and within 2.5%-6.4% to AAA doses,
respectively. For the film comparisons, the gamma indexes (+/-3%3 mm criteria) were 94%, 97%, and 98% for AAA, AXB_Dm,m, and AXB_Dw,m, respectively. The differences between AXB and AAA in dose-volume histogram mean doses were within 2% in the planning target volume, lung, heart, and within 5% in the spinal cord. However, differences up to 8% between AXB and AAA were found at lungsoft tissue interface regions for individual IMRT fields. AAA was found to be 5-6 times faster than AXB for IMRT, while AXB was 4-5 times faster than AAA for VMAT plan. Conclusions: AXB is satisfactorily accurate for the dose calculation in lung cancer for both IMRT and VMAT plans. The differences between AXB and AAA are generally small except in heterogeneous interface regions. AXB Dw,m and Dm,m calculations are similar inside the soft tissue and lung regions. AXB can benefit lung VMAT plans by both improving accuracy and reducing computation time.

[301]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zakowski MF
INSTITUCIÓN / INSTITUTION: - From the Pathology Fellowship Program, Memorial Sloan Kettering, New York, New York.
RESUMEN / SUMMARY: - Context.-The diagnosis and treatment of non-small cell lung cancer have changed dramatically in the past few years. The discovery of activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor and the use of drugs that successfully target those mutations are among the key advances that have led to a shift in the practice of oncology and pathology, with perhaps the greatest effect on the field of cytology. Objectives.-To present the perspective of a practicing thoracic pathologist and cytopathologist on the developments that have changed practice and to place those changes in a broader context. Data Sources.-Literature review, studies undertaken or participated in by the author, and personal experience. Conclusions.-Cytologists are in an ideal position to influence appropriate testing and treatment in the era of targeted therapy. Lung pathology has led the way in the era of targeted therapy, in no small part due to cytology.

[302]

TÍTULO / TITLE: - Toxicity and prognosis in overweight and obese women with lung cancer receiving Carboplatin-Paclitaxel doublet chemotherapy.

242
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


●●Enlace al texto completo (gratuito o de pago)
3109/07357907.2013.784778

AUTORES / AUTHORS: - Kashiwabara K; Yamane H; Tanaka H

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan.

RESUMEN / SUMMARY: - We retrospectively analyzed overdosing-related toxicity and prognosis in 127 women with lung cancer receiving carboplatin (6AUC) estimated by the Cockcroft-Gault formula using actual body weight and paclitaxel (200 mg/m²). Between the body mass index (BMI) > 25 group (n = 42) and the BMI ≤ 25 group (n = 85), there was no difference in dose intensity of carboplatin (122 mg/m²/week vs. 124 mg/m²/week, p = .323), median overall survival (285 days vs. 282 days, p = .820), and toxicity, except Grade 4 neutropenia in the second cycle. Women with BMI > 25 did not have an increased risk of toxicity because of an appropriate dose reduction.

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TÍTULO / TITLE: - Metformin inhibits growth and enhances radiation response of non-small cell lung cancer (NSCLC) through ATM and AMPK.

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


●●Enlace al texto completo (gratuito o de pago) 1038/bjc.2013.187

AUTORES / AUTHORS: - Storozhuk Y; Hopmans SN; Sanli T; Barron C; Tsiani E; Cutz JC; Pond G; Wright J; Singh G; Tsakiridis T

INSTITUCIÓN / INSTITUTION: - [1] Department of Research, Juravinski Cancer Center, 699 Concession Street, Hamilton L8V 5C2, ON, Canada [2] Department of Oncology, McMaster University, 1280 Main Street West, Hamilton, L8S 4LA, ON, Canada.

RESUMEN / SUMMARY: - Background: We examined the potential of metformin (MET) to enhance non-small cell lung cancer (NSCLC) responses to ionising radiation (IR). Methods: Human NSCLC cells, mouse embryonic fibroblasts from wild-type and AMP-activated kinase (AMPK) alpha1/2-subunit(-/-) embryos (AMPKalpha1/2(-/-)-MEFs) and NSCLC tumours grafted into Balb/c-nude mice were treated with IR and MET and subjected to proliferation, clonogenic, immunoblotting, cell cycle and apoptosis assays and immunohistochemistry (IHC). Results: Metformin (2.5 µM-5 mM) inhibited proliferation and radiosensitised NSCLC cells. Metformin (i) activated the ataxia telangiectasia-mutated (ATM)-AMPK-p53/p21(cip1) and inhibited the Akt-mammalian target of rapamycin (mTOR)-eIF4E-binding protein 1 (4EBP1) pathways, (ii) induced G1...
cycle arrest and (iii) enhanced apoptosis. ATM inhibition blocked MET and IR activation of AMPK. Non-small cell lung cancer cells with inhibited AMPK and AMPKalpha1/2(-/-)-MEFs were resistant to the antiproliferative effects of MET and IR. Metformin or IR inhibited xenograft growth and combined treatment enhanced it further than each treatment alone. Ionising radiation and MET induced (i) sustained activation of ATM-AMPK-p53/p21(cip1) and inhibition of Akt-mTOR-4EBP1 pathways in tumours, (ii) reduced expression of angiogenesis and (iii) enhanced expression of apoptosis markers. Conclusion: Clinically achievable MET doses inhibit NSCLC cell and tumour growth and sensitise them to IR. Metformin and IR mediate their action through an ATM-AMPK-dependent pathway. Our results suggest that MET can be a clinically useful adjunct to radiotherapy in NSCLC.

[304]


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


ENlace al texto completo (gratuito o de pago) 1016/j.lungcan.2013.04.015

AUTORES / AUTHORS: - V Laffert M; Warth A; Penzel R; Schirmacher P; Jonigk D; Kreipe H; Schildhaus HU; Merkelbach-Bruse S; Buttner R; Reu S; Kerler R; Jung A; Kirchner T; Wolfel C; Petersen I; Rodriguez R; Jochum W; Bartsch H; Fisseler-Eckhoff A; Berg E; Lenze D; Dietel M; Hummel M

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Campus Charite Mitte, Charite Universitätsmedizin, Chariteplatz 1, 10117 Berlin, Germany. Electronic address: maximilian.von-laffert@charite.de.

RESUMEN / SUMMARY: - BACKGROUND: The reliable identification of non-small cell lung cancers (NSCLC) with chromosomal breaks in the gene of the anaplastic lymphoma kinase (ALK) is crucial for the induction of therapy with ALK-inhibitors. In order to ensure a reliable detection of ALK-breaks by means of fluorescence in situ hybridization (FISH) testing, round robin tests are essential. In preparation of a nation (German)-wide round robin test we initiated a pre-testing phase involving 8 experts in FISH diagnostics to identify NSCLC cases (n=10) with a pre-tested ALK-status. In addition, ALK immunohistochemistry (IHC) was performed to assess ALK protein expression. MATERIAL AND METHODS: Sections derived from a tissue microarray, each consisting of 3 cores from 10 NSCLC cases, were independently tested for ALK protein expression by IHC and genomic ALK-breaks by FISH involving 8 institutes of pathology. Based on a pre-screening, 5 cases were identified to be clearly ALK-break negative, whereas the remaining 5 cases were ALK-break
positive including one case with low percentage (20%) of positive cells. The latter had been additionally tested by RT-PCR. RESULTS: The 5 unequivocal ALK-break negative NSCLC were almost consistently scored negative by means of FISH and IHC by all 8 experts. Interestingly, 4 of the 5 cases with pre-defined ALK-breaks revealed homogenous FISH results whereas IHC for the detection of ALK protein expression showed heterogeneous results. The remaining case (low number of ALK-break positive cells) was scored negative by 3 experts and positive by the other 5. RT-PCR revealed the expression of an EML4-ALK fusion gene variant 1. CONCLUSION: ALK-break negative NSCLC cases revealed concordant homogeneous results by means of FISH and IHC (score 0-1) by all 8 experts. Discordant FISH results were raised in one ALK-break positive case with a low number of affected tumor cells. The remaining 4 ALK-break positive cases revealed concordant FISH data whereas the ALK-IHC revealed very diverse results. The cases with concordant FISH results provide an excellent basis for round robin ALK-FISH testing. As long as standardized ALK-IHC protocols are missing, ALK protein expression cannot by regarded as the method of choice for identification of patients eligible for treatment with ALK inhibitors.

TÍTULO / TITLE: - Anticancer property of bromelain with therapeutic potential in malignant peritoneal mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pillai K; Akhter J; Chua TC; Morris DL
INSTITUCIÓN / INSTITUTION: - Department of Surgery, University of New South Wales, St. George Hospital, Kogarah, NSW, Australia.
RESUMEN / SUMMARY: - Bromelain is a mixture of proteolytic enzymes that is capable of hydrolyzing glycosidic linkages in glycoprotein. Glycoprotein’s are ubiquitously distributed throughout the body and serve a variety of physiologic functions. Faulty glycosylation of proteins may lead to cancer. Antitumor properties of bromelain have been demonstrated in both, in vitro and in vivo studies, along with scanty anecdotal human studies. Various mechanistic pathways have been proposed to explain the anticancer properties of bromelain. However, proteolysis by bromelain has been suggested as a main pathway by some researchers. MUC1 is a glycoprotein that provides tumor cells with invasive, metastatic, and chemo-resistant properties. To date, there is no study that examines the effect of bromelain on MUC1. However, the viability of MUC1 expressing pancreatic and breast cancer cells are adversely affected
by bromelain. Further, the efficacy of cisplatin and 5-FU are enhanced by adjuvant treatment with bromelain, indicating that the barrier function of MUC1 may be affected. Other studies have also indicated that there is a greater accumulation of 5-FU in the cell compartment on treatment with 5-FU and bromelain. Malignant peritoneal mesothelioma (MPM) expresses MUC1 and initial studies have shown that the viability of MPM cells is adversely affected by exposure to bromelain. Further, bromelain in combination with either 5-FU or cisplatin, the efficacy of the chemotherapeutic drug is enhanced. Hence, current evidence indicates that bromelain may have the potential of being developed into an effective anticancer agent for MPM.

[306]
**TÍTULO / TITLE:** - Frameless high dose rate stereotactic lung radiotherapy: Intrafraction tumor position and delivery time.

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


- Enlace al texto completo (gratuito o de pago) 1016/j.radonc.2013.04.019

**AUTORES / AUTHORS:** - Peguret N; Dahele M; Cuijpers JP; Slotman BJ; Verbakel WF

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands.

**RESUMEN / SUMMARY:** - Intrafraction change in tumor position (Delta) was evaluated for stereotactic lung radiotherapy delivered with flattening filter free volumetric modulated arc therapy. In 140 fractions from 32 patients mean Delta (+/-SD) was -0.7+/-1.4mm (vertical), -0.7+/-1.3mm (longitudinal) and +0.2+/-1.2mm (lateral) with mean vector 2.1+/-1.2mm. Mean delivery time was 4.4+/-3.4min (mean beam-on 1.9+/-0.4min).

[307]
**TÍTULO / TITLE:** - Genotype analysis of the NRF2 gene mutation in lung cancer.

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


- Enlace al texto completo (gratuito o de pago) 3892/ijmm.2013.1324

**AUTORES / AUTHORS:** - Sasaki H; Suzuki A; Shitara M; Hikosaka Y; Okuda K; Moriyama S; Yano M; Fujii Y

**INSTITUCIÓN / INSTITUTION:** - Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Japan.
RESUMEN / SUMMARY: - Nuclear factor (erythroid derived 2)-like 2 (NRF2, gene name NFE2L2) gene mutations have been previously identified in lung cancers. The constitutive activation of NRF2 resulting from gene mutations has been correlated with the poor prognosis of patients with squamous cell lung cancer. However, DNA sequencing using PCR methods described to date is time-consuming and requires significant quantities of DNA. Thus, this existing approach is not suitable for a routine pre-therapeutic screening program. We genotyped the NRF2 gene mutation status in 262 surgically treated lung cancer cases using LightCycler analysis. The presence of the NRF2 gene mutation was confirmed by direct sequencing. We detected 6 cases (2.3%) with NRF2 gene mutations in our cohort, particularly smokers (P=0.04) with squamous histology (P=0.0001). NRF2 gene mutations were present in 10% (6/60) of the lung squamous cell carcinoma (SqCC) cases. The NRF2 gene mutation was exclusive of epidermal growth factor receptor mutations. The NRF2 gene mutation occurred with a tendency towards a higher frequency in male patients. Patients with the NRF2 gene mutation (n=22, 11 succumbed to disease) had a significantly worse prognosis when compared with the patients with the wild-type NRF2 gene (n=521, 98 succumbed to disease) from a larger cohort study (log-rank test, P<0.0001) even upon multivariate analysis. In our study, NRF2 gene mutations played a role in the prognosis of patients with SqCC of the lung.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gomez-Morales M; Camara-Pulido M; Miranda-Leon MT; Sanchez-Palencia A; Boyero L; Gomez-Capilla JA; Farez-Vidal ME
INSTITUCIÓN / INSTITUTION: - Department of Pathology, School of Medicine, University of Granada, Granada, España.
RESUMEN / SUMMARY: - AIMS: Immunohistochemistry is a highly valuable and widely used tool in the subtyping of lung carcinomas. The aim of this study was to identify markers for the differential diagnosis of non-small-cell carcinomas.
METHODS AND RESULTS: We report on the immunohistochemical localization of plakophilin-1 (PKP1), keratin-15 (KRT15) and desmoglein-3 (DSG3) intercellular adhesion proteins in samples from 75 primary non-small-cell lung cancers in non-treated patients. The staining pattern of these proteins differed between squamous cell carcinomas and adenocarcinomas, with no membrane staining in the latter. Membrane staining for all three proteins was characteristic of squamous cell carcinomas. We observed a relationship between the presence/absence of these proteins in the membranes of
squamous cell carcinomas and the differentiation grade, with more intense staining in better differentiated areas. CONCLUSIONS: Staining for these proteins marked intercellular junctions that are characteristic of stratified squamous epithelium and of neoplasias with this type of differentiation, and can be useful in the diagnosis of patients with squamous cell carcinoma of the lung. The high specificity of membrane staining for PKP1 and DSG3 and high sensitivity of cytoplasmic and membrane staining for KRT15 for the diagnosis of squamous cell carcinoma may be useful for the differential diagnosis of non-small-cell carcinomas.


RESUMEN / SUMMARY: - This study was done to explore the role of microRNA-98 (miR-98) in cisplatin sensitization in human lung adenocarcinoma cell line. Differential expressions of miRNAs were analysed between cisplatin-resistant human lung adenocarcinoma cell line A549/DDP and its parental cell A549 by miRNAs microarray, of which 14 miRNAs were showed to be significantly (>2-fold) up-regulated and 8 miRNAs had marked down-regulation (<0.5-fold) in A549/DDP cells compared with in A549 cells. MiR-98, a member in the let-7 family, acts as a negative regulator in the expression of HMGA2 (high mobility group A2) oncogene, and it has been shown to have a nearly 3-fold decrease in A549/DDP cells. We found that elevated expression of miR-98 led to a higher sensitivity of A549/DDP cells to cisplatin, and the protein level of HMGA2, was clearly up-regulated in both A549/DDP and A549 cells by miR-98. Moreover, both Bcl-XL and Bcl-2, were down-regulated in the Pre-miR-98™ transfectants cells. We for the first time demonstrated that the expression of miR-98 increases cells spontaneous apoptosis and sensitizes cells to cisplatin at least in part via HMGA2 up-regulation. Our findings provided insight into some specific miRNAs in lung cancer as potential therapeutic targets.

[309]

TÍTULO / TITLE: - Clinical significance and biological roles of SPAG9 overexpression in non-small cell lung cancer.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
To investigate the expression pattern of SPAG9 protein and its clinical significance in human non-small cell lung cancer (NSCLC). We checked a panel of 120 NSCLC tissues and 20 corresponding normal lung tissues by immumohistochemistry. We observed negative staining in the normal bronchial epithelia and positive staining of SPAG9 in 63 out of 120 (52.5%) NSCLC samples. Overexpression of SPAG9 correlated with poor tumor differentiation (p = 0.002), advanced p-TNM stage (p = 0.0001), nodal metastasis (p = 0.0061) and poor overall survival (p = 0.0001). We silenced SPAG9 gene in A549 and H1299 cells by specific siRNA and found that silencing SPAG9 expression inhibited cell growth and invasion. In addition, the protein and mRNA levels of MMP9 were also down-regulated in SPAG9 knocked down cells. Further research demonstrated SPAG9 depletion could inhibit the activity of p-JNK. In conclusion, SPAG9 might act as an important promoter in lung cancer progression and invasion via MMP9 regulation and JNK activation.

[311]

Clinical perspective of afatinib in non-small cell lung cancer.

Reversible ATP-competitive inhibitors targeting the epidermal growth factor receptor (EGFR) have been established as the most effective treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring “activating” mutations in exons 19 and 21 of the EGFR gene. However, clinical activity is limited by acquired resistance which on average develops within 10 months of continued treatment. The mechanisms for acquired resistance include selection of the EGFR T790M mutation in approximately 50% of cases, and MET gene amplification, PIK3CA gene
mutation, transdifferentiation into small-cell lung cancer and additional rare or unknown mechanisms. Afatinib is a small molecule covalently binding and inhibiting the EGFR, HER2 and HER4 receptor tyrosine kinases. In preclinical studies, afatinib not only inhibited the growth of models with common activating EGFR mutations, but was also active in lung cancer models harboring wild-type EGFR or the EGFR L858R/T790M double mutant. Clinical efficacy of afatinib has been extensively studied in the LUX-Lung study program. These trials showed promising efficacy in patients with EGFR-mutant NSCLC or enriched for clinical benefit from EGFR tyrosine kinase inhibitors gefitinib or erlotinib. Here we review the current status of clinical application of afatinib in NSCLC. We also discuss clinical aspects of resistance to afatinib and strategies for its circumvention.
Furanodiene Presents Synergistic Anti-proliferative Activity With Paclitaxel Via Altering Cell Cycle and Integrin Signaling in 95-D Lung Cancer Cells.

Resumen / Summary: Furanodiene (FUR) is a natural terpenoid isolated from Rhizoma Curcumae, a well-known Chinese medicinal herb that presents anti-proliferative activities in several cancer cell lines. Recently, we found that the combined treatment of FUR with paclitaxel (TAX) showed synergetic anti-proliferative activities in 95-D lung cancer cells. Herein, we showed that FUR reduced the cell numbers distributed in mitosis phase induced by TAX while increased those in G1 phase. The protein levels of cyclin D1, cyclin B1, CDK6 and c-Myc were all down-regulated in the group of combined treatment. The dramatically down-regulated expression of integrin beta4, focal adhesion kinase and paxillin might partially contribute to the synergic effect. Though FUR alone obviously induced endoplasmic reticulum stress, this signaling pathway may not contribute to the synergetic anti-proliferative effect as the protein expression of CHOP and BIP was similar in FUR alone and combined treatment group.

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Hyperthermia-induced genotoxic effects in human A549 cells.

Resumen / Summary: Genotoxic effects of hyperthermia in vitro and in vivo have repeatedly been reported. Short-duration heat shocks and elevated temperature over longer time periods have been shown to induce DNA damage, chromosomal damage and to inhibit DNA repair. Using the comet assay and the
micronucleus test, we now investigated temperature- and time-related effects on DNA damage and chromosomal effects of hyperthermia on the A549 human lung cell line. We also related the genotoxic effects to cytotoxic effects and the induction of apoptosis. Our results indicate that exposure to hyperthermia (42-48 degrees C for 30-120min) induced genotoxic effects in a temperature- and time-related manner. Interestingly, hyperthermia-induced DNA damage measured by the comet assay was not rapidly removed by post-incubation at 37 degrees C but even increased after exposure to 48 degrees C for 60min. Cytotoxic effects occurred in parallel to the genotoxic effects but apoptosis was not significantly induced under these experimental conditions.

[315]

- CASTELLANO -
TÍTULO / TITLE: Single intestinal metastasis of non-small cell lung carcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Parejo-Sanchez MI; Pardo-Cabello AJ; Martinez-Ceres M; Sanchez-Ramos C

[316]
TÍTULO / TITLE: - Can hepatocellular carcinoma (HCC) produce unconventional metastases? Four cases of extrahepatic HCC.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Piccirillo M; Granata V; Albino V; Palaia R; Setola SV; Petrillo A; Tatangelo F; Botti G; Foggia M; Izzo F
INSTITUCIÓN / INSTITUTION: - Deparment of Surgical Oncology, Hepatobiliary Surgery Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori di Napoli, “Fondazione G Pascale”, Naples, Italy.
RESUMEN / SUMMARY: - AIMS AND BACKGROUND: Extrahepatic spread of hepatocellular carcinoma (HCC) diagnosed during the clinical course of the disease is not frequent; however, with the prolonged survival of HCC patients, the incidence of extrahepatic metastases seems to be increasing. METHODS AND STUDY DESIGN: We present four unusual cases of extrahepatic metastasis from HCC: the first concerns a patient who underwent a liver transplantation for HCC with cirrhosis and three years later developed metastases in the lung and the left orbit; the second is that of a patient who developed an extraperitoneal pararectal metastasis; in the third case a large
osteoelastic lesion developed on the left iliac bone, and in the fourth case we found an isolated metastasis in the left mandible. RESULTS AND CONCLUSIONS: These cases offer important information related to the unusual biology of isolated metastases from HCC after successful treatment of the primary cancer.
TÍTULO / TITLE: - Prospective cohort study on television viewing time and incidence of lung cancer: findings from the Japan Collaborative Cohort Study.

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


AUTORES / AUTHORS: - Ukawa S; Tamakoshi A; Wakai K; Noda H; Ando M; Iso H

INSTITUCIÓN / INSTITUTION: - Department of Public Health, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo, Hokkaido, 060-0812, Japan.

RESUMEN / SUMMARY: - PURPOSE: To ascertain whether prolonged television viewing time was associated with lung cancer incidence in Japanese adults aged 40-79 years from a nationwide large-scale cohort study. METHODS: A total of 54,258 adults (23,090 men and 31,168 women) without a history of cancer at baseline (1988-1990) were enrolled and followed for a median of 15.6 years. The Cox proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence interval (CI) for lung cancer according to television viewing time adjusted for age and other possible confounding factors. RESULTS: During the study period, 798 participants were diagnosed with lung cancer. The HR of male participants who watched television for more than 4 h daily was 1.36 (95% CI 1.04-1.80) compared with <2 h/day. CONCLUSION: Our findings suggest that reducing the amount of time spent watching television may be beneficial for preventing lung cancer.

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


AUTORES / AUTHORS: - Eichhorn F; Storz K; Hoffmann H; Muley T; Dienemann H

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Thoraxklinik, Heidelberg University, Heidelberg, Germany. Electronic address: florian.eichhorn@thoraxklinik-heidelberg.de.

RESUMEN / SUMMARY: - BACKGROUND: Sleeve pneumonectomy is a challenging therapeutic strategy for patients with non-small cell lung cancer (NSCLC) invading the carina. The aim of this study was to illustrate common...
indications and individual concepts for surgery and to investigate oncologic outcomes and complications. METHODS: Sixty-four consecutive sleeve pneumonectomies were performed between September 2000 and November 2011. All patients had histologically proven central NSCLC. Data were retrospectively reviewed for indications, complications, and factors influencing long-term survival. RESULTS: Sixty-four patients underwent sleeve pneumonectomy for curative (n = 50, 78%) or palliative therapy (n = 14, 22%). Complete resection was achieved in 83%. Pathologic N2 disease was found in 41%. Complications occurred in 41%, with severe anastomotic problems in 8% of cases. Thirty-day mortality was 3% (n = 2). Outcome was significantly influenced by pathologic nodal status with 5-year survival rates of 70%, 35%, and 9% for N0, N1, and N2 subgroups, respectively. Patients with multilevel N2 disease and contraindications for chemotherapy or radiotherapy had a mean survival of 13 months after palliative surgery. CONCLUSIONS: Sleeve pneumonectomy for central NSCLC invading the carina or proximal main bronchus can be performed with tolerable risk and encouraging survival rates in selected cases. Palliative sleeve pneumonectomy displays an option in the absence of alternative therapeutic strategies.
days) (step 2). Primary endpoint was end-of-cycle 1 dose-limiting toxicity (DLT) rate. Secondary endpoints included safety; relative dose intensities of paclitaxel, carboplatin, and bevacizumab; pharmacokinetics; and tumor response. Results Fifty-two patients were enrolled and received everolimus 5 mg/day plus carboplatin and paclitaxel (step 1 daily; n = 13); everolimus 30 mg/week plus carboplatin and paclitaxel (step 1 weekly; n = 13); everolimus 5 mg/day plus carboplatin, paclitaxel, and bevacizumab (step 2 daily; n = 13); or everolimus 30 mg/week plus carboplatin, paclitaxel, and bevacizumab (step 2 weekly; n = 13). End-of-cycle 1 DLT rate was 16.7 % (step 1 daily), 30.8 % (step 1 weekly), 30.0 % (step 2 daily), and 16.7 % (step 2 weekly). Cycle 1 DLTs were grade 3 neutropenia, anal abscess, diarrhea, and thrombocytopenia and grade 4 myalgia, cellulitis, neutropenia, febrile neutropenia, pulmonary embolism, and thrombocytopenia. The most common adverse events were neutropenia, fatigue, anemia, and thrombocytopenia. One patient (step 2 daily) experienced complete response, 10 patients partial response. Conclusions The feasible everolimus doses given with carboplatin and paclitaxel +/- bevacizumab were 5 mg/day and 30 mg/week. Neither schedule was very well tolerated in this unselected NSCLC population.

[321]
TÍTULO / TITLE: - Intratumour variation of biomarker expression by immunohistochemistry in resectable non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Jakobsen JN; Santoni-Rugiu E; Ravn J; Sorensen JB
INSTITUCIÓN / INSTITUTION: - Department of Oncology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. Electronic address: jan.nyrop.jakobsen@rh.regionh.dk.
RESUMEN / SUMMARY: - BACKGROUND: Prognostic and predictive biomarkers are increasingly used to customise the treatment of patients with solid tumours. Intra- and inter-tumour heterogeneous distribution of biomarker expression is a potential confounder for the use of biomarkers, as small biopsies may not necessarily truly reflect the pattern of biomarker expression. It may also be an important factor in chemo resistance, as tumours with heterogeneous biomarker expression may potentially harbour chemo resistant tumour clones.
MATERIALS AND METHODS: Immunohistochemical evaluation of the expression of excision repair cross complementation group 1 (ERCC1), epidermal growth factor receptor (EGFR), class III-beta-tubulin (TUBB-3), thymidylate synthase (TS), Ki-67 and ribonucleotide reductase M1 (RRM1) was performed in 15 separate areas in each of six small microscopically completely
resected adenocarcinomas of the lung in order to elucidate any heterogeneous
distribution. RESULTS: Clinically relevant biomarker heterogeneity with respect
to the expression of EGFR, ERCC1, RRM1, TUBB-3 and Ki-67 was observed in
four (66%), four (66%), one (16%), three (50%) and five (83%) out of six
tumours, respectively. Thus, heterogeneity could potentially allocate these
tumours erroneously into high or low expressers by chance alone, according to
previously reported cut-off values. In contrast, TS was almost completely
homogenously distributed. CONCLUSION: Most biomarkers examined, except
for TS, showed clinically significant intratumour heterogeneity in 33-87% of
tumours examined. This heterogeneity may influence results in studies
investigating the therapeutic impact of predictive biomarkers in non-small cell
lung cancer (NSCLC).

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TÍTULO / TITLE: - Trends in smoking and lung cancer mortality in Japan, by birth
cohort, 1949-2010.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - Bull World Health Organ. 2013 May 1;91(5):332-40. doi:
AUTORES / AUTHORS: - Funatogawa I; Funatogawa T; Yano E
INSTITUCIÓN / INSTITUTION: - Department of Public Health, Teikyo University
Graduate School of Public Health, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605,
Japan.
RESUMEN / SUMMARY: - OBJECTIVE: To determine smoking trends in Japan in
comparison with lung cancer mortality. METHODS: Age-specific smoking
prevalence among cohorts born between 1897 and 1985 were determined for
the period 1949-2010. The percentages of the cohorts born between 1893 and
1979 who initiated smoking early (e.g. before the age of 20 years) were
determined. The results were compared against lung cancer mortality rates in
people aged 40-84 years belonging to cohorts born between 1868 and 1968.
FINDINGS: In males, smoking prevalence was generally high, particularly
among those born before the late 1950s, and early initiation was fairly
uncommon. Early initiation was most common among recent birth cohorts of
males, who showed relatively low prevalences of smoking. In females, the
prevalence of smoking was generally low and early initiation was very
uncommon, particularly among those born in the late 1930s and before the late
1940s, respectively. Recent cohorts of females showed relatively high
prevalences of smoking and relatively high percentages of early initiation. In
both sexes, lung cancer mortality was generally low but increased over the
study period. CONCLUSION: Lung cancer mortality in Japanese males was
relatively low given the high prevalence of smoking, perhaps because early
initiation was fairly uncommon. Over the last four decades, however, early initiation of smoking has become more common in both sexes. The adverse effect this is likely to have on lung cancer mortality rates has probably not been observed because of the long time lag between smoking initiation and death from lung cancer.

[323]

TÍTULO / TITLE: - Phase 2 study of sorafenib in malignant mesothelioma previously treated with platinum-containing chemotherapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Papa S; Popat S; Shah R; Prevost AT; Lal R; McLennan B; Cane P; Lang-Lazdunski L; Viney Z; Dunn JT; Barrington S; Landau D; Spicer J
INSTITUCIÓN / INSTITUTION: - *Guy’s and St. Thomas’ NHS Foundation Trust, London, United Kingdom; daggerRoyal Marsden Hospital, London, United Kingdom; double daggerNational Heart and Lung Hospital, Imperial College London, United Kingdom; section signKent Cancer Centre, Maidstone, Kent, United Kingdom; and ||King’s College London, United Kingdom.
RESUMEN / SUMMARY: - INTRODUCTION: : The incidence of mesothelioma is rising. First-line cisplatin and pemetrexed confers a survival benefit, with a median progression-free survival (PFS) of 5.7 months. Sorafenib inhibits tyrosine kinases, including receptors for vascular endothelial growth factor, which are implicated in mesothelioma pathogenesis by preclinical and clinical data. METHODS: : Sorafenib, at 400 mg twice daily, was assessed in a single-arm multicenter phase 2 study, using Simon’s two-stage design. Eligible patients had received platinum combination chemotherapy earlier. The primary endpoint was PFS at 6 months, with secondary endpoints, including response rate and metabolic response, assessed using fluorodeoxyglucose positron emission tomography. Published reference values for PFS in mesothelioma provide a benchmark for the null hypothesis of 28% progression-free at 6 months, and for moderate or significant clinical activity of 35% or 43% progression-free at 6 months, respectively. RESULTS: : Fifty-three patients (72%) were treated. Most had epithelioid histology. Ninety-three percent of patients had a performance status 0 or 1. Treatment was well tolerated with few grade 3 or 4 toxicities. Median PFS was 5.1 months, with 36% of patients being progression-free at 6 months. Nine percent of patients remained on study beyond 1 year. Changes in fluorodeoxyglucose positron emission tomography parameters did not predict clinical outcome. CONCLUSIONS: : Sorafenib is well
tolerated in patients with mesothelioma after completion of platinum-containing chemotherapy. PFS of sorafenib compares favorably with that reported for other targeted agents, and suggests moderate activity in this disease.

[324]
**TITULO / TITLE:** - Nutrient intake and nutrient patterns and risk of lung cancer among heavy smokers: results from the COSMOS screening study with annual low-dose CT.

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

**REVISTA / JOURNAL:** - Eur J Epidemiol. 2013 Apr 11.

**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, European Institute of Oncology, Via Ramusio 1, Milan, 20141, Italy, patrizia.gnagnarella@ieo.it.

**RESUMEN / SUMMARY:** - The role of nutrients in lung cancer aetiology remains controversial and has never been evaluated in the context of screening. Our aim was to investigate the role of single nutrients and nutrient patterns in the aetiology of lung cancer in heavy smokers. Asymptomatic heavy smokers (>/=20 pack-years) were invited to undergo annual low-dose computed tomography. We assessed diet using a self-administered food frequency questionnaire and collected information on multivitamin supplement use. We performed principal component analysis identifying four nutrient patterns and used Cox proportional Hazards regression to assess the association between nutrients and nutrients patterns and lung cancer risk. During a mean follow-up of 5.7 years, 178 of 4,336 participants were diagnosed with lung cancer by screening. We found a significant risk reduction of lung cancer with increasing vegetable fat consumption (HR for highest vs. lowest quartile = 0.50, 95 % CI = 0.31-0.80; P-trend = 0.02). Participants classified in the high “vitamins and fiber” pattern score had a significant risk reduction of lung cancer (HR = 0.57; 95 % CI = 0.36-0.90, P-trend = 0.01). Among heavy smokers enrolled in a screening trial, high vegetable fat intake and adherence to the “vitamin and fiber” nutrient pattern were associated with reduced lung cancer incidence.

[325]
**TITULO / TITLE:** - KRAS mutations are associated with solid growth pattern and tumor-infiltrating leukocytes in lung adenocarcinoma.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
KRAS mutations define a clinically distinct subgroup of lung adenocarcinoma patients, characterized by smoking history, resistance to EGFR-targeted therapies, and adverse prognosis. Whether KRAS-mutated lung adenocarcinomas also have distinct histopathological features is not well established. We tested 180 resected lung adenocarcinomas for KRAS and EGFR mutations by high-sensitivity mass spectrometry-based genotyping (Sequenom) and PCR-based sizing assays. All tumors were assessed for the proportion of standard histological patterns (lepidic, acinar, papillary, micropapillary, solid, and mucinous), several other histological and clinical parameters, and TTF-1 expression by immunohistochemistry. Among 180 carcinomas, 63 (35%) had KRAS mutations (KRAS+), 35 (19%) had EGFR mutations (EGFR+), and 82 (46%) had neither mutation (KRAS-/EGFR-). Solid growth pattern was significantly over-represented in KRAS+ carcinomas: the mean+/-s.d. for the amount of solid pattern in KRAS+ carcinomas was 27+/-34% compared with 3+/-10% in EGFR+ (P<0.001) and 15+/-27% in KRAS-/EGFR- (P=0.033) tumors. Furthermore, at least focal (>=/=20%) solid component was more common in KRAS+ (28/63; 44%) compared with EGFR+ (2/35; 6%; P<0.001) and KRAS-/EGFR- (21/82; 26%; P=0.022) carcinomas. KRAS mutations were also over-represented in mucinous carcinomas and were significantly associated with the presence of tumor-infiltrating leukocytes and heavier smoking history. EGFR mutations were associated with non-mucinous non-solid patterns, particularly lepidic and papillary, lack of necrosis, lack of cytological atypia, hobnail cytology, TTF-1 expression, and never/light smoking history. In conclusion, extended molecular and clinicopathological analysis of lung adenocarcinomas reveals a novel association of KRAS mutations with solid histology and tumor-infiltrating inflammatory cells and expands on several previously recognized morphological and clinical associations of KRAS and EGFR mutations. Solid growth pattern was recently shown to be a strong predictor of aggressive behavior in lung adenocarcinomas, which may underlie the unfavorable prognosis associated with KRAS mutations in these tumors.

Modern Pathology advance online publication, 26 April 2013; doi:10.1038/modpathol.2013.74.

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TÍTULO / TITLE: Lung sparing and dose escalation in a robust-inspired IMRT planning method for lung radiotherapy that accounts for intrafraction motion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: - McCann C; Purdie T; Hope A; Bezjak A; Bissonnette JP

INSTITUCIÓN / INSTITUTION: - Odette Cancer Center, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada and Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, Ontario M4N 3M5, Canada.

RESUMEN / SUMMARY: - Purpose: To test the efficacy of a simple, robust-inspired intensity modulated radiotherapy (IMRT) planning strategy for lung radiotherapy designed to reduce lung dose and escalate tumor dose using realistic dose accumulation tools.Methods: A deformable image registration tool was used to plan and accumulate dose over all phases of the breathing cycle for conventional and robust-inspired IMRT strategies of eight nonsmall cell lung cancer patients exhibiting peak-to-peak respiratory motion with amplitudes ranging from 1 to 2 cm in the craniocaudal direction. The authors’ robust-inspired plans were designed to have smaller beam apertures based on target location during exhale, combined with edge-enhanced intensity maps to ensure target coverage during inspiration. For these, a new planning target volume defined as the rPTV was generated from a 5-mm isotropic expansion of the clinical target volume (CTV) on end-exhale combined with a boost volume, set to 110% of the prescription dose. Plans were evaluated in terms of (i) lung sparing and (ii) dose escalation for mean lung dose (MLD) isotoxicity. CTV and planning target volumes (PTV) coverage and lung dose were compared to the conventional IMRT approach.Results: Robust-inspired plans showed potential lung dose reductions in seven out of eight patients. For non-GTV lung, percent reductions of 3%-14% in MLD and 6%-15% in V20 were observed. For seven of eight cases, the robust-like approach yielded increased accumulated doses to CTV. Isotoxicity studies for MLD showed increased dose to the CTV and the rPTV, in the range of 104%-118% and 95%-114% of prescription dose, respectively.Conclusions: A 4D dose calculation based on deformable image registration was used to evaluate a robust-inspired planning strategy for lung radiotherapy. This method offers notable reductions to lung dose while improving tumor coverage through the use of reduced geometric margins combined with edge enhancements.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Abstract Radioresistance is one of the main reasons for the failure of radiotherapy in lung cancer. The aim of this study was to establish a radiation-resistant lung cancer cell line, to evaluate whether CpG oligodeoxynucleotide (CpG-ODN) 7909 could increase its radiosensitivity and to explore the relevant mechanisms. The radioresistant cell line, referred to as R-A549, was generated by reduplicative fractionated irradiation from the human lung adenocarcinoma cell line A549. The radioresistance of R-A549 cells were confirmed by the Cell Counting Kit-8 (CCK-8), cell viability assay, and clonogenic assay. Cell growth kinetics, morphological feature, and radiosensitivity were compared between the original A549 cells and R-A549 cells treated with or without CpG-ODN 7909 or radiation. To further explore the potential mechanisms of radiosensitivity, the cell cycle distributions and the expression of Toll-like receptor 9 (TLR-9) were examined by Western blot and flow cytometry. The R-A549 cell line was generated and its radioresistance was further confirmed. CpG-ODN 7909 was found to increase much more radiosensitivity of R-A549 cells under combined treatments with CpG-ODN 7909 and radiation compared with its control group without any treatments. They presented their respective D0 1.33+/−0.20 Gy versus 1.76+/−0.25 Gy with N 3.44+/−1.01 versus 4.96+/−0.32. Further, there was a larger cell population of R-A549 cells under combined treatment in the G2/M phase compared with the control group after treatment with CpG-ODN7909 or radiation alone at 24 and 48 hour. The expression level of TLR-9 in R-A549 cells was found higher than in A549 cells. These results suggested that CpG-ODN 7909 increased the radiosensitivity of R-A549 cells, which might be mediated via the upregulated TLR-9 and prolonged cell cycle arrest in the G2/M phase compared with A549 cells.
INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology, Affiliated FoShan Hospital of Sun Yat-Sen University, Foshan, 528000 Guangdong, China. Electronic address: lhlh2003@126.com.

RESUMEN / SUMMARY: - Sevoflurane, an inhalational anesthetic, and cisplatin (DDP)-based chemotherapy have been widely used during lung cancer surgery. However, the effect of sevoflurane on the sensitivity of lung cancer cells to DDP chemotherapy remains unclear. In this study, the effects of combined treatment with sevoflurane and cisplatin on the growth and invasion of human lung adenocarcinoma A549 cell line have been investigated. The underlying mechanism has also been explored. In our experiment, A549 cells were treated with 2.5% sevoflurane, 10μmol/L DDP, or the co-treatment of sevoflurane and DDP for 4h, respectively. Cell proliferation was evaluated by the MTT assay and colony formation assay. Apoptosis was assessed by flow cytometry. Cell invasion was detected by Transwell assay. The expressions of X-linked inhibitor of apoptosis protein (XIAP), Survivin, matrix metalloproteinase (MMP)-2 and MMP-9 were determined by western blotting. Our results showed that sevoflurane combined with DDP resulted in a more pronounced inhibition of tumor cells growth and invasion as compared with either drug alone. Besides, XIAP, Survivin, MMP-2, and MMP-9 were downregulated more significantly by the co-treatment of the two drugs as compared to sevoflurane treatment or DDP treatment alone. Taken together, the growth-inhibitory and invasion-inhibitory synergy between sevoflurane and DDP in human adenocarcinoma A549 cell line was found in this study. Furthermore, we showed that the growth-inhibitory synergy between sevoflurane and DDP might be associated with the downregulation of XIAP and Survivin, and the invasion-inhibitory synergy between sevoflurane and DDP might be involved in the downregulation of MMP-2 and MMP-9.

[329]

TÍTULO / TITLE: - Ataxia-telangiectasia group D complementing gene (ATDC) upregulates matrix metalloproteinase 9 (MMP-9) to promote lung cancer cell invasion by activating ERK and JNK pathways.

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


AUTORES / AUTHORS: - Tang ZP; Cui QZ; Dong QZ; Xu K; Wang EH

INSTITUCIÓN / INSTITUTION: - Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, 110001, China.

RESUMEN / SUMMARY: - Although the expression pattern and biological functions of ataxia-telangiectasia group D complementing gene (ATDC) had been
implicated in several types of cancer, the roles and potential mechanisms of ATDC in lung cancer cell invasion are still ambiguous. In this study, we used gain- and loss-of-function analyses to explore the roles and potential mechanisms of ATDC in lung cancer cell invasion. siRNA knockdown of ATDC impaired cell invasion in A549 and H1299 cell lines, and its overexpression promoted cell invasion in HBE cell line. ATDC may contribute to the invasive ability of lung cancer cells by promoting the expression of invasion-related matrix metalloproteinase 9 (MMP-9). In addition, ATDC increased activating protein 1 (AP-1) reporter luciferase activity and the protein and mRNA levels of c-Jun and c-Fos. We further demonstrated that the roles of ATDC on cell invasion, MMP-9 upregulation, and AP-1 activation were dependent on extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) pathway activation, and ERK inhibitor U0126 or JNK inhibitor SP600125 blocked these effects of ATDC. These results suggested that ATDC upregulates MMP-9 to promote lung cancer cell invasion by activating ERK and JNK pathways.

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TÍTULO / TITLE: - CCL19/CCR7 upregulates heparanase via specificity protein-1 (Sp1) to promote invasion of cell in lung cancer.

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


-●Enlace al texto completo (gratuito o de pago) 1007/s13277-013-0822-z

AUTORES / AUTHORS: - Zhang Q; Sun L; Yin L; Ming J; Zhang S; Luo W; Qiu X

INSTITUCIÓN / INSTITUTION: - Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences of China Medical University, Shenyang, 110001, People’s Republic of China, qingfu1981@126.com.

RESUMEN / SUMMARY: - CCL19/chemokine receptor 7 (CCR7) has been found to be associated with tumor growth, angiogenesis, invasion, and lymph node metastasis. Our previous study demonstrated that CCR7 overexpressed in non-small cell lung cancer (NSCLC) and had close relationship with tumor invasion and lymph node metastasis. However, the molecular mechanism of CCR7 promoting invasion of human NSCLC cells is still unclear. In this study, we demonstrated that human lung adenocarcinoma A549 cells treated with recombinant human CCL19 could obviously upregulate the expression of Sp1 and heparanase at both the mRNA and protein levels. After blockage of CCR7, Sp1 and heparanase expressions were inhibited. Following inhibition of Sp1, heparanase expression was downregulated. The analysis showed the promoter region of heparanase gene containing a number of potential sp1 binding sites (5’-GGGGC-3’). Chromatin immunoprecipitation analysis demonstrated that Sp1 could bind to the heparanase promoter. Cell invasion assays showed that the
invasion ability of A549 cells was increased with CCL19 incubation compared to the control cells. These results suggested that CCL19/CCR7 may upregulate the expression of heparanase via Sp1 and contribute to the invasion of A549 cells.

[331]
TÍTULO / TITLE: - MTA1 promotes the invasion and migration of non-small cell lung cancer cells by downregulating miR-125b.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Li Y; Chao Y; Fang Y; Wang J; Wang M; Zhang H; Ying M; Zhu X; Wang H
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China. zhuxx011@163.com.
RESUMEN / SUMMARY: - BACKGROUND: The metastasis-associated gene 1 (MTA1) has been identified as one critical regulator of tumor metastasis. Previously, we identified miR-125b as a downregulated miRNA in non-small cell lung cancer (NSCLC) cell line upon MTA1 depletion. However, the role of miR-125b and MTA1 in the regulation of NSCLC metastasis remains unclear.
METHODS: Stable MTA1 knockdown NSCLC cell lines 95D and SPC-A-1 were established by transfection with MTA1 shRNA. The effects of MTA1 depletion on the expression of miR-125b and cell migration and invasion were examined by real-time PCR, wound healing and matrigel invasion assay. RESULTS: MTA1 knockdown led to the upregulation of miR-125b level in NSCLC cells. Furthermore, MTA1 knockdown reduced while miR-125b inhibitor enhanced cell migration and invasion of NSCLC cells. Notably, miR-125b inhibitor antagonized MTA1 siRNA induced inhibition of cell migration and invasion. CONCLUSION: MTA1 and miR-125b have antagonistic effects on the migration and invasion of NSCLC cells. The newly identified MTA1-miR-125b axis will help further elucidate the molecular mechanism of NSCLC progression and suggest that ectopic expression of miR-125b is a potentially new therapeutic regimen against NSCLC metastasis.

[332]
TÍTULO / TITLE: - Quantitative assessment of lung cancer associated with genes methylation in the peripheral blood.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
ABSTRACT Background: Lung cancer is the leading cause of cancer-related deaths worldwide due mainly to late diagnosis and poor prognosis. Aberrant promoter methylation is an important mechanism for silencing of tumor suppressor genes during carcinogenesis and a promising tool for the development of molecular biomarkers. Methods: We evaluated the p16, RASSF1A, and FHIT genes promoter methylation status in peripheral blood DNA between 200 lung cancer patients and 200 normal controls by using SYBR green-based quantitative methylation-specific PCR (qMSP). Results: There were statistically significant differences in the methylation status of p16, RASSF1A, and FHIT between the cancer cases and controls (p16: P = .008, RASSF1A: P = .038, FHIT: P = .002). When the subjects were categorized into quartiles based on the genes methylation status, the risk of lung cancer was found to increase as methylation status increased (p16: Ptrend = .002, RASSF1A: Ptrend = .014, FHIT: Ptrend = .001). When the median of methylation status was used as the cutoff between high and low methylation status, individuals with high methylation status were at a significantly higher risk of lung cancer than those with low methylation status (p16: adjusted odds ratio = 1.597, P = .028; RASSF1A: adjusted odds ratio = 1.551, P = .039; FHIT: adjusted odds ratio = 1.763, P = .008). In addition, there were no significant correlations between p16, RASSF1A, or FHIT methylation status and gender (P > .05), age (P > .05), smoking history (P > .05), histological type (P > .05), or clinical stage (P > .05). Conclusions: These results suggest that the high methylation statuses of p16, RASSF1A, or FHIT genes were associated with a significantly increased risk of lung cancer; the risk of lung cancer increased as the methylation status increased. Further investigation of their definitive usefulness in clinical practice is warranted.
Claudin-4 (CL-4) is a tight junction-associated protein that is expressed in most epithelial cells but absent in mesothelial cells. The purpose of this study is to evaluate the utility of CL-4 immunostaining for assisting in the differential diagnosis of mesothelioma. Sixty mesotheliomas (40 epithelioid, 10 biphasic, and 10 sarcomatoid), 185 carcinomas of different origins that can potentially be confused with mesotheliomas, 37 soft-tissue sarcomas, and 5 melanomas were investigated for CL-4 expression. All 60 mesotheliomas were CL-4 negative. In contrast, 169 (91%) of 185 carcinomas expressed this marker. Five of 8 desmoplastic small round cell tumors and the epithelial component of all 5 biphasic synovial sarcomas were CL-4 positive, whereas none of the remaining soft-tissue sarcomas or melanomas expressed this marker. It is concluded that CL-4 is a highly specific and sensitive immunohistochemical marker for assisting in distinguishing epithelioid mesotheliomas from metastatic carcinomas to the serosal membranes.
PC9/AB2 which has acquired resistance to gefitinib. Knockdown and overexpression of beta-catenin in the PC9/AB2 and PC9 cells were performed. The cell survival rate and the activation of the EGFR and its downstream pathways were detected in the two cell lines after transfection. RESULTS: Nuclear translocation of beta-catenin was increased in the PC9/AB2 cells and the baseline expression of members of the beta-catenin signaling pathway was also higher in the PC9/AB2 cells. Knocking down the expression of beta-catenin increased the sensitivity of the PC9/AB2 cells to gefitinib by blocking the activation of the EGFR and its downstream pathways, while beta-catenin overexpression improved PC9 cells resistance to gefitinib by enhancing the activation of the EGFR and its downstream signaling. CONCLUSION: beta-catenin plays an important role in acquired resistance to EGFR-TKIs in NSCLC cell lines and may be a potential therapeutic target for NSCLC patients who have failed to respond to targeted therapy.
differentiation in NSCLC. The overall survival rates of patients with high PRDM14 expression and low PRDM14 expression were 41.30 and 65.06 %, respectively (hazard ratio: 3.051, 95 % CI: 1.752, 5.312, P < 0.0001). The progression-free survival rates were 34.78 % for patients in the high expression group and 59.03 % for patients in the low OLC1 expression group (hazard ratio: 2.775, 95 % CI: 1.648, 4.675, P < 0.0001). Thus, our study showed that increased expression of PRDM14 correlated with cell differentiation of NSCLC cells. PRDM14 was a potential biomarker for predicting unfavorable prognosis in NSCLC.

[336]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 5858/arpa.2012-0287-RA.
AUTORES / AUTHORS: - Raparia K; Villa C; DeCamp MM; Patel JD; Mehta MP
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois 60611, USA. kraparia@northwestern.edu
RESUMEN / SUMMARY: - CONTEXT: Lung carcinoma is the result of sequential accumulation of genetic and epigenetic changes. Lung adenocarcinoma is a heterogeneous disease with diverse somatic mutations, and several of them include the so-called driver mutations, which may serve as “druggable” therapeutic targets. Thus, development of personalized approaches for the treatment of non-small cell lung carcinoma (NSCLC) mandates that pathologists make a precise histologic classification inclusive of routine molecular analysis of such tumors. OBJECTIVE: To address the molecular mechanisms underlying NSCLC and how this knowledge reflects the multidisciplinary approach in the diagnosis and management of these patients. We will also summarize the current available and investigational personalized therapies for patients with resectable early-stage, unresectable locally advanced, and metastatic NSCLC.
DATA SOURCES: Peer-reviewed published literature and personal experience.
CONCLUSIONS: There are multiple mechanisms involved in the pathogenesis of lung cancer, which operate in parallel and involve pathways of activation and inhibition of various cellular events. Further research is essential to characterize the histologic and mutational profiles of lung carcinomas, which will ultimately translate into improved and more personalized therapeutic management of patients with lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hochhegger B; Marchiori E; Irion K
INSTITUCIÓN / INSTITUTION: - Complexo Hospitalar Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil.

[338] TÍTULO / TITLE: - In non-small cell lung cancer mitogenic signaling leaves Sprouty1 protein levels unaffected.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kral RM; Mayer CE; Vanas V; Gsur A; Sutterluty-Fall H
INSTITUCIÓN / INSTITUTION: - Institute of Cancer Research, Department of Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

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

AUTORES / AUTHORS: - Oki M; Saka H; Kitagawa C; Kogure Y; Murata N; Adachi T; Ando M
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Nagoya Medical Center, Nagoya, Japan.

RESUMEN / SUMMARY: - Background: Although rapid on-site cytologic evaluation (ROSE) is widely used during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), its role remains unclear. Objectives: The purpose of the present study was to evaluate the efficacy of ROSE during EBUS-TBNA in the diagnosis of lung cancer. Methods: One hundred and twenty patients highly suspected of having lung cancer who had hilar/mediastinal lymphadenopathy or a tumor adjacent to the central airway were enrolled in this study and randomized to undergo EBUS-TBNA with or without ROSE. Results: Twelve patients with visible endobronchial lesions were excluded in the analysis. Thus, a total of 108 patients (55 in the ROSE group, 53 in the non-ROSE group) were analyzed. Additional procedures including EBUS-TBNA for lesions other than the main target lesion and/or transbronchial biopsy in the same setting were performed in 11% of patients in the ROSE group and 57% in the non-ROSE group (p < 0.001). Mean puncture number was significantly lower in the ROSE group (2.2 vs. 3.1 punctures, p < 0.001), and mean bronchoscopy time was similar between both groups (22.3 vs. 22.1 min, p = 0.95). The sensitivity and accuracy for diagnosing lung cancer were 88 and 89% in the ROSE group, and 86 and 89% in the non-ROSE group, respectively. No complications were associated with the procedures. Conclusions: ROSE during EBUS-TBNA is associated with a significantly lower need for additional bronchoscopic procedures and puncture number.

[340]

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

AUTORES / AUTHORS: - Jo M; Yun HM; Park KR; Hee Park M; Myoung Kim T; Ho Pak J; Jae Lee S; Moon DC; Park CW; Song S; Lee CK; Bae Han S; Tae Hong J
INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Medical Research Center, Cheongju, Chungbuk 361-763, Korea.
RESUMEN / SUMMARY: - This study compared lung tumor growth in PRDX6-overexpressing transgenic (Tg) mice and normal mice. These mice expressed elevated levels of PRDX6 mRNA and protein in multiple tissues. In vivo, Tg mice displayed a greater increase in the growth of lung tumor compared with normal mice. Glutathione peroxidase and calcium-independent phospholipase 2 (iPLA2) activities in tumor tissues of Tg mice were much higher than in tumor tissues of normal mice. Higher tumor growth in PRDX6-overexpressing Tg mice was associated with an increase in activating protein-1 (AP-1) DNA-binding activity. Moreover, expression of proliferating cell nuclear antigen, Ki67, vascular endothelial growth factor, c-Jun, c-Fos, metalloproteinase-9, cyclin-dependent kinases, and cyclins was much higher in the tumor tissues of PRDX6-overexpressing Tg mice than in tumor tissues of normal mice. However, the expression of apoptotic regulatory proteins including caspase-3 and Bax was slightly less in the tumor tissues of normal mice. In tumor tissues of PRDX6-overexpressing Tg mice, activation of mitogen-activated protein kinases (MAPKs) was much higher than in normal mice. In cultured lung cancer cells, PRDX6 siRNA suppressed glutathione peroxidase and iPLA2 activities and cancer cell growth, but the enforced overexpression of PRDX6 increased cancer cell growth associated with their increased activities. In vitro, among the tested MAPK inhibitors, c-Jun NH2-terminal kinase (JNK) inhibitor clearly suppressed the growth of lung cancer cells and AP-1 DNA binding, glutathione peroxidase activity, and iPLA2 activity in normal and PRDX6-overexpressing lung cancer cells. These data indicate that overexpression of PRDX6 promotes lung tumor growth via increased glutathione peroxidase and iPLA2 activities through the upregulation of the AP-1 and JNK pathways.

[341]

TÍTULO / TITLE: - Recurrent respiratory papillomatosis with lung involvement and malignant transformation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Shiau EL; Li MF; Hsu JH; Wu MT
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Kaohsiung Veterans General Hospital, , Kaohsiung, Taiwan.

[342]

TÍTULO / TITLE: - Hypofractionated three-dimensional conformal radiation therapy alone for centrally located cT1-3N0 non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago)
1097/JTO.0b013e31828cb6db
AUTORES / AUTHORS: - Oh D; Ahn YC; Kim B; Pyo H
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
RESUMEN / SUMMARY: - PURPOSE: We retrospectively analyzed the treatment outcomes and toxicities by hypofractionated three-dimensional conformal radiation therapy (RT) alone in the patients with centrally located cT1-3N0 non-small-cell lung cancer (NSCLC). METHODS: Sixty patients with centrally located cT1-3N0 NSCLC received definitive RT alone at 3.0 Gy per fraction for either medical comorbidity or refusal of surgery, between January 2001 and December 2010. The central tumor was defined as being within 2 cm around the proximal bronchial tree. The median total dose was 60 (39-60) Gy.
RESULTS: The local control (LC), overall survival (OS), and cause-specific survival rates at 2 and 5 years were 57.9%, 59.6%, 61.7%, and 50.1%, 33.5%, and 40.5%, respectively. Multivariate analyses showed that high cT stage (p = 0.007) and histology with NSCLC-not otherwise specified (p = 0.008) were the significantly unfavorable prognostic factors for OS, and that high cT stage (p = 0.031) and poor performance state (p = 0.007) were for LC. The LC rate at 2 years was 100% for cT1 tumor, 56.5% for cT2 tumor, and 28.6% for cT3 tumor, respectively. No patients experienced grade 3 or higher esophagitis, and three experienced grade 3 or higher pneumonitis. CONCLUSION: Hypofractionated RT regimen for centrally located cT1-3N0 NSCLC proved safe with minimal toxicity, and, based on the excellent clinical outcomes in cT1 tumors, might serve as an alternative option for the patients who might not tolerate stereotactic body radiation therapy. As the clinical outcomes in cT2-3 tumors were still unsatisfactory, further dose intensifying regimen coupled with the use of concurrent systemic chemotherapy might be warranted.

[343]
TITULO / TITLE: - Infection of a bronchogenic cyst after ultrasonography-guided fine needle aspiration.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago)
1016/j.athoracsur.2012.10.071
AUTORES / AUTHORS: - Gamrekeli A; Kalweit G; Schafer H; Huwer H
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, Volklingen Heart Centre, Volklingen, Germany. Electronic address: a.gamrekeli@vk.shg-kliniken.de.

RESUMEN / SUMMARY: - Standard recommendation for therapy of benign mediastinal cysts is surgery. Endobronchial ultrasound fine needle aspiration (EBUS-FNA) has been used by some researchers as a diagnostic tool. This approach may be associated with severe life-threatening complications. We describe a case of life-threatening purulent pericardial effusion with tamponade by infection of a bronchogenic cyst after EBUS-FNA.

[344]

TÍTULO / TITLE: - Identification of accurate reference genes for RT-qPCR analysis of formalin-fixed paraffin-embedded tissue from primary Non-Small Cell Lung Cancers and brain and lymph node metastases.

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


AUTORES / AUTHORS: - Soes S; Sorensen BS; Alsner J; Overgaard J; Hager H; Hansen LL; Kristensen LS

INSTITUCIÓN / INSTITUTION: - Department of Biomedicine, Aarhus University, The Bartholin Building, Wilhelm Meyers Alle 4, DK-8000 Aarhus C, Denmark. Electronic address: signe_soes@hotmail.com.

RESUMEN / SUMMARY: - Lung cancer is the most common cause of cancer-related deaths worldwide, and metastatic spread of the cancer rather than the primary tumor is the main cause of death. However, the molecular alterations of cancer cells leading to the formation of metastasis are poorly understood. This is partly a result of most solid tumor samples available for retrospective studies being archived as formalin-fixed paraffin-embedded (FFPE) specimens causing the nucleic acids to be highly degraded. Furthermore, stably expressed reference genes for normalization of gene expression data using reverse transcriptase quantitative PCR (RT-qPCR) have not been identified for combined analysis of primary lung tumors and the tissues whereto the cancer metastasize. Using an optimized RT-qPCR workflow we have analyzed the expression of 23 candidate reference genes in a total of 54 FFPE specimens derived from primary Non-Small Cell Lung Cancer tumors, brain metastases, and lymph node metastases as well as normal lung, lymph node, and brain tissues. We show that every aspect of the workflow is highly reproducible, and the PUM1, TBP, and IPO8 genes were identified as the most stably expressed reference genes among the candidates, by using the GeNorm and NormFinder software programs. Furthermore, we demonstrate that commonly used
reference genes such as ACTB (beta-actin), GAPDH, and rRNA18S are less stably expressed in the studied samples. The presented workflow and the identified reference genes may facilitate more reliable gene expression studies in lung cancer using RNA from FFPE tissues.

[345]

**Título** / **Title**: Stage IIIA Non-Small Cell Lung Cancer: Morbidity and Mortality of Three Distinct Multimodality Regimens.

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


**Autores** / **Authors**: Seder CW; Allen MS; Cassivi SD; Deschamps C; Nichols FC; Olivier KR; Shen KR; Wigle DA

**Institución** / **Institution**: Division of General Thoracic Surgery, Mayo Clinic, Rochester, Minnesota.

**Resumen** / **Summary**: BACKGROUND: Although concurrent chemoradiation therapy can cure stage IIIA non-small cell lung cancer (NSCLC), studies have demonstrated that anatomic resection following high-dose or standard-dose chemoradiation may benefit selected patients. We examined morbidity and mortality associated with 3 multimodality treatment regimens for stage IIIA disease. METHODS: Institutional databases identified patients with stage IIIA (N2) NSCLC who underwent concurrent platinum-based chemoradiotherapy with or without pulmonary resection between 1998 and 2011. Exclusion criteria included palliative regimens, sequential chemoradiotherapy, radiation-surgery interval greater than 12 weeks, superior sulcus tumors, or radiotherapy other than standard external beam radiation. Treatment-related morbidity and mortality were examined for the following treatment regimens: neoadjuvant chemoradiotherapy with 45 Gy followed by surgery (trimodality-45); neoadjuvant chemoradiotherapy with 60 Gy or more followed by surgery (trimodality-60); and definitive chemoradiotherapy with 60 Gy or more without surgery (D-CRT). RESULTS: During the study period, 144 patients met eligibility criteria including 27 trimodality-45, 29 trimodality-60, and 88 D-CRT patients. Treatment-related morbidity and mortality rates for D-CRT were 74% [65 of 88] and 2.3% [2 of 88], respectively. Postoperative morbidity and mortality rates for patients who proceeded to surgery were 48% [27 of 56] and 1.8% [1 of 56], respectively, and did not differ based on dose of neoadjuvant radiation. Despite varied anatomic resections and methods of bronchial closure and coverage, no bronchopleural fistulae were observed. CONCLUSIONS: Chemoradiotherapy carries a significant morbidity profile. However, high-dose neoadjuvant radiation is not associated with increased postoperative morbidity.
or mortality relative to standard-dose radiation in patients selected for anatomic resection.

[346]


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


**AUTORES / AUTHORS:** - Kramer GM; Yaqub M; Bahce I; Smit EF; Lubberink M; Hoekstra OS; Boellaard R

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam 1081 HZ, The Netherlands.

**RESUMEN / SUMMARY:** - Purpose: Nowadays, PET and dynamic contrast enhanced CT or MRI are used to assess tumor blood perfusion. Although [(15)O]H2O PET is the gold standard, it is hardly available for routine clinical practice, due to the short half-life of (15)O. However, the lack of uniformity in scanning and analytic methods limits the use of CT perfusion (CTP) in clinical trials and practice. This study compares [(15)O]H2O PET with CT based perfusion in lung tumors and assesses the effects of various CTP postprocessing and analytical methods on the CTP results using [(15)O]H2O PET as the reference technique.

Methods: Various CTP analysis and image postprocessing methods were assessed. Furthermore, parametric images were obtained using the Slope method. Volumes of interests were defined using several different segmentation methods including Hounsfield unit based contouring thresholds, both with and without framewise application of dynamic contouring thresholds to exclude lung tissue or intravascular contrast. A head-to-head comparison of tumor perfusion obtained by CTP and [(15)O]H2O PET was performed using linear regressions, Bland-Altman plots, and an intracllass correlation coefficient (ICC). In addition, the different postprocessing methods were compared reciprocally.

Results: In six lung cancer patients, perfusion assessed using CTP studies combined with the Slope method correlated best with [(15)O]H2O PET (ICC = 0.88; R(2) = 0.89; Y = 0.80). The Mullani-Gould method showed best correlation with the Slope method (ICC >/= 0.71; R(2) >/= 0.80; Y = 0.71-1.35). These correlations were obtained using dynamic contouring thresholds and show the influence of CTP postprocessing methods.

Conclusions: Tumor perfusion assessed by CTP in combination with dynamic contouring thresholds using the Slope method correlates well with [(15)O]H2O PET. This suggests that CTP can be used as a method to evaluate tumor perfusion in lung cancer.
TÍTULO / TITLE: - miR-150, p53 protein and relevant miRNAs consist of a regulatory network in NSCLC tumorigenesis.

RESUMEN / SUMMARY: - microRNAs (miRNAs) are a class of non-coding small RNAs that act as negative regulators of gene expression by binding to the 3’-untranslated region (3’-UTR) of target mRNAs. Tumor protein p53, a transcriptional factor, plays an important role in the progression of tumorigenesis. miR-150 was the only miRNA predicted to target 3’-UTR of p53 by Targetscan. In order to investigate the function of miR-150, p53 and relevant miRNAs in non-small cell lung cancer (NSCLC), we constructed two expression vectors of p53 (pcDNA3.1-p53 and pcDNA3.1-p53-3’-UTR) and two reporter vectors (pGL3-p53-3’-UTR and pGL3-p53-3’-mUTR). The activity of luciferase transfected with miR-150 mimics was lower by 30% when compared to that of the miRNA-negative control (miRNA-NC). Moreover, the p53 protein was downregulated by at least 50% when miR-150 mimics were cotransfected with pcDNA3.1-p53-3’-UTR when compared to miRNA-NC. We also determined the expression of miR-150 and p53 in NSCLC patient tissue samples. The expression of miR-150 in T2 stage tissue samples was higher than that in T1 stage tissue samples. The corresponding target gene p53 was correlated with miR-150 expression. In the present study, we further analyzed the cell cycle distribution. The cells transfected with pcDNA3.1-p53 were significantly arrested in the G1 phase when compared to the control cells. When miR-150 mimics were cotransfected with pcDNA3.1-p53-3’-UTR, the percentage of cells in the G1 phase was significantly lower by 4% when compared to miRNA-NC. To identify miRNAs that are regulated by the p53 protein, qRT-PCR was performed after pcDNA3.1-p53 transfection. miR-34a, miR-184, miR-181a and miR-148 were upregulated significantly. However, there was no distinct difference in the expression of miR-10a, miR-182 and miR-34c. Our results showed that miR-150 targets the 3’-UTR of p53, and p53 protein promotes the expression of miRNAs which affect cell cycle progression. These findings suggest that miR-150, p53 protein and relevant miRNAs are members of a regulatory network in NSCLC tumorigenesis.
TÍTULO / TITLE: - New weighted maximum-intensity-projection images from cine CT for delineation of the lung tumor plus motion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pan T; Riegel AC; Ahmad MU; Sun X; Chang JY; Luo D
INSTITUCIÓN / INSTITUTION: - Department of Imaging Physics, M.D. Anderson Cancer Center, The University of Texas, Houston, Texas 77030.

RESUMEN / SUMMARY: - Purpose: In treatment planning of the lung tumor with 4D-CT, maximum-intensity-projection (MIP) images have been used for delineation of the gross tumor volume plus motion or iGTV, which can then be revised with the multiple phases of the 4D-CT images. Although majority of contouring can be performed with MIP, the MIP images are not recommended for delineation of iGTV if the tumor is near or connected to the diaphragm or other structures of a similar density due to insufficient contrast between the tumor and the surrounding tissues in the MIP images. To remedy this shortcoming, the authors developed a new weighted MIP (wMIP) from cine CT without respiratory gating for contouring the iGTV. Methods: The wMIP images are obtained by keeping one phase of the cine CT images with the largest tumor in the overlap region of the tumor and the diaphragm. Outside the overlap region, the wMIP images are identical to the MIP images. Both MIP and wMIP images are obtained without respiratory gating from cine CT. Results: The authors demonstrated in a study of seven patients that wMIP can achieve 92% of the iGTV from 4D-CT. The maximum surface separation of the two iGTVs between wMIP and 4D-CT was 1.7 mm and six out of the seven studies had less than 1 mm in surface separation between the iGTVs of wMIP and 4D-CT. Conclusions: This development has the potential of enabling many CT scanners capable of cine CT to assess the respiratory motion of a lung tumor without 4D-CT.

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TÍTULO / TITLE: - Well-differentiated papillary mesothelioma: clustering in a Portuguese family with a germline BAP1 mutation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ribeiro C; Campelos S; Moura CS; Machado JC; Justino A; Parente B
INSTITUCIÓN / INSTITUTION: - Departments of Pulmonology.
RESUMEN / SUMMARY: - BACKGROUND: Well-differentiated papillary mesothelioma (WDPM) is a rare variant of epithelioid mesothelioma and is considered to be associated with good prognosis due to its clinically indolent behavior and long survival. Most reported cases involve the peritoneum of women at reproductive age with no history of exposure to asbestos, with pleural involvement being less common. The optimal management, including the role of chemotherapy in the treatment of WDPM, remains unsettled. PATIENTS AND METHODS: The authors describe two cases of WDPM in women of the same family (siblings); the elder with WDPM of the pleura and peritoneum with a 12-year survival period and the younger with a WDPM of the peritoneum diagnosed in 2011 and uveal melanoma diagnosed in 2012. Neither patient had any known exposure to asbestos fibers or any other mineral carcinogens. RESULTS: After the concurrent diagnosis of WDPM and uveal melanoma, genetic diagnosis was carried out taking into consideration that these two malignancies were recently associated with hereditary BAP1 gene mutations and it was positive for both the patients. CONCLUSIONS: To our knowledge, this is the first description of WDPM in two siblings who also presented with a germline BAP1 mutation. This article provides evidence of the wide clinical spectrum of cancer susceptibility associated with a BAP1 germline mutation.

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TÍTULO / TITLE: - Membrane Phospholipids, EML4-ALK, and Hsp90 as Novel Targets in Lung Cancer Treatment.

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


AUTORES / AUTHORS: - Laszlo A; Thotala D; Hallahan DE

INSTITUCIÓN / INSTITUTION: - From the *Department of Radiation Oncology, daggerSiteman Cancer Center, double daggerMallinckrodt Institute of Radiology and section signHope Center, Washington University in Saint Louis, St. Louis, MO.

RESUMEN / SUMMARY: - Approximately one third of patients with non-small cell lung cancer have unresectable stage IIIA or stage IIIB disease; combined cytotoxic chemotherapy and radiation therapy delivered concurrently has been established as the standard treatment for such patients. Despite many clinical trials that tested several different radiochemotherapy combinations, it seems that a plateau of efficiencies at the acceptable risk of complications has been reached. Clinical studies indicate that the improved efficacy of radiochemotherapy is associated with the radiosensitizing effects of chemotherapy. Improvement of outcomes of this combined modality by
developing novel radiosensitizers is a viable therapeutic strategy. In addition to causing cell death, ionizing radiation also induces a many-faceted signaling response, which activates numerous prosurvival pathways that lead to enhanced proliferation in the endothelial cells and increased vascularization in tumors. Radiation at doses used in the clinic activates cytoplasmic phospholipase A2, leading to increased production of arachidonic acid and lysophosphatidylcholine. The former is the initial step in the generation of eicosanoids, while the later is the initial step in the formation of lysophosphatidic acid, leading to the activation of inflammatory pathways. The echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) is member of the insulin superfamily of receptor tyrosine kinases. The EML4-ALK fusion gene appears unique to lung cancer and signals through extracellular signal regulated kinase and phosphoinositide 3-kinase. Heat shock protein 90 (Hsp90) is often overexpressed and present in an activated multichaperone complex in cancer cells, and it is now regarded as essential for malignant transformation and progression. In this review we focus on radiosensitizing strategies involving the targeting of membrane phospholipids, EML4-ALK, and Hsp90 with specific inhibitors and briefly discuss the combination of radiation with antivascular agents.

[351]

TÍTULO / TITLE: - Unusual bilateral cervical metastases as first clinical evidence of lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Radu BE; Marioara P; Constantin BN; Maria CA; Raluca CA; Marius R; Caius D
INSTITUCIÓN / INSTITUTION: - Victor Babes University of Medicine and Pharmacy, Department of Histology, Angiogenesis Research Center, Timisoara, Piata Eftimie Murgu nr. 2, Timisoara, Timis, Romania.
ancacimpean1972@yahoo.com
RESUMEN / SUMMARY: - We report on an unusual case of laterocervical bilateral metastatatic masses with unknown clinical, radiological or computer tomographic detected primary site of origin. Cancer of an unknown primary site is a clinical syndrome, accounting for 2%-5% of patients with cancer. The peculiarities of our case are its evolution as fast-growing bilateral tumor masses with involvement of other neck structures and its unexpected origin from the lung, certified by complementary immunohistochemical tests following surgery, in the absence of any other clinical signs or any detectable lung tumor mass by radiological or computer tomographic tests.

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[352] **TÍTULO / TITLE:** Chemoradiation for definitive, preoperative, or postoperative therapy of locally advanced non-small cell lung cancer.

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


●●Enlace al texto completo (gratuito o de pago) 1097/PPO.0b013e318293238d

**AUTORES / AUTHORS:** Feliciano J; Feigenberg S; Mehta M

**INSTITUCIÓN / INSTITUTION:** From the *University of Maryland Greenebaum Cancer Center; and daggerClinical Research and double daggerMaryland Proton Treatment Center, Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD.

**RESUMEN / SUMMARY:** Over the last few decades, the integration of chemotherapy and radiation has played a crucial role in the management of locally advanced non-small cell lung cancer (NSCLC). Locally advanced NSCLC is a very heterogeneous disease. Because of this heterogeneity, advanced NSCLC can be managed in various ways depending on the bulk of disease, the comorbidities of the patient, and the expertise and resources of the treating physicians and facilities. This review describes the evolution of current treatment strategies and predicted future changes for the management of locally advanced NSCLC.

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[353] **TÍTULO / TITLE:** Effects of PPP1R13L and CD3EAP variants on lung cancer susceptibility among nonsmoking Chinese women.

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


●●Enlace al texto completo (gratuito o de pago) 1016/j.gene.2013.04.017

**AUTORES / AUTHORS:** Yin J; Guo L; Wang C; Wang H; Ma Y; Liu J; Liang D; Ma J; Zhao Y

**INSTITUCIÓN / INSTITUTION:** Key Laboratory of Environment and Population Health of Liaoning Education Ministry (Shenyang Medical College), Shenyang 110034, Liaoning Province, People’s Republic of China; Department of Cell Biology and Genetics, Shenyang Medical College, Shenyang 110034, Liaoning Province, People’s Republic of China. Electronic address: yinjye@163.com.

**RESUMEN / SUMMARY:** The pathogenesis of lung cancer in the never-smokers could possibly be different from the one in smokers. PPP1R13L and CD3EAP on chromosome 19q13.3 are mainly involved in apoptosis and transcription. PPP1R13L and CD3EAP variants may be associated with cancer risk. We addressed the effects of variants/haplotypes of PPP1R13L rs1970764 and
CD3EAP rs967591 and rs735482 on susceptibility of lung cancer among nonsmoking Chinese women. A hospital-based case-control study consisted of 79 lung cancer cases and 108 cancer-free controls matched by age (+/-3 years), gender, ethnicity and lifetime never-smoking. Genotyping and statistical analysis were performed by using the method of ligase detection reaction coupled with polymerase chain reaction (LDR-PCR) and SHEsis program and SPSS software. The presence of variant A-allele for CD3EAP rs967591 was associated with increased lung cancer risk [GA versus GG, OR (95% CI)=2.53 (1.16-5.48), P=0.02 and GA+AA versus GG, OR (95% CI)=2.46 (1.16-5.20), P=0.02]. Both D’ values and r2 values accorded with marker distances on chromosome 19q13.3. No associations were found for two other individual SNPs and haplotype distributions of three markers in the whole or single. In conclusion, this study suggests that CD3EAP rs967591 variant allele carriers are at increased susceptibility of lung cancer among nonsmoking Chinese women.

[354]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Almeida FA; Casal RF; Jimenez CA; Eapen GA; Uzbeck M; Sarkiss M; Rice D; Morice RC; Ost DE
RESUMEN / SUMMARY: - ABSTRACT BACKGROUND: Evidence-based guidelines recommend mediastinal sampling as the first invasive test in patients with suspected lung cancer and mediastinal adenopathy. The goal of this study was to assess practice patterns and outcomes of diagnostic strategies in this patient population. METHODS: We conducted a retrospective analysis of all patients in 2009 that had mediastinal adenopathy without distant metastatic disease to determine whether or not guideline consistent care was delivered. Guideline consistent care was defined as mediastinal lymph node sampling being performed as part of the first invasive procedure. RESULTS: 137 patients were included. Guideline consistent care was provided in 30 (22%) cases. Patients receiving guideline consistent care had fewer invasive tests than patients with guideline inconsistent care (1.3 +/- 0.5 vs. 2.3 +/- 0.5 tests/patient respectively, p&lt;0.0001) and fewer complications (0 of 30, 0% vs. 18 of 108, 17%; p=0.01). Most of the complications (16 of 18) were related to CT guided needle biopsy. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was sufficient to guide treatment decisions without any other invasive tests in 88 (64%) patients. While not all of the complications and costs due to CT guided biopsies could have been avoided,
roughly two thirds could have been eliminated by just changing the testing sequence. CONCLUSION: Quality gaps in lung cancer staging in patients with mediastinal adenopathy are common and lead to unnecessary testing and increased complications. In patients with suspected lung cancer without distant metastatic disease with mediastinal adenopathy, EBUS-TBNA should be the first test.

[355]

TÍTULO / TITLE: - The Autophagy Inhibitor Chloroquine Overcomes the Innate Resistance of Wild-Type EGFR Non-Small-Cell Lung Cancer Cells to Erlotinib.

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


AUTORES / AUTHORS: - Zou Y; Ling YH; Sironi J; Schwartz EL; Perez-Soler R; Piperdi B

INSTITUCIÓN / INSTITUTION: - Departments of Medicine and Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York.

RESUMEN / SUMMARY: - INTRODUCTION: The epidermal growth factor receptor (EGFR) inhibitor erlotinib is much less effective in non-small-cell lung cancer (NSCLC) tumors with wild-type EGFR, than in tumors with activating EGFR mutations. Autophagy is a tightly regulated lysosomal self-digestion process, which may alternatively promote cell survival or type II cell death. This study assessed the role of autophagy in erlotinib-mediated cytotoxicity.

METHODS: We used wild-type EGFR erlotinib-sensitive and erlotinib-resistant NSCLC cell lines to determine whether inhibiting autophagy by a therapeutic agent potentiated the antitumor activity of erlotinib in vitro and in vivo.

RESULTS: Erlotinib at a clinically relevant concentration (2 μM) induced autophagy in NSCLC cells with wild-type EGFR, and the degree of induction was greater in cells that were resistant than sensitive, suggesting that autophagy is cytoprotective. This was confirmed by knockdown of the autophagy-related gene Atg-5, and by using the autophagy inhibitor chloroquine (CQ), both of which increased the cytotoxicity of erlotinib. The synergistic activity of CQ was not because of the potentiation of erlotinib’s effects on autophagy, cell-cycle arrest, and inhibition of both EGFR or downstream signaling of EGFR. Rather, CQ markedly activated apoptosis in the cells. The ability of CQ to potentiate the antitumor activity of erlotinib was also seen in mice bearing NSCLC tumor xenografts.

CONCLUSIONS: The ability to adapt to anti-EGFR therapy by triggering autophagy may be a key determinant for resistance to erlotinib in wild-type EGFR NSCLC. Inhibition of autophagy by CQ
represents a novel strategy to broaden the spectrum of erlotinib efficacy in wild-type EGFR NSCLC tumors.

[356]

**TÍTULO / TITLE:** Role of PTEN in Basal Cell Derived Lung Carcinogenesis.

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


**AUTORES / AUTHORS:** Malkoski SP; Cleaver TG; Thompson JJ; Sutton WP; Haeger SM; Rodriguez KJ; Lu SL; Merrick D; Wang XJ

**INSTITUCIÓN / INSTITUTION:** Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado; Department of Pathology, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado.

**RESUMEN / SUMMARY:** Lung adenocarcinoma (AdC) and lung squamous cell carcinoma (SCC) are the most common non-small cell lung cancer (NSCLC) subtypes, however, most genetic mouse models of lung cancer produce predominantly, if not exclusively, AdC. Whether this is secondary to targeting mutations to the distal airway cells or to the use of activating Kras mutations that drive AdC formation is unknown. We previously showed that targeting KrasG12D activation and transforming growth factor beta receptor type II (TGFbetaRII) deletion to airway basal cells via a keratin promoter induced formation of both lung AdC and SCC. In this study we assessed if targeting phosphatase and tensin homologue (PTEN) deletion to airway basal cells could initiate lung tumor formation or increase lung SCC formation. We found that PTEN deletion is capable of initiating both lung AdC and SCC formation when targeted to basal cells and although PTEN deletion is a weaker tumor initiator than KrasG12D with low tumor multiplicity and long latency, tumors initiated by PTEN deletion were larger and displayed more malignant conversion than KrasG12D initiated tumors. That PTEN deletion did not increase lung SCC formation compared to KrasG12D activation, suggests that the initiating genetic event does not dictate tumor histology when genetic alterations are targeted to a specific cell. These studies also confirm that basal cells of the conducting airway are capable of giving rise to multiple NSCLC tumor types. © 2013 Wiley Periodicals, Inc.

[357]

**TÍTULO / TITLE:** Predictors of biomarkers guiding targeted therapeutic strategies in locally advanced lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
Lung cancer accounts for the majority of cancer-related deaths worldwide. We sought out to summarize the current state of molecular predictors for response and toxicity in locally advanced lung cancer. Several changes have been introduced in recent years in the standard-of-care treatment of advanced non-small cell lung cancer based on the identification of specific molecular alterations that determine response probability to certain therapies. Eligibility for these treatments is assessed by a biomarker test, evaluating if the molecular alteration is present or not in a patient’s tumor. In particular, tissue testing for epidermal growth factor receptor and anaplastic lymphoma kinase alterations is currently recommended for certain patients with advanced non-small cell lung cancer, whereas excision repair cross-complementation group 1 and ribonucleotide reductase 1 as markers for outcome after platinum and gemcitabine therapy are promising but are currently not recommended outside a clinical trial. However, their application to the therapy of locally advanced disease is still mostly investigational. Moreover, additional candidate markers for response and toxicity for locally advanced lung cancer are under further investigation.

[358]

**TÍTULO / TITLE:** - Ritodrine for Intractable Uterine Pain Due to Extrapelvic Malignant Tumor Metastases: A Case Report.

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


**AUTORES / AUTHORS:** - Sugiura Y; Nemoto E; Kadohira I; Kaseda S

**INSTITUCIÓN / INSTITUTION:** - *National Hospital Organization, Kanagawa National Hospital, Pulmonary and Thoracic Surgery, Hadano, Kanagawa; and daggerDepartment of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan.

**RESUMEN / SUMMARY:** - BACKGROUND:: Effective pain management is an essential component of cancer treatment as approximately 75% of all cancer patients experience excruciating nociceptive pain even at maximum safe doses of nonsteroidal anti-inflammatory drugs and/or opioids. We report a case where
ritodrine hydrochloride effectively controlled refractory pain due to uterine metastases from thymic carcinoma. CASE PRESENTATION:: A 40-year-old woman presented at our hospital with chest discomfort, severe right femoral pain, and intermittent hypogastralgia. Computed tomography, magnetic resonance imaging, and positron emission tomography revealed a large mass in the anterior mediastinum, multiple nodules in the lungs, and multiple metastases on the uterus, lumbar vertebrae, and pelvic bones. Needle biopsies of the mediastinal and uterine cervical tumors revealed undifferentiated carcinoma of the thymus metastasizing to the uterus. Oxycodone and nonsteroidal anti-inflammatory drugs relieved the right femoral pain but not the hypogastralgia. We speculated that hypogastralgia did not result from somatalgia but from splanchnodynia. Ritodrine was administered in an effort to inhibit uterine contractions and to reduced the refractory pain and improved her quality of life. CONCLUSION:: Ritodrine relieved the pain caused by uterine contraction due to metastases and enhanced the quality of life.
statistically significant (p=0.973). The mean percentage of MPC was 20.4% in the recurrent group and 18.3% in the non-recurrent group, with no significant correlation (p=0.996). Of the 10 recurrent cases, 6 cases exhibited EGFR mutations; the 5 cases treated with a tyrosine kinase inhibitor (TKI) achieved long survival (median, 64.6 months). No KRAS mutations were detected in any of the 10 cases. PA-MPCs were strongly associated with recurrence, but were not influenced by the MPC percentage even in early-stage lesions. Moreover, PA-MPCs with recurrence were associated with relatively better survival. These findings indicate that PA-MPCs were biologically aggressive but could be controlled with EGFR-TKIs.

[360]

**TÍTULO / TITLE:** Downregulation of miR-497 promotes tumor growth and angiogenesis by targeting HDGF in non-small cell lung cancer.

**RESUMEN / SUMMARY:** MicroRNAs (miRNAs) play important roles in the development of various cancers. MiRNA-497 functions as a tumor-suppressor that is downregulated in several malignancies; however, its role in non-small cell lung cancer (NSCLC) has not been examined in detail. Here, we showed that miR-497 is downregulated in NSCLC tumors and cell lines and its ectopic expression significantly inhibits cell proliferation and colony formation. Integrated analysis identified HDGF as a downstream target of miR-497, and the downregulation of HDGF by miR-497 overexpression confirmed their association. Rescue experiments showed that the inhibitory effect of miR-497 on cell proliferation and colony formation is predominantly mediated by the modulation of HDGF levels. Furthermore, tumor samples from NSCLC patients showed an inverse relationship between miR-497 and HDGF levels, and ectopic expression of miR-497 significantly inhibited tumor growth and angiogenesis in a SCID mouse xenograft model. Our results suggest that miR-497 may serve as a biomarker in NSCLC, and the modulation of its activity may represent a novel therapeutic strategy for the treatment of NSCLC patients.

[361]
**TÍTULO / TITLE:** - Shikonin attenuates lung cancer cell adhesion to extracellular matrix and metastasis by inhibiting integrin beta1 expression and the ERK1/2 signaling pathway.

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

**REVISTA / JOURNAL:** - Toxicology. 2013 Apr 4;308C:104-112. doi: 10.1016/j.tox.2013.03.015.

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**INSTITUCIÓN / INSTITUTION:** - Shanghai Pulmonary Hospital, Tongji University School of Medicine, 507 Zhengmin Rd, Shanghai 200433, People’s Republic of China.

**RESUMEN / SUMMARY:** - Integrin beta1 facilitates cancer cell adhesion, migration and metastasis by activating intracellular signaling pathways including the ERK and PI3K signaling pathways. In previous studies, shikonin, an active naphthoquinone isolated from the Chinese medicine Zi Cao (gromwell), showed effective anticancer activity both in vivo and in vitro. However, the mechanisms underlying shikonin’s anticancer activity are not fully elucidated. Increasing evidence indicates that shikonin inhibits tumor metastasis, but little is known about the effect of shikonin on lung cancer cells. To better understand the anti-metastatic role of shikonin in lung cancer, in this study we sought to investigate the effect of shikonin on lung cancer cell proliferation, adhesion to extracellular matrices (ECM), migration and invasion in non-small cell lung cancer A549 cells. We also sought to investigate the molecular mechanisms underlying shikonin’s anticancer effects. Here we showed that when non-small cell lung cancer A549 cells were treated with shikonin for 24h, 8.0μM shikonin significantly inhibited cell proliferation, while cells treated with less than 2.0μM shikonin for 24h significantly suppressed cell adhesion to the ECM, invasion and migration in a dose-dependent manner. Moreover, real-time PCR and Western blot analysis showed that shikonin led to a reduction in the expression of integrin beta1 at the mRNA and protein levels. Further elucidation of the mechanisms involved revealed that shikonin repressed the phosphorylation of extracellular signal-regulated kinase (ERK1/2). Taken together, our findings provide new evidence that shikonin suppresses lung cancer invasion and metastasis by inhibiting integrin beta1 expression and the ERK1/2 signaling pathway.

[362]

**TÍTULO / TITLE:** - Locoregional recurrence of early-stage surgically resected non-small-cell lung cancer: the importance of close follow-up and consistent definitions.

**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
Investigation of the dose- and time-dependence of the induction of different types of cell death in a small cell lung cancer cell line: Implementation of the repairable-conditionally repairable model.

The purpose of this study was to quantify and model various types of cell death for a small-cell lung cancer (SCLC) cell line (U1690) after exposure to a 137Cs source and as well as to compare the linear-quadratic (LQ) and repairable-conditionally repairable model (RCR). This study is based on four different experiments that were taken place at Cancer Centrum Karolinska (CCK). A human small-cell lung cancer (SCLC) cell line after the exposure to a 137Cs source was used for the extraction of the clonogenic cell survival curve. Additionally, for the determination and quantification of various modes of cell death the method of fluorescence staining was implemented, where the cell deaths were categorized based on morphological characteristics. The percentage of cells in each phase of the cell cycle was investigated with flow cytometry analysis. The quantification of senescent cells was performed by staining the samples with senescence-associated beta-galactosidase (SA-beta-Gal) solution and then scoring as senescent cells those that had incorporated the substance. These data were introduced into a maximum likelihood fitting to calculate the best estimates of the parameters used by the examined model. In this model, the modes of cell death are divided into three categories: apoptotic, senescent and other types of cell death (necrotic/apoptotic, necrotic, micronuclei and giant). In the clonogenic cell survival assay, the fitting of the RCR model gives a chi(2)-value of 6.10 whereas for the LQ model became 9.61. In the fluorescence microscopy and senescence assay, the probability of the three different modes of cell death on day 2 seems to increases with a dose up to about 10 Gy where there is
saturation. On day 7 a significant induction of apoptosis in a dose- and time-dependent manner was evident, whereas senescence was slightly increased in response to dose but not to time. As for the ‘other types of cell death’ mode on day 7 showed a higher probability than the one on day 2 and as well as a prominent dose-dependence. The RCR model fits better to the experimental data than the LQ model. On day 2 there is a slight increase of the apoptotic and senescent probability with dose. On the other hand, on day 7 the shape of the curve of apoptosis differs and a sigmoidal increase with dose is observed. At both time-points, the present model fits the data reasonably well. Due to the fact that the clonogenic survival does not coincide with the one extracted from the fluorescence microscopy, a more accurate way to quantify cell death needs to be used, e.g. computerized video time-lapse (CVTL).

[364]

TÍTULO / TITLE: - High circulating VEGF level predicts poor overall survival in lung cancer.

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


AUTORES / AUTHORS: - Hu P; Liu W; Wang L; Yang M; 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: - PURPOSE: Vascular endothelial growth factor (VEGF) is considered as the best-validated key regulator of angiogenesis, while the prognostic role of circulating VEGF in lung cancer remains controversial. We conducted a meta-analysis to evaluate the prognostic role of circulating VEGF. METHODS: Nineteen studies with a total number of 2,890 patients were analyzed in our meta-analysis. Hazard ratios (HRs) and their 95 % confidence intervals (CIs) were used to quantify the predictive ability of circulating VEGF on survival. RESULTS: The pooled HR of all 17 studies evaluating overall survival (OS) was 1.29 (95 % CI 1.19-1.40, p < 0.001), indicating high circulating VEGF predicted poor OS. When grouped by disease stages, the pooled HRs were 0.97 (95 % CI 0.47-1.47, p < 0.001) for operable stage and 1.34 (95 % CI 1.18-1.49, p < 0.001) for inoperable stage. The pooled HRs were 1.28 (95 % CI 1.15-1.42, p < 0.001) for serum and 1.31 (95 % CI 1.13-1.49, p < 0.001) for plasma, when categorized by blood sample. Meta-analysis of circulating VEGF related to progression-free survival (PFS) was performed in 7 studies, and the pooled HR was 1.03 (95 % CI 0.96-1.09). CONCLUSIONS: Our results indicate that high level of circulating VEGF predicts poor OS in lung cancer, yet it does not predict poor PFS.
PURPOSE: Due to the complexity of 4D target tracking radiotherapy, the accuracy of this treatment strategy should be experimentally validated against established standard 3D technique. This work compared the accuracy of 3D and 4D dose calculations in respiration tracking stereotactic body radiotherapy (SBRT). METHODS: Using the 4D planning module of the CyberKnife treatment planning system, treatment plans for a moving target and a static off-target cord structure were created on different four-dimensional computed tomography (4D-CT) datasets of a thorax phantom moving in different ranges. The 4D planning system used B-splines deformable image registrations (DIR) to accumulate dose distributions calculated on different breathing geometries, each corresponding to a static 3D-CT image of the 4D-CT dataset, onto a reference image to compose a 4D dose distribution. For each motion, 4D optimization was performed to generate a 4D treatment plan of the moving target. For comparison with standard 3D planning, each 4D plan was copied to the reference end-exhale images and a standard 3D dose calculation was followed. Treatment plans of the off-target structure were first obtained by standard 3D optimization on the end-exhale images. Subsequently, they were applied to recalculate the 4D dose distributions using DIRs. All dose distributions that were initially obtained using the ray-tracing algorithm with equivalent path-length heterogeneity correction (3D EPL and 4D EPL) were recalculated by a Monte Carlo algorithm (3D MC and 4D MC) to further investigate the effects of dose calculation algorithms. The calculated 3D EPL, 3D MC, 4D EPL, and 4D MC dose distributions were compared to measurements by Gafchromic EBT2 films in the axial and coronal planes of the moving target object, and the coronal plane for the static off-target object based on the gamma metric at 5%/3mm criteria (gamma5%/3mm). Treatment plans were considered acceptable if the percentage of pixels passing gamma5%/3mm (Pgamma<1) >= 90%. RESULTS: The averaged Pgamma<1 values of the 3D EPL, 3D MC, 4D EPL, and 4D MC dose calculation methods for the moving target plans are 95%, 95%, 94%, and 95% for reproducible.
motion, and 95%, 96%, 94%, and 93% for nonreproducible motion during actual treatment delivery. The overall measured target dose distributions are in better agreement with the 3DMC dose distributions than the 4DMC dose distributions. Conversely, measured dose distributions agree much better with the 4D EPL/MC than the 3D EPL/MC dose distributions in the static off-target structure, resulting in higher P\(_{\text{gamma}<1}\) values with 4D EPL/MC (91%) vs 3D EPL (24%) and 3D MC (25%). Systematic changes of target motion reduced the averaged P\(_{\text{gamma}<1}\) to 47% and 53% for 4D EPL and 4D MC dose calculations, and 22% for 3D EPL/MC dose calculations in the off-target films. CONCLUSIONS: In robotic tracking SBRT, 4D treatment planning was found to yield better prediction of the dose distributions in the off-target structure, but not necessarily in the moving target, compared to standard 3D treatment planning, for reproducible and nonreproducible target motion. It is important to ensure on a patient-by-patient basis that the cumulative uncertainty associated with the 4D-CT artifacts, deformable image registration, and motion variability is significantly smaller than the cumulative uncertainty occurred in standard 3D planning in order to make 4D planning a justified option.

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**TITULO / TITLE:** Low papillary structure in lepidic growth component of lung adenocarcinoma: a unique histologic hallmark of aggressive behavior.

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

**REVISTA / JOURNAL:** Hum Pathol. 2013 May 3. pii: S0046-8177(13)00092-0. doi: 10.1016/j.humpath.2013.02.008.

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**RESUMEN / SUMMARY:** Small-sized lung adenocarcinomas often contain a lepidic growth component in part. The term lepidic growth has recently been used to represent a growth pattern of neoplastic cells along preexisting alveolar structures. We reviewed 91 small-sized (≤3 cm) invasive lung adenocarcinomas with a lepidic component to study the histopathologic and clinicopathologic characteristics. In the lepidic component of invasive adenocarcinoma, we have identified a morphologically unique structure characterized by proliferation of low papillae, consisting of neoplastic cells piling up toward the alveolar space, and we defined this architecture as “low papillary structure.” There were 18 cases with the low papillary structure in the lepidic components, whereas 73 cases did not have the structure. In the lepidic
component, the cases with the low papillary structure had higher Ki-67 labeling index (15.7%) and more frequent p53 overexpression (50.0%) than did those without the structure (9.4% and 16.4%, respectively). Based on clinicopathologic findings, the presence of low papillary structure was significantly associated with lymphatic invasion (\( P = .023 \)) and lymph node metastasis (\( P = .001 \)). Furthermore, the patients with the low papillary structure in the lepidic components demonstrated significantly shorter disease-free and overall survival than did those without the structure (\( P = .001 \) and \( P = .010 \), respectively). We conclude that the low papillary structure is a significant histologic feature in a lepidic component and is associated with aggressive cancer behavior in lung adenocarcinoma.
similar effects were observed for both fir and beech PM2.5. However, the combustion of beech pellets generated approximately three times more PM2.5 than fir pellets. Regarding the mechanism of PM2.5 uptake, in both THP-1 and A549 cells, cytochalasin D prevented PM2.5-induced IL-8 mRNA expression and cytokine release, indicating a key role for actin polymerization in particles uptake and that the production of IL-8 correlated with particle phagocytosis. As signal transduction pathway involvement, in both THP-1 and A549 cells, PM2.5-induced IL-8 release could be completely blocked by the selective inhibitor SB203580, indicating a role of p38 MAPK activation. PM2.5 from both fir and beech pellets also induced modest DNA lesions dose related, measured as strand breaks, whereas no increase in the number of micronucleus was observed. Similar effects were observed with DEP, arguing against less dangerous effects of wood smoke particles than other categories of combustion-derived particles in the same size range. Overall, results suggest that combustion conditions can significantly affect the characteristics of particles and the consequent toxicity, and that different woods can generate different amounts of PM2.5.

[368]
TÍTULO / TITLE: - Tomatidine inhibits invasion of human lung adenocarcinoma cell A549 by reducing matrix metalloproteinases expression.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yan KH; Lee LM; Yan SH; Huang HC; Li CC; Lin HT; Chen PS
INSTITUCIÓN / INSTITUTION: - Department of Urology, Wan Fang Hospital, Taipei Medical University, Taipei 116, Taiwan.
RESUMEN / SUMMARY: - Tomatidine is an aglycone of glycoalkaloid tomatine in tomato. Tomatidine is found to possess anti-inflammatory properties and may serve as a chemosensitizer in multidrug-resistant tumor cells. However, the effect of tomatidine on cancer cell metastasis remains unclear. This study examines the effect of tomatidine on the migration and invasion of human lung adenocarcinoma A549 cell in vitro. The data demonstrates that tomatidine does not effectively inhibit the viability of A549 cells. When treated with non-toxic doses of tomatidine, cell invasion is markedly suppressed by Boyden chamber invasion assay, while cell migration is not affected. Tomatidine reduces the mRNA level of matrix metalloproteinase-2 (MMP-2), MMP-9 and increases the expression of reversion-inducing cysteine-rich protein with kazal motifs (RECK), as well as tissue inhibitor of metalloproteinase-1 (TIMP-1). The immunoblotting assays indicate that tomatidine is very effective in suppressing the
phosphorylation of Akt and extracellular signal regulating kinase (ERK). In addition, tomatidine significantly decreases the nuclear level of nuclear factor kappa B (NF-kappaB), which suggests that tomatidine inhibits NF-kappaB activity. Furthermore, the treatment of inhibitors specific for PI3K/Akt (LY294002), ERK (U0126), or NF-kappaB (pyrrolidine dithiocarbamate) to A549 cells reduced cell invasion and MMP-2/9 expression. The results suggest that tomatidine inhibits the invasion of A549 cells by reducing the expression of MMPs. It also inhibits ERK and Akt signaling pathways and NF-kappaB activity. These findings demonstrate a new therapeutic potential for tomatidine in antimetastatic therapy.

[369]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Alamgeer M; Ganju V; Neil Watkins D
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RESUMEN / SUMMARY: Oncogenic driver mutations frequently occur in lung cancer and play role in carcinogenesis. These mutations are usually associated with distinct clinical and histological features and are attractive targets for anticancer therapy. Recently, several molecularly distinct phenotypes of NSCLC based on specific and mutually exclusive genetic derangements have been described. Few targets like epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements have successfully been targeted with EGFR tyrosine kinase inhibitors (TKIs) and crizotinib, respectively. Many more inhibitors of specific driver mutations involving genes like ROS, c-MET, FGFR, mTOR, IGFR and RET are currently under development. However, efforts to target some mutated genes like K-RAS have been unsuccessful. Moreover, the emerging challenge of acquired resistance to initially effective therapy is becoming another major concern. In this review recent data on novel molecular targets and their future prospects are discussed.

[370]
TÍTULO / TITLE: Sleeve lobectomy compared with pneumonectomy after induction therapy for non-small-cell lung cancer.

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RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
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AUTORES / AUTHORS: Maurizi G; D’Andrilli A; Anile M; Ciccone AM; Ibrahim M; Venuta F; Rendina EA
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RESUMEN / SUMMARY: BACKGROUND: We compared morbidity, mortality, and oncolgical results of bronchial and/or vascular sleeve lobectomy (SL) with those of pneumonectomy (PN) after induction therapy for lung cancer.
METHODS: Between 1998 and 2011, 82 patients receiving induction therapy (chemo or chemo-radiotherapy) for non-small-cell-lung-cancer underwent sleeve lobectomy (n = 39) or pneumonectomy (n= 43). Only patients undergoing preoperative chemotherapy (39 in the SL group and 39 in the PN group) were included in the study. SL was bronchial in 21, vascular in 12, and broncho-vascular in six cases, respectively. Clinical stage before induction therapy was IIb in seven patients (1 in PN group; 6 in SL group), IIIa in 66 (36 in PN group; 30 in SL group), and IIIb in five patients (2 in PN group; 3 in SL group), respectively. N3 patients were not included in this series. RESULTS: The rate of downstaged patients (pathological complete response and stage I-II) was 79.5% in the SL group and 53.8% in the PN group (p = 0.01). Postpneumonectomy mortality rate was 2.6 %. There was no postoperative mortality after SL. Complications occurred in 12 patients (30.8%) after PN and in 11 patients (28.2%) after SL (p = 0.6). Three-year and 5-year survival rates were 68 +/- 3% and 64 +/- 8% in the SL group; and 59.5 +/- 5% and 34.5 +/- 8% in the PN group (p = 0.02). The difference in terms of recurrence rate (locoregional and distant) between the two groups was not significant (p = 0.2). CONCLUSIONS: SL represents a valid therapeutic option even after induction chemotherapy, providing better long-term survival than PN, with no increase of postoperative complications or recurrence rate. Pathological downstaging is a favorable prognostic factor.

TÍTULO / TITLE: Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer.
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296
AUTORES / AUTHORS: - Rudin CM; Brahmer JR; Juergens RA; Hann CL; Ettinger DS; Sebree R; Smith R; Aftab BT; Huang P; Liu JO

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RESUMEN / SUMMARY: - INTRODUCTION: Preclinical studies have suggested that the oral antifungal agent itraconazole specifically inhibits proliferation, migration, and tube formation of endothelial cells. Itraconazole has potent antiangiogenic activity and enhances the efficacy of cytotoxic chemotherapy in multiple primary xenograft lung cancer models. On the basis of these data, we performed an exploratory clinical study, assessing the efficacy of itraconazole with cytotoxic chemotherapy in the treatment of patients with advanced lung cancer. METHODS: The study enrolled patients with progressive nonsquamous non-small-cell lung cancer after one prior cytotoxic therapy for metastatic disease, randomized 2:1 to intravenous administration of pemetrexed 500 mg/m2 on day 1, with or without itraconazole 200 mg orally daily, on a 21-day cycle. Outcome measures included percent progression-free at 3 months, progression-free survival, overall survival, and observed toxicity. RESULTS: A total of 23 patients were enrolled; the study was stopped early because of increasing use of pemetrexed in the first-line setting. At 3 months, 67% of the patients on itraconazole plus pemetrexed were progression-free versus 29% on the control arm of pemetrexed alone (p = 0.11). Median progression-free survivals were 5.5 months (itraconazole) versus 2.8 months (control) (hazard ratio = 0.399, p = 0.089). Overall survival was longer in patients receiving itraconazole (median 32 months) versus control (8 months) (hazard ratio = 0.194, p = 0.012). There were no evident differences in toxicity between the study arms. CONCLUSION: Itraconazole is well tolerated in combination with chemotherapy for advanced lung cancer.


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


AUTORES / AUTHORS: - Rottmann J; Keall P; Berbeco R

INSTITUCIÓN / INSTITUTION: - Brigham and Women’s Hospital, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA.
RESUMEN / SUMMARY: - Compensation of target motion during the delivery of radiotherapy has the potential to improve treatment accuracy, dose conformity and sparing of healthy tissue. We implement an online image guided therapy system based on soft tissue localization (STiL) of the target from electronic portal images and treatment aperture adaptation with a dynamic multi-leaf collimator (DMLC). The treatment aperture is moved synchronously and in real time with the tumor during the entire breathing cycle. The system is implemented and tested on a Varian TX clinical linear accelerator featuring an AS-1000 electronic portal imaging device (EPID) acquiring images at a frame rate of 12.86 Hz throughout the treatment. A position update cycle for the treatment aperture consists of four steps: in the first step at time $t = t_0$ a frame is grabbed, in the second step the frame is processed with the STiL algorithm to get the tumor position at $t = t_0$, in a third step the tumor position at $t = t_i + \Delta t$ is predicted to overcome system latencies and in the fourth step, the DMLC control software calculates the required leaf motions and applies them at time $t = t_i + \Delta t$. The prediction model is trained before the start of the treatment with data representing the tumor motion. We analyze the system latency with a dynamic chest phantom (4D motion phantom, Washington University). We estimate the average planar position deviation between target and treatment aperture in a clinical setting by driving the phantom with several lung tumor trajectories (recorded from fiducial tracking during radiotherapy delivery to the lung). DMLC tracking for lung stereotactic body radiation therapy without fiducial markers was successfully demonstrated. The inherent system latency is found to be $\Delta t = (230 \pm 11)$ ms for a MV portal image acquisition frame rate of 12.86 Hz. The root mean square deviation between tumor and aperture position is smaller than 1 mm. We demonstrate the feasibility of real-time markerless DMLC tracking with a standard LINAC-mounted (EPID).


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


AUTORES / AUTHORS: - Tanaka K; Hata A; Kaji R; Fujita S; Otoshi T; Fujimoto D; Kawamura T; Tamai K; Takeshita J; Matsumoto T; Monden K; Nagata K; Otsuka K; Nakagawa A; Tachikawa R; Otsuka K; Tomii K; Katakami N

INSTITUCIÓN / INSTITUTION: - *Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Minatojima-Minamimachi, Chuo-Ku, Kobe, Japan; and daggerDepartment of Respiratory Medicine, Kobe City
RESUMEN / SUMMARY: - BACKGROUND:: EGFR gene mutation is independently associated with a favorable response in non-small-cell lung cancer (NSCLC) patients receiving epidermal growth factor receptor -tyrosine kinase inhibitors (EGFR-TKIs), regardless of sex or smoking history. Squamous cell carcinoma patients harboring EGFR mutations show a significantly worse response to EGFR-TKIs compared with adenocarcinoma patients. We hypothesized that the serum cytokeratin 19 fragment (CYFRA 21-1) is associated with the efficacy of EGFR-TKIs in EGFR-mutated NSCLC patients.

METHODS:: We retrospectively screened 160 NSCLC patients harboring EGFR mutations, who had received either gefitinib, or erlotinib between 1992 and 2011. Patients were screened for clinical characteristics, the efficacy of EGFR-TKI, and tumor markers (carcinoembryonic antigen [CEA]/CYFRA 21-1) at the initial diagnosis.

RESULTS:: Of 160 eligible patients treated with EGFR-TKIs, 77 patients with high CYFRA 21-1 level (>2 ng/ml) showed significantly shorter progression-free survival (PFS) than the 83 patients with normal CYFRA 21-1 level (median PFS, 7.5 versus 13.3 months; p < 0.001). No significant difference in PFS was observed between the high-CEA group (>5 ng/ml) and the normal-CEA group (median PFS, 8.6 versus 11.2 months; p = 0.242). A multivariate analysis revealed that high CYFRA 21-1 level is independently associated with PFS (hazard ratio, 1.27; p = 0.002). No significant difference in overall survival was observed between the high- and the normal-CYFRA 21-1 groups (median overall survival, 24.8 versus 39.1 months; p = 0.104).

CONCLUSIONS:: Patients with a high CYFRA 21-1 level have significantly shorter PFS. CYFRA 21-1 is not a prognostic but a predictive marker of EGFR-TKI treatment in EGFR-mutated NSCLC patients.

[374]
TITULO / TITLE: - Effect of ghrelin and anamorelin (ONO-7643), a selective ghrelin receptor agonist, on tumor growth in a lung cancer mouse xenograft model.

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

AUTORES / AUTHORS: - Northrup R; Kuroda K; Duus EM; Barnes SR; Cheatham L; Wiley T; Pietra C

RESUMEN / SUMMARY: - PURPOSE: Anamorelin (ONO-7643) is an orally active ghrelin receptor agonist in development for non-small cell lung cancer
(NSCLC)-related anorexia/cachexia. It displays both orexigenic and anabolic properties via ghrelin mimetic activity and transient increases in growth hormone (GH). However, increasing GH and insulin-like growth factor-1 in cancer patients raises concerns of potentially stimulating tumor growth. Therefore, we investigated the effect of ghrelin and anamorelin on tumor growth in a murine NSCLC xenograft model. METHODS: Female nude mice (15-21/group) with established A549 tumors were administered ghrelin (2 mg/kg i.p.), anamorelin (3, 10, or 30 mg/kg p.o.), or vehicle controls daily for 28 days. Tumor growth, food consumption, and body weight were monitored. Murine growth hormone (mGH) and murine insulin-like growth factor-1 (mIGF-1) were measured in plasma. RESULTS: Tumor growth progressed throughout the study, with no significant differences between treatment groups. Daily food consumption was also relatively unchanged, while the percentage of mean body weight gain at the end of treatment was significantly increased in animals administered 10 and 30 mg/kg compared with controls (p < 0.01). Peak mGH levels were significantly higher in ghrelin- and anamorelin-treated animals than in controls, while peak mIGF-1 levels were slightly elevated but not statistically significant. All regimens were well tolerated. CONCLUSIONS: These findings demonstrate that neither anamorelin nor ghrelin promoted tumor growth in this model, despite increased levels of mGH and a trend of increased mIGF-1. Together with anamorelin’s ability to increase body weight, these results support the clinical development of ghrelin receptor agonist treatments for managing NSCLC-related anorexia/cachexia.
repair was monitored by gamma-H2AX foci formation after RNF8 depletion. Expression of Ku70 and Rad51 were assessed by immunofluorescent staining and Western blotting. Cell cycle and apoptosis were measured by flow cytometry assays. Results: After lentivirus-mediated siRNA transfection, expression of RNF8 in A549 cells downregulated which led to an increased radiosensitivity and impaired DNA repair. RNF8 knockdown did not affect Ku70 expression, however, Rad51, a key player in homologous recombination (HR) repair, was abrogated at sites of DNA damage. Furthermore, we observed an extended G2/M arrest and an increased induction of apoptosis after ionizing radiation in the absence of RNF8. Conclusions: RNF8 silencing effectively downregulates Rad51 therefore maybe impairing HR repair, and prolongs the G2/M accumulation as well as cell apoptosis upon radiation, which all suggest an enhanced radiosensitivity on A549 cells.
the first time that autophagy occurred earlier than apoptosis during dioscin-induced human lung cancer cell line apoptosis. Dioscin-induced autophagy via ERK1/2 and JNK1/2 pathways may provide a protective mechanism for cell survival against dioscin-induced apoptosis to act as a cytoprotective reaction.

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TITULO / TITLE: - Tuberculosis is associated with increased lung cancer mortality.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUtoRES / AUTHORS: - Leung CC; Hui L; Lee RS; Lam TH; Yew WW; Hui DS; Chan RC; Mok TY; Law WS; Chang KC; Leung EC; Tam CM
INSTITUCIÓN / INSTITUTION: - Tuberculosis and Chest Service, Department of Health, Hong Kong SAR, China. cc_leung@dh.gov.hk

RESUMEN / SUMMARY: - SETTING: Elderly persons living in the community in Hong Kong. OBJECTIVE: To examine the association between tuberculosis (TB) and lung cancer. DESIGN: Elderly clients enrolled in a health programme from 2000 to 2003 were retrospectively cross-matched with the territory-wide TB notification registry for TB before enrolment. The cohort was followed up prospectively through linkage with the territory-wide death registry for cause of death until 31 December 2011. All subjects with suspected malignancy or recent weight loss (>\(\geq\)=5%) at enrolment and deaths within the first 2 years of follow-up were excluded. RESULTS: Of the 61,239 subjects included, 516 had TB before enrolment. After 490,258 person-years of follow-up, respectively 1344, 910 and 2003 deaths were caused by lung cancer, other tobacco-related malignancies and non-tobacco-related malignancies. TB before enrolment was associated with death due to lung cancer (Mantel-Haenszel weighted relative risk 2.61, 95%CI 1.82-3.74, \(P < 0.001\)) but not other malignancies after stratification by sex. TB remained an independent predictor of lung cancer death (adjusted hazard ratio 2.01, 95%CI 1.40-2.90; \(P < 0.001\)), after adjustment for multiple potential confounders. CONCLUSIONS: TB was independently associated with subsequent mortality due to lung cancer. This finding calls for intensification of tobacco control and better targeting of lung cancer screening in high TB burden areas.

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TITULO / TITLE: - Rapid increase of serum neuron specific enolase level and tachyphylaxis of EGFR-tyrosine kinase inhibitor indicate small cell lung cancer transformation from EGFR positive lung adenocarcinoma?
RESUMEN / SUMMARY: We report the case of an 80-year-old male with relapsed EGFR exon 19 deletion lung adenocarcinoma treated with EGFR-tyrosine kinase inhibitor (TKI), but with poor response and rapid increase of serum neuron specific enolase (NSE). Repeat biopsy identified pathological transformation to small cell lung cancers (SCLC) retaining the same EGFR mutation. This case highlights routine serological testing of NSE may benefit for the lung adenocarcinoma patients resistant to TKIs.

TÍTULO / TITLE: Aryl hydrocarbon receptor and lung cancer.

RESUMEN / SUMMARY: The leading cause of lung cancer is exposure to cigarette smoke and other environmental pollutants, which include formaldehyde, acrolein, benzene, dioxin, and polycyclic aromatic hydrocarbons (PAHs). PAHs and dioxins are exogenous ligands that directly bind to the aryl hydrocarbon receptor (AhR), a transcription factor that activates xenobiotic metabolism, histone modification (an important step in DNA methylation) and, ultimately, tumorigenesis. In this review article we summarize the current understanding of AhR and its role in the development of lung cancer, including its influence on cell proliferation, angiogenesis, inflammation, and apoptosis.

TÍTULO / TITLE: Mesotelioma de la tunica vaginal.

TÍTULO / TITLE: Mesothelioma of the tunica vaginalis. Case report.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Busto Martin L; Portela Pereira P; Sacristan Lista F; Busto Castanon L
INSTITUCIÓN / INSTITUTION: - Urology Department.Complexo Hospitalario Universitario de La Coruña. España.

RESUMEN / SUMMARY: - OBJECTIVE: To report a case of a mesothelioma of the tunica vaginalis and to review the published literature. METHODS / RESULTS: A 61-year-old patient complained of one-month increase of right scrotum size with pain. An ultrasound showed a right hydrocele with a mass attached to the tunica vaginalis. He didn’t refer any urological history or known exposure to asbestos. Blood levels of tumor markers (alpha-fetoprotein and beta-HCG) were within normal limits. We performed a radical inguinal orchiectomy with an en-bloc resection of the tunica vaginalis. The pathology described a potentially malignant biphasic mesothelioma. The patient has remained asymptomatic with negative extension studies after 10 years of follow up. CONCLUSIONS: Paratesticular mesotheliomas are rare tumors (approximately 250 cases reported) with uncertain etiology (only 30-40% are associated with asbestos exposure). The age range is between 50-70 years. Its presentation is usually as a scrotal mass with recurrent reactive hydrocele, which may delay early diagnosis. During surgery, intraoperative biopsy is recommended. It is important to do a differential diagnosis with other benign diseases. Treatment is only curative in early stages with radical orchiectomy and resection in-block of the tunica vaginalis. Despite being multidisciplinary, it is not curative in most cases due to rapid local and distant spread.

[381]

TÍTULO / TITLE: - Vimentin expression predicts the occurrence of metastases in non small cell lung carcinomas.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Dauphin M; Barbe C; Lemaire S; Nawrocki-Raby B; Lagonotte E; Delepine G; Birembaut P; Gilles C; Polette M
INSTITUCIÓN / INSTITUTION: - INSERM UMR-S 903, SFR CAP-Sante, University of Reims-Champagne-Ardenne, 51100 Reims, France; Laboratory of Histology, CHU of Reims, 51100 Reims, France.
RESUMEN / SUMMARY: - Epithelial-to-mesenchymal transition (EMT) is believed to contribute to tumour invasion. Vimentin expression by carcinoma cells is a largely recognized marker of EMT. This study aimed at examining vimentin

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expression in non small cell lung carcinomas (NSCLC) by immunohistochemistry to evaluate potential correlations between vimentin expression and the differentiation status, the TNM stage and the outcome of the patients. 295 NSCLC including 164 squamous cell carcinomas (SCC), 108 adenocarcinomas (AC) and 23 other NSCLC carcinomas have been examined by immunohistochemistry. Vimentin was indeed detected in 145 cases (49.2%). It was principally present in isolated tumour cells and invasive clusters, particularly in cells at the tumour/stroma interface. Vimentin expression was significantly more expressed in large cell neuroendocrine, adeno-squamous and sarcomatoid carcinomas than in SCC and AC and was significantly associated with the differentiation status of carcinomas. The follow-up of 193 patients further demonstrated that an extensive expression of vimentin (>50% of tumour cells) was associated with the occurrence of metastases. In conclusion, our data demonstrate that vimentin expression is a frequent event in NSCLC and that its expression can be associated with a lack of differentiation and the occurrence of metastases.

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[TITULO / TITLE: - Prx1 modulates the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.

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


AUTORES / AUTHORS: - Hwang KE; Park DS; Kim YS; Kim BR; Park SN; Lee MK; Park SH; Yoon KH; Jeong ET; Kim HR

INSTITUCION / INSTITUTION: - Department of Internal Medicine, Institute of Wonkwang Medical Science, Wonkwang University, School of Medicine, Iksan, Jeonbuk 570-749, Republic of Korea.

RESUMEN / SUMMARY: - The expression levels of Prx1 are frequently elevated in several human cancers, including lung cancer and may confer increased resistance to treatment. In this study, we investigated the role of Prx1 in docetaxel-induced apoptosis in A549 lung cancer cells. To test whether Prx1 knockdown affected the sensitivity of A549 cells to docetaxel treatment, we generated short hairpin RNA (shRNA) constructs targeting Prx1 and analyzed the effect of Prx1 knockdown on growth and apoptosis. Tumor growth was evaluated in scrambled shRNA- or shPrx1-infected A549 cell tumors receiving docetaxel treatment. In addition, mechanistic information was gathered by western blot analysis from cell lysates of scrambled- and shPrx1-infected A549 cells pretreated with or without LY294002 and subsequently treated with docetaxel. We found that Prx1 knockdown resulted in enhanced docetaxel-induced cytotoxicity in a dose-dependent manner. In vivo, the growth rate of
shPrx1-infected A549 tumors was significantly reduced compared to that of scrambled shRNA-infected A549 tumors. Prx1 knockdown also augmented the inhibitory effects of docetaxel on tumor growth. Prx1 knockdown increased the apoptotic potential through activation of the caspase cascade and suppressed docetaxel-induced phosphorylation of Akt and its substrate forkhead box O1 (FOXO1). Moreover, treatment with the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 reduced the phosphorylation of FOXO1 and increased the cytotoxicity of docetaxel in A549 cells. Our findings suggest that Prx1 may modulate the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.
(P<.0001), p-N-Status (P=0.046) and p-IMIG stage (P<.0001). No difference could be observed with regard to age, histology, laterality, surgical morbidity and mortality, respectively. Only 3 out of 88 patients (3.4%) would have been eligible for EPP to achieve MCR. Not resectable T4-disease and impaired cardiopulmonary reserves were the main reasons for ineligibility for EPP in 35.5% (11/31) and 48.4% (15/31), respectively. CONCLUSIONS: R2 in patients undergoing RP is associated with inferior outcomes. Only very selected cases would have qualified for EPP to achieve MCR. EPP might be an important surgical extension in selected patients to achieve MCR. There is a need for further investigation of effective intrapleural additive treatment options for patients undergoing R2.

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TÍTULO / TITLE: - How and when to use genetic markers for nonsmall cell lung cancer.

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


AUTORES / AUTHORS: - Lazarus DR; Ost DE

INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

RESUMEN / SUMMARY: - PURPOSE OF REVIEW: Many driver mutations that determine the malignant behavior of lung cancer have been identified in recent years. The promise of therapies targeted to the specific molecular pathways altered by such mutations has made genetic testing in nonsmall cell lung cancer (NSCLC) attractive to clinicians. We reviewed recent research on clinically relevant genetic and molecular tests for patients with NSCLC, with an emphasis on the tests linked to actionable mutations that influence therapy and improve outcomes. RECENT FINDINGS: Mutations in the epidermal growth factor receptor gene (EGFR) and translocations involving the anaplastic lymphoma kinase (ALK) gene have been shown to be common driver mutations in lung adenocarcinoma. The presence or absence of these mutations has been demonstrated to predict response to targeted therapy in many recent studies. Targeted therapies for patients with mutations in the EGFR domain or the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase translocation have been shown to be effective and are approved for use. Ongoing studies continue to define the extent of their utility and may continue to expand their indications. Sufficient tissue for genetic analysis can be obtained from cytologic samples, including those obtained from endobronchial ultrasound-guided transbronchial needle aspiration. SUMMARY: Genetic
testing for driver mutations is useful in identifying patients with NSCLC who are likely to respond to targeted therapy. These tests are best used in patients with adenocarcinoma who have advanced-stage cancer.
OBJETIVO. El objetivo de este estudio fue determinar si la reproducibilidad de las medidas puede mejorar utilizando corrección de movimiento computarizada y cubierta total del tumor en la perfusión CT adaptativa de 4D de los pacientes con cáncer de pulmón.

MÉTODOS. Se realizó una perfusión CT que cubría el eje completo de un nódulo en 40 pacientes con cáncer de pulmón. Cada estudio de perfusión CT se realizó en 93.5 segundos y se incluyeron 17 escáneres dinámicos repetidos utilizando el modo Spiral 4D adaptativo. La fluencia sanguínea (BF), el volumen sanguíneo (BV) y la permeabilidad fueron medidos de cuatro maneras: en el área del tumor (cubierta total del tumor) sin uso de corrección de movimiento; en el área del tumor con corrección de movimiento; en un área de interés (VOI) del tumor sin uso de corrección de movimiento; y en un VOI con corrección de movimiento. Se evaluó la reproducibilidad intra- e interobserbadora a través de análisis de Bland-Altman. RESULTADOS. Los límites de confianza del 95% de la reproducibilidad intraobservador para BF, BV, y permeabilidad fueron como sigue: -52.1% a 48.0%, -22.4% a 27.8%, y -33.2% a 38.5% respectivamente, en el área del tumor sin corrección de movimiento; -53.3% a 45.6%, -17.7% a 20.6%, y -31.5% a 37.0% en el área del tumor con corrección de movimiento; -107.8% a 97.4%, -98.3% a 93.7%, y -132.3% a 100.7% en un VOI del tumor sin corrección de movimiento; y -74.9% a 98.6%, -74.5% a 88.1%, y -109.8% a 114.1% en un VOI con corrección de movimiento. Los límites de confianza del 95% de la reproducibilidad interobservador para BF, BV, y permeabilidad fueron como sigue: -57.0% a 62.5%, -36.8% a 52.6%, y -47.7% a 66.0%, respectivamente, en el área del tumor sin corrección de movimiento; -55.7% a 55.8%, -25.8% a 42.0%, y -35.3% a 46.7% en el área del tumor con corrección de movimiento; -146.6% a 165.1%, -117.1% a 137.7%, y -143.2% a 149.8% en un VOI del tumor sin corrección de movimiento; y -106.2% a 133.6%, -99.5% a 122.4%, y -108.6% a 170.0% en un VOI con corrección de movimiento. En general, la mejor reproducibilidad se obtuvo cuando las mediciones se obtuvieron en el área del tumor (cubierta total del tumor) y cuando se utilizó corrección de movimiento. CONCLUSIÓN. La reproducibilidad de los parámetros de perfusión mejoró cuando las mediciones en el área del tumor (cubierta total del tumor) se obtuvieron y se utilizó corrección de movimiento computarizada. La mejor reproducibilidad en los valores de parámetros se obtuvo con corrección de movimiento y cubierta total del tumor.

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


AUTORES / AUTHORS: - Wang J; Sun L; Yang M; Luo W; Gao Y; Liu Z; Qiu X; Wang E

INSTITUCIÓN / INSTITUTION: - Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences of China Medical University, Shenyang, Liaoning, China (JW,LS,MY, WL, YG, ZL, XQ, EW).

RESUMEN / SUMMARY: - The human DEK proto-oncogene is a nuclear protein with suspected roles in human carcinogenesis. DEK appears to function in several nuclear processes, including transcriptional regulation and modulation of chromatin structure. To investigate the clinicopathological significance of DEK in patients with non-small cell lung cancer (NSCLC), we analyzed DEK immunohistochemistry in 112 NSCLC cases. The results showed that DEK was overexpressed mainly in the nuclear compartment of tumor cells. In squamous cell carcinoma, DEK-positive expression occurred in 47.9% (23/48) of cases, and in lung adenocarcinoma, DEK-positive expression occurred in 67.2% (43/64) of cases and correlated with differentiation, p-TNM stage, and nodal status. Moreover, in lung adenocarcinoma, DEK expression was significantly higher compared with DEK expression in squamous cell carcinoma. Kaplan-Meier analysis showed that patients with low DEK expression had higher overall survival compared with patients with high DEK expression. Depleting DEK expression inhibited cellular proliferation and migration. Furthermore, in DEK-depleted NSCLC cells, we found that RhoA expression was markedly reduced; in conjunction, active RhoA-GTP levels and the downstream effector phosphorylated MLC2 were also reduced. Taken together, DEK depletion inhibited cellular migration in lung cancer cell lines possibly through inactivation of the RhoA/ROCK/MLC signal transduction pathway.

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TÍTULO / TITLE: - Morphometry Analysis of Lymphatics in Pulmonary Adenocarcinomas with a Lepidic Growth Pattern.

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


AUTORES / AUTHORS: - Sannier A; Kambouchner M; Danel C; Callard P; Bernaudin JF
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: She J; Yang P; Hong Q; Bai C
INSTITUCIÓN / INSTITUTION: Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai, China.
RESUMEN / SUMMARY: In 2008, lung cancer replaced liver cancer as the number one cause of death among people with malignant tumors in China. The registered lung cancer mortality rate increased by 464.84% in the past 3 decades, which imposes an enormous burden on patients, health-care professionals, and society. We performed a systematic review of the published data on lung cancer in China between 1990 and 2011 to analyze the incidence and mortality rates, economic burden, and risk factors of cancer and the effectiveness of interventions. Lung cancer incidence varies within China. People in eastern China, especially women, likely have a higher risk of developing lung cancer than those in western China. The crude mortality rates from lung cancer in 2008 were 47.51 per 100,000 men and 22.69 per 100,000 women. The crude mortality rate was highest in Shanghai (76.49 per 100,000 men and 35.82 per 100,000 women) and lowest in Tibet (25.14 per 100,000 men) and Ningxia (12.09 per 100,000 women). Smoking and environmental pollution are major risk factors for lung cancer in China. Continuous efforts should be concentrated on education of the general public regarding lung cancer to increase prevention and early detection. Specific interventions need to be implemented to reduce smoking rates and environmental risk factors. Standardized treatment protocols should be adapted in China.

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

AUTORES / AUTHORS: Meenach SA; Anderson KW; Zach Hilt J; McGarry RC; Mansour HM
INSTITUCIÓN / INSTITUTION: University of Kentucky, College of Pharmacy, Department of Pharmaceutical Sciences - Drug Development Division,
Pulmonary inhalation chemotherapeutic drug delivery offers many advantages for lung cancer patients in comparison to conventional systemic chemotherapy. Inhalable particles are advantageous in their ability to deliver drug deep in the lung by utilizing optimally sized particles and higher local drug dose delivery. In this work, spray-dried and co-spray dried inhalable lung surfactant-mimic PEGylated lipopolymers as microparticulate/nanoparticulate dry powders containing paclitaxel were rationally designed via organic solution advanced spray drying (no water) in closed-mode from dilute concentration feed solution. Dipalmitoylphosphatidylcholine (DPPC) and dipalmitoylphosphatidylethanolamine poly(ethylene glycol) (DPPE-PEG) with varying PEG chain length were mixed with varying amounts of paclitaxel in methanol to produce co-spray dried microparticles and nanoparticles. Scanning electron microscopy showed the spherical particle morphology of the inhalable particles. Thermal analysis and X-ray powder diffraction confirmed the retention of the phospholipid bilayer structure in the solid-state following spray drying, the degree of solid-state molecular order, and solid-state phase transition behavior. The residual water content of the particles was very low as quantified analytically Karl Fisher titration. The amount of paclitaxel loaded into the particles was quantified which indicated high encapsulation efficiencies (43-99%). Dry powder aerosol dispersion performance was measured in vitro using the Next Generation Impactor (NGI) coupled with the Handihaler® dry powder inhaler device and showed mass median aerodynamic diameters in the range of 3.4-7 micrometers. These results demonstrate that this novel microparticulate/nanoparticulate chemotherapeutic PEGylated phospholipid dry powder inhalation aerosol platform has great potential in lung cancer drug delivery.

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TÍTULO / TITLE: Commentary: bilobed flap for reconstruction of small alar rim defects.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Martinez JC
INSTITUCIÓN / INSTITUTION: Mayo Clinic, Jacksonville, Florida, USA.
martinez.juancarlos@mayo.edu
TÍTULO / TITLE: - Wif1 hypermethylation as unfavorable prognosis of non-small cell lung cancers with EGFR mutation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Lee SM; Park JY; Kim DS
INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Kyungpook National University, Daegu, 702-422, Korea.

RESUMEN / SUMMARY: - Lung cancer is a leading cause of cancer-related mortality across the world and tobacco smoking is the major risk factor. The Wnt signaling pathway is known to be involved in smoke-induced tumorigenesis in the lung. Promoter hypermethylation of Wnt inhibitory factor 1 (Wif1) has become a common event in a number of human tumors. Using a methylation-specific PCR, hypermethylation of the Wif1 gene promoter was evaluated in 139 primary non-small cell lung cancers (NSCLCs) and its correlation with clinicopathological and prognostic parameters was evaluated. Methylation of Wif1 was observed in 47.5% and 20.9% of neoplastic and adjacent normal lung tissues, respectively. Its methylation rate tended to be higher in stage I than stages II-III A. Results of Kaplan-Meier analysis showed no significant difference in overall survival according to Wif1 methylation status. However, Wif1 methylation showed an association with unfavorable prognosis of adenocarcinoma (AC) patients with EGFR mutation. According to our current findings, Wif1 promoter methylation is an early, frequent event as an epigenetic field manner and could be considered as a useful prognostic marker for AC patients with EGFR mutation. Further investigation into the therapeutic potential of this finding is warranted.

TÍTULO / TITLE: - Numblike regulates proliferation, apoptosis, and invasion of lung cancer cell.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Yingjie L; Jian T; Changhai Y; Jingbo L
INSTITUCIÓN / INSTITUTION: - Department of Cardio-thoracic Surgery, First Affiliated Hospital of Chinese PLA General Hospital, Beijing, 100048, People’s Republic of China.
RESUMEN / SUMMARY: - Numblike (Numbl), a conserved homolog of Drosophila Numb, has been proved to be implicated in early development of the nervous system. A recent study also showed that Numbl played an important role in tumorigenesis and invasion by suppressing NF-kappaB activation. However, the biological role of Numbl remains unknown in lung cancer up to now. To address the expression of Numbl in the lung cancer cell, four lung cancer cell lines (metastatic cell lines NCI-H292, 95-D, and non-metastatic cell lines A549, HCC827) and non-cancerous human bronchial epithelial cells were used to detect the protein expression of Numbl by western blotting. The results in this study indicated that the expression of Numbl was downregulated in human lung cancer cell lines, especially in metastatic cell lines. To investigate the role of Numbl in lung cancer cell proliferation, apoptosis, and invasion, we generated human lung cancer 95-D cell lines in which Numbl was either overexpressed or depleted. Subsequently, the effects of Numbl on the cell viability, cycle, apoptosis, and invasion properties in 95-D cells were determined with MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay, flow cytometry analysis, and Transwell invasion assays. The results indicated that Numbl could decrease cell viability, suppress cell proliferation and invasion, and promote cell apoptosis. In addition, we investigated the effects of Numbl on the expression of the following proteins: TRAF6 (tumor necrosis factor receptor-associated factor 6), p-p65 (phosphor-NF-kappaB), cyclin D1, caspase-3, and matrix metalloproteinase 9 (MMP9). Results showed that Numbl could decrease the expression of TRAF6, p-p65, cyclin D1, and MMP9 and increase the expression of caspase-3. All these results suggested that Numbl might be involved in the inhibition of growth, proliferation, and invasion of 95-D cells, as well as the potentiation of apoptosis of 95-D cells by abrogating TRAF6-induced activation of NF-kappaB.

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TITULO / TITLE: - Pleural cancer antigen-125 levels in benign and malignant pleural effusions.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Choi WI; Qama D; Lee MY; Kwon KY
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Keimyung University, Dongsan Hospital, Daegu, Republic of Korea. wichoi@dsmc.or.kr
RESUMEN / SUMMARY: - OBJECTIVE: To examine the properties of mesothelial cells by measuring pleural cancer antigen 125 (CA-125) levels in different types of benign and malignant pleural effusions. DESIGN: In this retrospective study, pleural fluid was collected from 326 patients; pleural CA-125 levels were
measured using radioimmunoassay. Patients were classified into five groups according to the aetiology of pleural effusions: I) tuberculosis, II) malignant, III) pyogenic, IV) congestive heart failure, and V) hepatic hydrothorax. RESULTS: CA-125 levels were significantly higher in the malignant group than in all benign groups. There was no difference in pleural CA-125 levels between transudate and exudate benign aetiologies. Although pleural CA-125 levels were significantly higher in malignant than benign effusions, about one third of malignant pleural effusions had levels of <600 U/ml. Among malignancies, there were no significant differences in pleural CA-125 levels between histological types. CONCLUSION: CA-125 levels in benign pleural effusions may not be influenced by pleural inflammation or hydrostatic or oncotic pressure changes. Pleural CA-125 levels may not be influenced by the histological type of tumour in malignant pleural effusions, suggesting that mesothelial cell properties may not be altered by these factors in the pleural space.

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**TÍTULO / TITLE:** - Prognostic significance of CD151 overexpression in non-small cell lung cancer.

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


**AUTORES / AUTHORS:** - Kwon MJ; Seo J; Kim YJ; Kwon MJ; Choi JY; Kim TE; Lee DH; Park S; Shin YK; Han J; Choi YL

**INSTITUCIÓN / INSTITUTION:** - Department of Pathology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea.

**RESUMEN / SUMMARY:** - The overexpression of tetraspanin CD151 - a transmembrane protein that promotes tumor invasion and metastasis - is associated with poor prognosis in various cancers. However, its clinical significance in non-small cell lung cancers (NSCLCs) has not been fully elucidated. We investigated CD151 expression status by immunohistochemical analysis in paraffin-embedded specimens obtained from 380 patients with surgically resected NSCLCs (245 squamous cell carcinomas [SCCs] and 135 adenocarcinomas [ADCs]) between 1994 and 2001. High CD151 expression was detected in 28.7% NSCLCs (20.8% of SCCs and 42.9% of ADCs) and was significantly associated with male gender, smokers, and ADCs. Moreover, elevated CD151 levels were correlated with reduced overall (OS) and disease-free survival (DFS), and were an independent negative prognostic factor for OS in NSCLC. According to histological type, high CD151 expression was an independent prognostic factor for lower OS in ADC, although not in each
subtype, and the elevated CD151 expression levels were more common in solid-predominant tumors (48.3%). In contrast, there was no prognostic correlation in SCC. High CD151 expression appeared to correlate with aggressive behavior in NSCLC, suggesting that it may be a useful prognostic marker for lung ADC patients and a potential molecular target for NSCLC treatment.

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


AUTORES / AUTHORS: Gu J; Ding JY; Lu CL; Lin ZW; Chu YW; Zhao GY; Guo J; Ge D

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, The Affiliated Zhongshan Hospital of Fudan University, Shanghai 200032, PR China.

RESUMEN / SUMMARY: CD88 (C5aR), a G-protein-coupled receptor, is well known as it functions in various inflammatory diseases, however, its role in tumorigenesis remains unclear. In this study we investigated the prognostic value of CD88 in patients with non-small-cell lung cancer (NSCLC) after surgical resection. Five NSCLC cell lines and one normal bronchial epithelial cell line were used to analyze the CD88 expression at the mRNA level. Then, the expression of CD88 and E-cadherin were further examined by immunohistochemistry (IHC) in tissue microarray (TMA) consisting of 208 cases of NSCLCs. Data revealed that CD88 expression was significantly higher in NSCLC cells than that in normal bronchial epithelial cells, and compared with the adjacent non-tumorous lung tissues, the CD88 protein overexpressed in NSCLC tissues. Furthermore, high levels of CD88 were found to be correlated with lymph node metastasis in NSCLC patients (p=0.012). The 5-year overall survival of patients with CD88high was significantly lower than those in the CD88low group (p=0.001), and multivariate analysis revealed that CD88 expression was an independent prognostic factor in patients’ overall survival (HR=1.614, 95% CI 1.082-2.407, p=0.019). Finally, we confirmed the CD88 expression negatively correlated with E-cadherin expression (p<0.001). Interference of CD88 expression impaired the migration of lung cancer cells and up-regulated the E-cadherin protein expression. Thus, our results indicate that CD88 is overexpressed in NSCLC. High levels of CD88 are associated with poor prognosis of NSCLC after resection and promote tumor metastasis via
down-regulation of E-cadherin. CD88 can be a potential prognostic marker to screen patients for unfavorable prognosis.

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TÍTULO / TITLE: - Utility of the Quantitative Ki-67 Proliferation Index and CD56 Together in the Cytologic Diagnosis of Small Cell Lung Carcinoma and Other Lung Neuroendocrine Tumors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Zheng G; Ettinger DS; Maleki Z
INSTITUCIÓN / INSTITUTION: - Department of Pathology, The Johns Hopkins Hospital, Baltimore, Md., USA.
RESUMEN / SUMMARY: - Background: Distinction of small cell lung carcinoma (SCLC) from non-small cell lung carcinoma (NSCLC) is critical because of the differences in prognosis and management. Patients with SCLC usually present with distant metastasis, and clinicians demand an accurate diagnosis in order to initiate appropriate therapy. Limited cytology material, occasionally with crush artifact, is not uncommon. Therefore, robust cytomorphologic features and a small immunostaining panel would be ideal to differentiate SCLC from NSCLC and other neuroendocrine neoplasms. We evaluated CD56 and the quantitative Ki-67 immunohistochemical panel in comparison to synaptophysin and chromogranin, along with cytomorphology to diagnose SCLC. Design: Eighty-eight cases of SCLC were retrieved from the cytology archives of The Johns Hopkins Hospital. Forty neuroendocrine neoplasms were used as control cases. Results: SCLCs included 33 lung cases and 55 metastatic lesions. The specimens were obtained by fine needle aspiration, thoracocentesis, bronchoalveolar lavage and abdominal paracentesis. CD56 was expressed in 98.9% of SCLCs, which is significantly more sensitive than synaptophysin and chromogranin. The Ki-67 labeling index was high (>70%) in all cases, which is a reliable marker to differentiate SCLC from other neuroendocrine neoplasms and NSCLC. Conclusion: CD56 and quantitative Ki-67 along with cytomorphology is a robust immunohistochemical panel to differentiate SCLC from other neuroendocrine neoplasms and NSCLC.

[398]
TÍTULO / TITLE: - Serum HMGB1 as a Diagnostic Marker for Malignant Peritoneal Mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago)

**1097/MCG.0b013e318297fa65**  
**AUTORES / AUTHORS:** Tabata C; Kanemura S; Tabata R; Masachika E; Shibata E; Otsuki TI; Nishizaki T; Nakano T  
**INSTITUCIÓN / INSTITUTION:** Department of *Internal Medicine, Division of Respiratory Medicine* double daggerDepartment of Physiology, Division of Bioinformation, Hyogo College of Medicine daggerDepartment of Internal Medicine, Hyogo Prefectural Tsukaguchi Hospital, Hyogo, Japan.  
**RESUMEN / SUMMARY:** BACKGROUND:: Diffuse malignant peritoneal mesothelioma (DMPM) is an aggressive malignant tumor of mesothelial origin that shows a limited response to cytoreductive surgery along with intraperitoneal chemotherapy. Therefore, early diagnosis of DMPM is very important. Some researchers have previously reported that high-mobility group box 1 (HMGB1) was correlated with pulmonary fibrosis. DMPM involves the malignant transformation of mesothelial cells, which originate from mesenchymal cells, similar to lung fibroblasts. Here, we investigated serum levels of HMGB1 in patients with MPM and compared them with those of a population that had been exposed to asbestos without developing MPM.  
**STUDY::** The serum concentrations of HMGB1 were measured in 13 DMPM patients and 45 individuals with benign asbestos-related diseases. RESULT:: We demonstrated that the patients with DMPM had significantly higher serum levels of HMGB1 compared with the population who had been exposed to asbestos but did not develop DMPM. CONCLUSION:: Our data suggest that serum HMGB1 concentration is a useful serum marker for DMPM.

[399]  
**TÍTULO / TITLE:** D2-40-positive lymphatic vessel invasion is not a poor prognostic factor in stage I lung adenocarcinoma.  
**RESUMEN / SUMMARY:** The present study investigates whether lymphatic vessel invasion (LVI) detected by D2-40 staining is a prognostic factor for stage I adenocarcinoma of the lung. We retrospectively reviewed 124 patients who underwent complete resection for stage I adenocarcinoma of the lung from January 1983 to June 2003. LVI was microscopically evaluated using D2-40 immunostaining. The median follow-up was 71 months. The LVI positive rate was 37%. The 5-year cancer-specific survival rates of the D2-40 positive LVI
and negative groups were 88.8% and 84.3%, respectively (P = 0.630). The stage I lung adenocarcinoma patients who were determined to be LVI positive based on D2-40 immunostaining did not have a significantly poorer prognosis than the LVI negative cases. Thus, lymphatic microinvasion may not be a prognostic indicator in early lung cancer, although advanced LVI does appear to correlate with survival. It is therefore unnecessary to use D2-40 immunostaining to diagnose LVI in practical settings, and Hematoxylin-Eosin and Elastica van Gieson staining should continue to be used to predict the prognosis of patients with stage I lung adenocarcinoma.

[400]

TÍTULO / TITLE: - Proposal on incorporating blood vessel invasion into the T classification parts as a practical staging system for stage I non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kudo Y; Saji H; Shimada Y; Matsubayashi J; Nagao T; Kakihana M; Usuda J; Kajiwara N; Ohira T; Ikeda N
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Department of Surgery, Tokyo Medical University, Japan. Electronic address: yjnkudo@gmail.com.

RESUMEN / SUMMARY: - BACKGROUND: We investigated blood vessel invasion (BVI) as a possible negative prognostic factor in patients with stage I non-small cell lung cancer (NSCLC) according to the 7th edition of the TNM classification. METHODS: Between 1999 and 2007, a total of 694 consecutive patients with pathological stage I NSCLC underwent complete resection with systematic lymph node dissection at Tokyo Medical University Hospital. All sections of the specimens were stained by Elastica van Gieson to visualize elastic fibers and were examined to determine the prognostic symptoms of BVI. We statistically analyzed the association between BVI and clinicopathologic factors, as well as clinical outcomes. RESULTS: BVI was detected in 201 patients with stage I NSCLC (29.0%). The 5-year overall survival (OS) rates of the non-BVI and BVI patients were 90.5% and 66.0%, respectively (p<0.0001). BVI was found to be a significant independent prognostic factor by multivariate survival analysis in stage I A and stage IB NSCLC (HR 2.591, p<0.001; HR 2.347, p=0.009, respectively). The 5-year OS rate of patients with BVI was significantly worse than that of patients without BVI in the T1a (94.5% vs 87.5%, p<0.0001), T1b (82.7% vs 65.9%, p<0.0001), and T2a (90.9% vs 61.8%, p<0.0001) subgroups. CONCLUSION: We identified the presence of BVI as an independent poor
prognostic factor in patients with stage I NSCLC. In the future revision of the TNM staging system, the routine use of elastic fiber stains in pathological evaluations of lung cancer for BVI determination might be recommended, and tumors with BVI should be upstaged to the higher current T staging.

[401]

**TITULO / TITLE:** Identification of integrin beta1 as a prognostic biomarker for human lung adenocarcinoma using 2D-LCMS/MS combined with iTRAQ technology.

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


●●Enlace al texto completo (gratuito o de pago) 3892/or.2013.2477

**AUTORES / AUTHORS:** Zhang PF; Zeng GQ; Yi LZ; Liu JP; Wan XX; Qu JQ; Li JH; Li C; Tang CE; Hu R; Ye X; Chen Y; Chen ZC; Xiao ZQ

**INSTITUCIÓN / INSTITUTION:** Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China.

**RESUMEN / SUMMARY:** To discover novel lung adenocarcinoma (AdC) biomarkers, isobaric tags for relative and absolute quantitation (iTRAQ)-tagging combined with 2D-LC-MS/MS analysis was used to identify differentially expressed plasma membrane proteins in lung AdC and paired paraneoplastic normal lung tissues (PNLTs) adjacent to tumors. In this study, significant caveolin-1 downregulation and integrin beta1 upregulation was observed in primary lung AdC vs. PNLT. As there has been no report on the association of integrin beta1 with lung AdC, immunohistochemical staining was performed to detect the expression of integrin beta1 in an independent set of archival tissue specimens including 42 cases of PLNT, 46 cases of without lymph node metastasis primary AdC (non-LNM AdC) and 62 cases of LNM AdC; the correlation of their expression levels with clinicopathological characteristics and clinical outcomes were evaluated. Based on the data, upregulation of integrin beta1 was significantly correlated with advanced clinical stage and lymph node metastasis. Integrin beta1 overexpression was significantly associated with advanced clinical stage (P<0.05), lymph node metastasis (P<0.05), increased relapse rate (P<0.05) and decreased overall survival (P<0.05) in AdCs. Cox regression analysis indicated that integrin beta1 overexpression is an independent prognostic factor. The data suggest that integrin beta1 is a potential biomarker for LNM and prognosis of AdC and integrin beta1 upregulation may play an important role in the pathogenesis of AdC.

[402]
Modulation of u-PA, MMPs and their inhibitors by a novel nutrient mixture in human lung cancer and mesothelioma cell lines.

Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 3892/ijo.2013.1880

Roomi MW; Kalinovsky T; Niedzwiecki A; Rath M

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Lung cancer, the most prevalent cancer worldwide and malignant mesothelioma are highly aggressive tumors that are characterized by high levels of matrix metalloproteinase (MMP)-2 and -9 secretion. Proteases play a key role in tumor cell invasion and metastasis by digesting the basement membrane and ECM components. Strong clinical and experimental evidence demonstrates association of elevated levels of u-PA and MMPs with cancer progression, metastasis and shortened patient survival. MMP activities are regulated by specific tissue inhibitors of metalloproteinases (TIMPS). Our main objective was to study the effect of a nutrient mixture (NM) on the activity of u-PA, MMPs and TIMPs on human lung and malignant mesothelioma (MM) cell lines. Human lung cancer (A-549 and Calu-3) and malignant mesothelioma (MSTO-211H) cell lines were cultured in their respective media and treated at confluence with NM at 0, 50, 100, 250, 500 and 1000 microg/ml. Analysis of u-PA activity was carried out by fibrin zymography, MMPs by gelatinase zymography and TIMPs by reverse zymography. Both lung cancer cell lines expressed u-PA, which was inhibited by NM in a dose-dependent manner. However, no bands corresponding to u-PA were detected for the MSTO-211H MM cell line. On gelatinase zymography, A-549 cells showed one band corresponding to MMP-2 and induction of MMP-9 with PMA (100 ng/ml) treatment. MSTO-211H showed two bands, an intense band corresponding to MMP-2 and a faint band corresponding to MMP-9; MMP-9 was enhanced significantly with PMA treatment. NM inhibited their expression in both cell lines in a dose-dependent manner. Calu-3 showed no MMP-2 or MMP-9 expression. Activity of TIMPs was upregulated by NM in all cancer cell lines in a dose-dependent manner. Analysis revealed a positive correlation between u-PA and MMPs and a negative correlation between u-PA/MMPs and TIMPs. These findings suggest the therapeutic potential of NM in the treatment of lung and mesothelioma cancers.

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Ciliary body medulloepithelioma associated with pleuropulmonary blastoma.

Enlace al Resumen / Link to its Summary

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The mitochondrial dysfunction plays an important role in urethane-induced lung carcinogenesis.

Mitochondrial dysfunction is an important factor as genetic change in controlling the growth of tumors. The current study explored whether mitochondrial dysfunction correlated with urethane-induced lung carcinogenesis in BALB/c and C57BL/6 mice that were given single- or multi-dose intraperitoneal injections of urethane. We found that mice susceptible to lung tumor formation displayed a rapid increase in the respiratory control ratio in lung mitochondria after urethane exposure, whereas resistant mice that failed to develop lung tumors maintained the same respiratory control ratio as normal, untreated mice. Furthermore, repeated urethane administration or continuous 2,4-dinitrophenol (an uncoupling agent of oxidative phosphorylation) treatment, following a single urethane exposure, could overcome resistance to carcinogenesis. In contrast, multi-dose urethane-treated mice that received genipin (a highly selective inhibitor of uncoupling protein 2) following their first dose of urethane showed a lower tumor incidence. In addition, a higher uncoupling protein 2 level and a lower complex IV level in the lungs correlated with subsequent tumor formation in BALB/c and C57BL/6 mice. In vitro, urethane suppressed cell proliferation and induced soft-agar colonies in parental L929 cells with complete mitochondrial DNA but not in rho degrees L929 cells lacking mitochondrial DNA. These studies suggest that abrogation of mitochondrial is essential during urethane induced lung carcinogenesis and that uncoupling inhibition can reverse cancer morphogenesis, thus presenting an appealing method to prevent lung carcinogenesis.
Since the publication of the Radiologic Diagnostic Oncology Group Report in 1991, the clinical application of pulmonary magnetic resonance imaging (MRI) in patients with lung cancer has been limited. In contrast, MRI for lung cancer has undergone continuous development, and several promising techniques have been introduced to overcome the previously suggested limitations. In addition, comparative studies involving multidetector-row computed tomography and positron emission tomography or positron emission tomography/computed tomography with 2-deoxy-2-[F]fluoro-D-glucose have shown useful new clinical applications for MRI in lung cancer. Moreover, MRI can provide not only morphologic information based on various parameters such as T1 and T2 relaxation times, tissue diffusion, perfusion, etc. but also functional information; it also has a significant role in nuclear medicine studies. In this review article, we describe recent advances made in MRI with respect to lung cancer, focusing on (1) detection of solid pulmonary nodules; (2) characterization of solid pulmonary nodules; (3) TNM staging assessment using chest and whole-body MRI examinations; (4) prediction of postsurgical lung function; and (5) prediction of tumor treatment response. We believe that further basic studies, as well as studies on clinical applications of new MRI techniques, are important for improving the management of lung cancer patients.
Glycoprotein nonmetastatic melanoma B (GPNMB) is a type I transmembrane glycoprotein which is overexpressed in many tumors and seems to play a critical role in metastasis of malignant tumors. The purpose of this study was to determine GPNMB expression in small cell lung cancer (SCLC) and analyze the prognostic value in patients with SCLC. A total of 132 cases of SCLCs were analyzed immunohistochemically on tissue microarrays (TMAs). Patients were divided into weak-positive and strong-positive GPNMB groups. In addition, serum GPNMB was evaluated by enzyme-linked immunosorbent assay (ELISA). The average serum GPNMB concentration was 1054.15 +/- 363.71 pg/mL in the weak-positive group, 2611.52 +/- 457.57 pg/mL in the strong-positive group, and 427.61 +/- 273.9 pg/mL in the control. The strong-positive group showed significantly higher serum GPNMB levels than the weak-positive group and healthy control (p < 0.01). Overall survival in the weak-positive GPNMB group was significantly longer than in the strong-positive group (27 months vs 15 months, p < 0.01). These results suggest that the expression of GPNMB may be useful as a prognostic indicator in patients with SCLC.
For cases living within a 500-m radius of the plant, the geographical location in relation to the factory was also assessed. RESULTS: The incidence rate of environmental pleural mesothelioma was higher in the population living within 500 m of the plant than in those living in a radius of 500-2000 m and much higher than those living at 2000-10 000 m. The highest incidence rate ratio for pleural mesothelioma (161.9) was found in the southeast quadrant of the 500-m area, coinciding with the predominant wind direction. CONCLUSIONS: Residential distance from an industrial source of asbestos and local wind conditions have a considerable impact on the risk of developing environmental pleural mesothelioma.

[408]
TÍTULO / TITLE: - Accurate diagnosis of mesothelioma: more important than ever.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 5858/arpa.2012-0260-ED
AUTORES / AUTHORS: - Allen TC
INSTITUCIÓN / INSTITUTION: - From the Department of Pathology, University of Texas Health Science Center, Tyler.

[409]
TÍTULO / TITLE: - Fate of newly detected lesions during postoperative surveillance for 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.2013.03.084
AUTORES / AUTHORS: - Lee JI; Lee YJ; Park KY; Park CH; Jeon YB; Choi CH; Ko KP
INSTITUCIÓN / INSTITUTION: - Department of Thoracic and Cardiovascular Surgery, Gachon University Gil Hospital, Incheon, Korea. Electronic address: pitz@hanmail.net.
RESUMEN / SUMMARY: - BACKGROUND: Chest computed tomography (CT) is the mainstay of postoperative surveillance for non-small cell lung cancer (NSCLC). However, there is no clear consensus about the optimal management of newly detected lesions on follow-up CT. Our goals were (1) to determine the eventual outcome of newly detected lesions on follow-up CT in patients with
previously resected NSCLC and (2) to determine the characteristics of the detected lesions that suggest recurrence. METHODS: In this retrospective study, we investigated 116 patients with NSCLC who underwent operations between February 2004 and December 2011 and had newly detected lesions on postoperative surveillance CT at least once during the follow-up period (median, 29 months). We investigated lesion size, growth, laterality, multiplicity, and recurrence patterns, as well as demographic data. RESULTS: One hundred fifty-seven new lesions were detected during the follow-up period. Of the 157 lesions, 139 were intrathoracic (lung, 83; lymph node, 34; pleura, 14; others, 8) and 18 were extrathoracic. Further investigation or follow-up confirmed that 78 lesions (49.7% [78 of 157]) were recurrences. Extrathoracic lesions showed a higher correlation with recurrence compared with intrathoracic ones (83.3% versus 45.3%; p = 0.002). Regarding lung lesions, solid nodules (p = 0.003; hazard ratio, 13.190) and lesions in patients with stage III disease (p = 0.043; hazard ratio, 6.464), were much more likely to reflect recurrence. CONCLUSIONS: In patients with newly detected lesions on follow-up chest CT after resection of NSCLC, special attention should be paid to lesions with the following characteristics: extrathoracic lesions, solid lung nodules, and lung lesions in patients with stage III disease. It is necessary to investigate these lesions more aggressively because they suggest the presence of recurrent disease.
that 63 patients had increased level of OLC1. The 5-year overall survival (OS) rates of patients with high OLC1 expression and low OLC1 expression were 24.8% and 75.2%, respectively (hazard ratio: 21.43, 95% CI: 2.54, 7.12, \( P < 0.0001 \)). The 5-year progression-free survival (PFS) rates were 30.1% for patients in the high-expression group and 69.9% for patients in the low OLC1 expression group (hazard ratio: 17.04, 95% CI: 0.33, 5.96, \( P < 0.0001 \)).


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[411]

TÍTULO / TITLE: - Thrombocytosis has a negative prognostic value in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Maraz A; Furak J; Varga Z; Kahan Z; Tiszlavicz L; Hideghety K
INSTITUCIÓN / INSTITUTION: - Department of Oncotherapy, University of Szeged, Szeged, Hungary. dr.manna@freemail.hu
RESUMEN / SUMMARY: - BACKGROUND: Solid tumours have worse prognosis when associated with thrombocytosis. Our study assessed the prognostic value of thrombocytosis, and its relation with smoking habits in lung cancer.

PATIENTS AND METHODS: A total of 398 patients were operated on then divided into two groups, those with normal platelet counts (n=312), and those with thrombocytosis (n=86); 348 out of 398 patients had data for smoking habits (99 non-smokers, 249 smokers). RESULTS: The frequency of thrombocytosis was 18.6%, 19.3%, 27.5 and 28.6% in patients with tumor stages I to IV, respectively. Thrombocytosis appeared most frequently in patients with squamous cell lung cancer, and among smokers. The overall 5-year survival was worse in patients with thrombocytosis (p<0.001). By uni- and multivariate analyses, platelet count, and T and N status were found to be independent prognostic factors. CONCLUSION: Our study indicates that the presence of perioperative thrombocytosis in patients undergoing surgery should be considered as an independent prognostic factor of poor survival, and should be taken into account in regard to therapy.

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[412]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
BACKGROUND: The TP53 codon 72 polymorphism has been associated with the individual susceptibility to lung cancer. However, the association remains uncertain and varies with ethnicity, smoking status, cancer histology, and stage. METHODS: We performed a meta-analysis to evaluate the relationship between TP53 Arg72Pro polymorphism and lung cancer susceptibility basing on 15,647 lung cancer patients and 14,391 controls from 36 published literatures. We also performed stratified analysis in populations of different ethnicities, smoking statuses, lung cancer stages, and histological types. RESULTS: The analysis showed a significantly increased lung cancer susceptibility among Pro allele carriers (P < 0.001, odds ratio (OR) = 1.14, 95% confidence interval (CI) = 1.1-1.19), especially for smokers (P < 0.001, OR = 1.29, 95% CI = 1.12-1.47). Stratified analysis indicated that Pro72 elevates lung cancer susceptibility in Asians, while it has no effect on lung cancer risk of Caucasians. Moreover, Pro carriers present an increased risk of developing squamous cell carcinoma and adenocarcinoma, instead of large cell carcinoma and small cell carcinoma. Interestingly, patients with the Pro allele seemed to be diagnosed with lung cancer at the early stages (stage I-II, P = 0.008, OR = 1.2, 95% CI = 1.05-1.37). CONCLUSIONS: Our results suggest that the Pro allele acts as a risk factor for development of lung cancer, especially for smokers and Asians.
small cell lung cancer (NSCLC) than corresponding normal tissues (P<0.001). In addition, up-regulation of H4K16 acetylation was also more frequent in NSCLC than normal tissues (P=0.002). Furthermore, hMOF promotes the cell proliferation, migration and adhesion of NSCLC cell lines. Microarray analysis and chromatin immunoprecipitation (ChIP) assays suggest that hMOF modulates proliferation and metastasis by regulating histone H4K16 acetylation at the promoter regions of downstream target genes. Moreover, hMOF promotes S phase entry via Skp2. These findings suggest that hMOF contributes to NSCLC tumorigenesis.

[414] TÍTULO / TITLE: - Ectopic Cushing’s Syndrome Secondary to Pulmonary Carcinoid Tumor.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hashemzadeh S; Asvadi Kermani A; Ali-Asgharzadeh A; Halimi M; Soleimani M; Ladan A
INSTITUCIÓN / INSTITUTION: - Tuberculosis and Lung Diseases Research Center, Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
RESUMEN / SUMMARY: - Adrenocorticotropic hormone (ACTH) overproduction within the pituitary gland or ectopically leads to hypercortisolism. In this study a case of Cushing’s syndrome caused by an ectopic ACTH-secreting carcinoid tumor in lung is discussed, as are the available diagnostic procedures. The patient was a 28-year-old woman with clinical features starting about 6 months previously. The results of her biochemical tests suggested ectopic Cushing’s syndrome. Full-body computed tomography revealed a single nodule in the inferior lobe of the right lung. After removal of the nodule, the patient’s symptoms subsided clinically, and laboratory tests confirmed remission of the hypercortisolism.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hashemzadeh S; Asvadi Kermani A; Ali-Asgharzadeh A; Halimi M; Soleimani M; Ladan A
INSTITUCIÓN / INSTITUTION: - Tuberculosis and Lung Diseases Research Center, Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[AUTORES / AUTHORS: - Hochhegger B; Zanetti G; Marchiori E  
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

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

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

AUTORES / AUTHORS: - Mateen S; Raina K; Agarwal R
INSTITUCIÓN / INSTITUTION: - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences.
RESUMEN / SUMMARY: - The use of systemic chemotherapeutic drugs and molecular-targeted therapies in the treatment of patients with locally advanced or metastatic lung cancer has its limitations due to the associated acute and cumulative dose limiting toxicities and acquisition of drug resistance. Prevention and therapeutic intervention by dietary agents including nutraceuticals which are non-toxic, cost-effective, and physiologically bioavailable, are emerging approaches in lung cancer management. In this regard, silibinin, a natural flavonolignan, has been rigorously evaluated for the prevention and growth control of lung cancer through extensive in vitro and in vivo studies. Successful studies conducted so far, have established that silibinin is effective both alone and in combination with other agents (e.g., chemotherapeutic and epigenetic agents) in significantly inhibiting the growth of lung cancer cells. In vivo, its effects have been shown to be mediated through inhibition of proliferation, angiogenesis and epigenetic—related events. Therefore, the present review focuses on encompassing the efficacy and mechanisms of silibinin against lung cancer.

[Link al texto completo (gratuito o de pago)]

AUTORES / AUTHORS: - Chen P; Li J; Wang Y; Zhu LR; Hu YM; Tong XP
INSTITUCIÓN / INSTITUTION: - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences.
RESUMEN / SUMMARY: - The use of systemic chemotherapeutic drugs and molecular-targeted therapies in the treatment of patients with locally advanced or metastatic lung cancer has its limitations due to the associated acute and cumulative dose limiting toxicities and acquisition of drug resistance. Prevention and therapeutic intervention by dietary agents including nutraceuticals which are non-toxic, cost-effective, and physiologically bioavailable, are emerging approaches in lung cancer management. In this regard, silibinin, a natural flavonolignan, has been rigorously evaluated for the prevention and growth control of lung cancer through extensive in vitro and in vivo studies. Successful studies conducted so far, have established that silibinin is effective both alone and in combination with other agents (e.g., chemotherapeutic and epigenetic agents) in significantly inhibiting the growth of lung cancer cells. In vivo, its effects have been shown to be mediated through inhibition of proliferation, angiogenesis and epigenetic—related events. Therefore, the present review focuses on encompassing the efficacy and mechanisms of silibinin against lung cancer.

[Link al texto completo (gratuito o de pago)]

AUTORES / AUTHORS: - Chen P; Li J; Wang Y; Zhu LR; Hu YM; Tong XP
INSTITUCIÓN / INSTITUTION: - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences.
RESUMEN / SUMMARY: - The use of systemic chemotherapeutic drugs and molecular-targeted therapies in the treatment of patients with locally advanced or metastatic lung cancer has its limitations due to the associated acute and cumulative dose limiting toxicities and acquisition of drug resistance. Prevention and therapeutic intervention by dietary agents including nutraceuticals which are non-toxic, cost-effective, and physiologically bioavailable, are emerging approaches in lung cancer management. In this regard, silibinin, a natural flavonolignan, has been rigorously evaluated for the prevention and growth control of lung cancer through extensive in vitro and in vivo studies. Successful studies conducted so far, have established that silibinin is effective both alone and in combination with other agents (e.g., chemotherapeutic and epigenetic agents) in significantly inhibiting the growth of lung cancer cells. In vivo, its effects have been shown to be mediated through inhibition of proliferation, angiogenesis and epigenetic—related events. Therefore, the present review focuses on encompassing the efficacy and mechanisms of silibinin against lung cancer.

[Link al texto completo (gratuito o de pago)]

AUTORES / AUTHORS: - Chen P; Li J; Wang Y; Zhu LR; Hu YM; Tong XP
INSTITUCIÓN / INSTITUTION: - a Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences.
RESUMEN / SUMMARY: - The use of systemic chemotherapeutic drugs and molecular-targeted therapies in the treatment of patients with locally advanced or metastatic lung cancer has its limitations due to the associated acute and cumulative dose limiting toxicities and acquisition of drug resistance. Prevention and therapeutic intervention by dietary agents including nutraceuticals which are non-toxic, cost-effective, and physiologically bioavailable, are emerging approaches in lung cancer management. In this regard, silibinin, a natural flavonolignan, has been rigorously evaluated for the prevention and growth control of lung cancer through extensive in vitro and in vivo studies. Successful studies conducted so far, have established that silibinin is effective both alone and in combination with other agents (e.g., chemotherapeutic and epigenetic agents) in significantly inhibiting the growth of lung cancer cells. In vivo, its effects have been shown to be mediated through inhibition of proliferation, angiogenesis and epigenetic—related events. Therefore, the present review focuses on encompassing the efficacy and mechanisms of silibinin against lung cancer.
The purpose of this study was to investigate the diagnostic value of the deletion of fragile histidine triad (FHIT) and p16INK4a (p16) mRNA in biopsies obtained by bronchoscopy. Biopsies were analyzed using RT-PCR in 52 patients with lung cancer and 19 patients with benign lung disease. The results showed that the detection rates of FHIT and p16 gene transcript deletion were significantly higher in lung cancer patients than in patients with benign lung disease (65.4% versus 10.5%, p=0.001 and 59.6% versus 5.3%, p<0.001, respectively). The sensitivities for detecting FHIT and p16 transcript deletion in biopsies were 65.4% and 59.6% (combined 80.8%), respectively, which were markedly better than those of histology and cytology (42.3% and 34.6%, respectively; combined 57.7%). In 22 lung cancer patients with negative histology and cytology at initial bronchoscopy, FHIT and p16 mRNA loss was detected in 40.9% (9/22) and 36.4% (8/22) cases, respectively. FHIT mRNA loss was associated with smoking status in lung cancer patients. In conclusion, deletion of FHIT and p16 mRNA can be identified in biopsies obtained during bronchoscopic procedures. FHIT and p16 mRNA deletion can be used as biomarkers in the clinical diagnosis of lung cancer and may serve as adjuncts to histology and cytology in lung cancer diagnosis.

Inhibition of CK2 enhances UV-triggered apoptotic cell death in lung cancer cell lines.

Lung cancer is a high-grade malignancy with poor 5-year survival rates that remains incurable with current therapies. Different cellular stresses, including antitumor agents, ionizing radiation and ultraviolet (UV) light, can induce apoptosis and activate signaling pathways. UV has multiple effects on tumor cells, including DNA damage, and increases the expression of some genes involved in tumor cell apoptosis and DNA repair. It has been reported that UV can also activate casein kinase 2 (CK2). CK2, a Ser/Thr protein kinase, has been reported to be frequently overexpressed in various types of human cancer, including lung cancer, and is associated with tumor development. Thus, combination of UV and CK2 inhibitors may be a new...
strategy for the treatment of lung cancer. Our results demonstrated that inhibition of CK2a through CK2 siRNA or a CK2 inhibitor [(4,5,6,7-tetrabromobenzotriazole (TBB)] enhances the decrease in cell viability of lung cancer cells (A549 and H2030) induced by UV. Western blot analysis demonstrated that the combination increased the expression of apoptotic protein markers cytochrome c and the cleavage of poly ADP-ribose polymerase (PARP) and caspase-3. Furthermore, our results indicated that UV decreased the expression of the tumor suppressor protein PML through activation of CK2. Inhibition of CK2 by CK2 siRNA and TBB can recover the reduction of PML induced by UV. Collectively, these results demonstrate the significant apoptosis of lung cancer cells induced by combination treatment of the CK2 inhibitor and UV radiation. CK2 enhanced cell apoptosis by UV radiation may due, at least partly, to recover the expression of PML. These findings warrant the clinical testing of CK2 inhibitors which, when used in conjunction with DNA-damaging agents such as radiation, may be an effective cancer therapeutic strategy.

[419]

TÍTULO / TITLE: - Mixed Form of Pericardial Mesothelioma with Osseous Differentiation in a Dog.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

●●Enlace al texto completo (gratuito o de pago) 1016/j.jcpa.2013.01.009

AUTORES / AUTHORS: - Yamamoto S; Fukushima R; Kobayashi M; Machida N
INSTITUCIÓN / INSTITUTION: - Laboratory of Veterinary Clinical Oncology, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan.

RESUMEN / SUMMARY: - An 8-year-old female Yorkshire terrier was referred for evaluation and treatment of recurrent pericardial effusion. Echocardiographic examination revealed a markedly and irregularly thickened pericardial sac with frequent hyperechoic areas with acoustic shadows. Pericardiocentesis produced only a small amount of thick serosanguineous fluid. The dog underwent subtotal pericardiectomy, but died during surgery. At necropsy examination, the heart was encased by voluminous, grey-white to red-tan, soft to firm proliferative tissue arising from the pericardial sac. The pericardial cavity was obliterated. Microscopically, the tissue was predominantly sarcomatoid with osseous differentiation and epithelioid elements were admixed with bundles of spindle cells. Immunohistochemically, the constituent cells, especially those that were epithelioid, co-expressed cytokeratin and vimentin. A diagnosis of mixed form pericardial mesothelioma with osseous differentiation was made. This appears to be the first report of such a tumour in a dog.
Primary solitary extramedullary plasmacytoma involving the true vocal cords in a pregnant woman.

Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Ghatak S; Dutta M; Kundu I; Ganguly RP

INSTITUCIÓN / INSTITUTION: Department of Otorhinolaryngology and Head-Neck Surgery, RG Kar Medical College and Hospital, Kolkata, West Bengal, India.

RESUMEN / SUMMARY: Primary solitary extramedullary plasmacytoma of the larynx involving the true vocal cords is an extremely rare entity. Extramedullary plasmacytoma has the potential to transform into multiple myeloma and mandates strict vigilance and routine follow-up. We describe such a case in a 29-year-old pregnant woman who presented with progressive hoarseness, dysphagia and intermittent respiratory difficulty. Fiberoptic laryngoscopy revealed a fleshy mass involving the posterior third of the true vocal cords, encroaching on the ventricle and false cords. Histopathology and immunohistochemistry revealed extramedullary plasmacytoma of a monoclonal nature. In spite of Bence Jones proteinuria and a rising serum beta 2-microglobulin level, a thorough search for metastasis and subsequent treatment with radiotherapy were delayed due to the patient’s pregnancy. She is the youngest adult ever reported with primary solitary extramedullary plasmacytoma involving the true cords. Described for the first time in pregnancy, the relevant issues in management are highlighted.

Cytomorphologic overlap of differentiated thyroid carcinoma and lung adenocarcinoma and diagnostic value of TTF-1 and TGB on cytologic material.

Enlace al Resumen / Link to its Summary


AUTORES / AUTHORS: Sathiyamoorthy S; Maleki Z

INSTITUCIÓN / INSTITUTION: Department of Pathology, Division of Cytopathology, The Johns Hopkins Hospital, Baltimore, Maryland.

RESUMEN / SUMMARY: Thyroid carcinomas and lung adenocarcinoma share cytomorphological features yet have different prognoses. Thyroid Transcription Factor-1 (TTF-1) is an immunohistochemical (IHC) marker used to confirm pulmonary and thyroid carcinoma, while Thyroglobulin (TGB) is expressed by thyroid carcinoma. The cytopathology archive of The Johns Hopkins Hospital
was searched for cases of lung adenocarcinoma versus thyroid carcinoma with TTF-1 and TGB IHC. Forty-four cases of lung adenocarcinoma (25) and thyroid carcinoma (19) were retrieved. One was metastatic lung adenocarcinoma to the thyroid and three were metastatic papillary thyroid carcinoma (PTC) to the lung. The initial interpretation of two cases from bony lesions was metastatic lung adenocarcinoma. In light of additional clinical information and TGB immunostain, the diagnoses of these two cases changed to metastatic thyroid carcinoma. TTF-1 and TGB is a small immunostain panel that can differentiate lung adenocarcinoma from thyroid carcinoma and prevent misdiagnosis and its consequences. Diagn. Cytopathol. 2013. © 2013 Wiley Periodicals, Inc.

[422]
TÍTULO / TITLE: - Angiogenesis of lung cancer utilizes existing blood vessels rather than developing new vessels using signals from carcinogenesis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Uramoto H; Yamada S; Tanaka F
INSTITUCIÓN / INSTITUTION: - Second Department of Surgery, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. hidetaka@med.uoeh-u.ac.jp.
RESUMEN / SUMMARY: - Cancer cells metastasize via angiogenesis and are a long-standing therapeutic target in malignant tumors. Vascular endothelial growth factor (VEGF) antibodies have been developed for clinical use, with limited benefits. Therefore, identifying the underlying mechanisms of angiogenesis regarding whether tumor vessels are derived from cancer cells or blood vessels in existence, is highly anticipated. Recently, epidermal growth factor receptor (EGFR) antibodies were utilized to detect cancer cells with somatic mutations of EGFR. The concordance rate is high for detection between immunohistochemical staining and polymerase chain reaction (PCR)-based methods. We hypothesized that endothelial cells exhibiting lymphatic and venous tumor invasiveness will be immunoreactive if new blood vessels are derived from the lung cancer itself, because EGFR mutations occur at a relatively early phase in carcinogenesis. We examined endothelial cells with EGFR mutations exhibiting lymphatic and venous tumor invasiveness using these antibodies. Tumor samples were obtained from 848 consecutive patients with lung cancer. Among 153 of 595 adenocarcinomas with EGFR-sensitive mutations, the number of lymphatic and venous invasive tumors was 35 and 19, respectively. Consequently, 12 available tumor specimens (five specimens for delE746-A750 and seven specimens for L858R) with both factors were evaluated. The main cancer cells were highly immunoreactive; however, no obvious lesions were detected with endothelial cells exhibiting lymphatic or venous invasiveness. Therefore, the angiogenesis of lung cancer seems to
utilize blood vessels in existence, rather than create new vessels using signals from carcinogenesis.

[423]
TÍTULO / TITLE:  - Intra-abdominal bronchogenic cyst: a challenge in diagnosis and management.
RESUMEN / SUMMARY:  - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS:  - Kfoury E; Moynihan JJ
INSTITUCIÓN / INSTITUTION:  - Inova Fairfax Hospital, Department of Surgery, Falls Church, Virginia 22042, USA. elias.kfoury@hotmail.com

[424]
TÍTULO / TITLE:  - Fengycin inhibits the growth of the human lung cancer cell line 95D through reactive oxygen species production and mitochondria-dependent apoptosis.
RESUMEN / SUMMARY:  - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1097/CAD.0b013e3283611395
AUTORES / AUTHORS:  - Yin H; Guo C; Wang Y; Liu D; Lv Y; Lv F; Lu Z
INSTITUCIÓN / INSTITUTION:  - aLaboratory of Enzyme Engineering, College of Food Science and Technology, Nanjing Agricultural University bState Key Laboratory of Natural Medicines, China Pharmaceutical University cDepartment of Microbiology, Institute of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu Province, China.
RESUMEN / SUMMARY:  - To investigate the antitumor activity and action mechanism of fengycin using the human lung cancer cell line 95D. The antitumor activity of fengycin was tested in vitro and in vivo. Reactive oxygen species production, Ca uptake, and mitochondrial membrane potential loss induced by fengycin in 95D cells were measured by flow cytometry and a laser confocal microscope. Lactate dehydrogenase release and caspase activity in fengycin-treated 95D cells were assayed using cytotoxicity detection kits. Apoptosis triggered by fengycin was identified by 4,6-diamidino-2-phenylindole (DAPI) staining and flow cytometry. The effects of fengycin on cell-cycle and apoptosis-related proteins were evaluated by quantitative reverse-transcription PCR and western blot. Treatment with fengycin not only significantly decreased cell proliferation in various cancer cell lines including 95D but inhibited the growth of xenografted 95D cells in nude mice. Fengycin also induced reactive oxygen species production and Ca uptake, as well as lactate dehydrogenase
release and mitochondrial membrane potential loss. Further experiments showed that fengycin could trigger apoptosis in 95D cells and cause cell-cycle arrest at the G0/G1 stage by downregulating cyclin D1 and cyclin-dependent kinase 4 (CDK4). While investigating caspase activity and the expression of apoptosis-related proteins, fengycin was found to induce apoptosis in 95D cells through the mitochondrial pathway, evidenced by increased caspase activity, Bax expression, and cytochrome c release into the cytoplasm, as well as decreased Bcl-2 levels. Fengycin can inhibit the growth of the cancer cell line 95D by regulating the cell cycle and promoting apoptosis, suggesting that it may have potential as an anticancer treatment.

[425]
TÍTULO / TITLE: - The oncological value of video-assisted thoracoscopic lobectomy for early-stage non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Baisi A; Raveglia F; De Simone M; Cioffi U
INSTITUCIÓN / INSTITUTION: - Thoracic Surgery Unit, Azienda Ospedaliera San Paolo, University of Milan, Milan, Italy.

[426]
TÍTULO / TITLE: - Phosphorylation of eIF2alpha Suppresses Cisplatin-Induced A549 Cell Apoptosis via p38 Inhibition.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Guo L; Chen R; Ma N; Xiao H; Chen Y; Chen F; Mei J; Ding F; Zhong H
INSTITUCIÓN / INSTITUTION: - 1 Department of Cardio-Thoracic Surgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200092, P.R. China.
RESUMEN / SUMMARY: - Abstract Cisplatin-based chemotherapy is considered a golden standard for treatment of advanced non-small cell lung cancer (NSCLC). However, drug resistance is one of the major problems in NSCLC chemotherapy. The mechanisms and related biological pathways that contribute to chemoresistance are relatively poorly understood. Here, we demonstrated that the phosphorylation of eukaryotic translation initiation factor 2alpha (eIF2alpha) suppresses cisplatin-induced A549 cell apoptosis. Cisplatin induced eIF2alpha phosphorylation through protein kinase RNA. Importantly, phospho-eIF2alpha inhibited cisplatin-induced A549 cells apoptosis, at least in part, by
suppressing the p38 pathway. Moreover, analysis of tissue microarrays information demonstrated that phospho-eIF2alpha predicted a poor prognosis in patients with NSCLC. Taken together, these results provide a potential mechanism that is used for explaining how eIF2alpha promotes cisplatin resistance in A549 cells. Therefore, the regulation of eIF2alpha may improve treatment outcomes of cisplatin-based chemotherapy for patients with NSCLC.

[427]

**TITULO / TITLE:** Potential importance of Maackia amurensis agglutinin in non-small cell lung cancer.

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


**AUTORES / AUTHORS:** Mehta S; Chhetra R; Srinivasan R; Sharma SC; Behera D; Ghosh S

**RESUMEN / SUMMARY:** Abstract Maackia amurensis agglutinin is a NeuNAcα(2-3) Galβ(1-4) GlcNAc/Glc specific lectin, which was shown to have diagnostic potential in cancer of different origin. In the previous report, we have demonstrated that GM3 specific IgG from bronchoalveolar lavage fluid (BALF) of non-small cell lung cancer (NSCLC) patients interacted with ~66kDa membrane glycoprotein band of NSCLC cell lines, which was also recognized by this lectin. This observation prompted us to assess the potential of Maackia amurensis agglutinin in NSCLC. Accordingly, we examined the reactivity of this lectin with NSCLC cell lines as well as the tissue biopsies and cells obtained from fine needle aspirations of NSCLC patients. Maackia amurensis agglutinin showed strong reactivity specifically with cells and biopsy samples of NSCLC origin. Further, this lectin was found to induce apoptosis in NSCLC cells. The mechanism of this lectin induced apoptosis involved downregulation of Bcl-XL, upregulation of Bax, release of cytochrome c and activation of procaspase-3. Collectively our results have suggested that Maackia amurensis agglutinin may have the potential to serve as a unique probe for detection of NSCLC and also as a specific apoptosis inducing agent in NSCLC cells.

[428]

**TITULO / TITLE:** Well-differentiated papillary mesothelioma, possibly giving rise to diffuse malignant mesothelioma: A case report.

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


**AUTORES / AUTHORS:** Mehta S; Chhetra R; Srinivasan R; Sharma SC; Behera D; Ghosh S
Well-differentiated papillary mesothelioma (WDPM) is a distinct subtype of mesothelial tumor from diffuse malignant mesothelioma (DMM), with an uncertain malignant potential. The relationship between WDPM and DMM, with regard to the ability of the former to develop into the latter, is also unknown. A 58-year-old woman, diagnosed with a rectal carcinoid tumor, underwent removal of the lymph nodes via the abdomen in 2004. A large number of white miliary nodules were identified on the mesentery and peritoneum, which were histologically diagnosed as WDPM. No further therapy was administered, but the patient was followed-up using imaging methods. Seven years later, an abdominal wall mass was discovered using positron emission tomography-computed tomography, and a laparotomy biopsy was performed. DMM was diagnosed, because mesothelioma with extended invasion had been histologically identified. Mesothelioma similar to papillary proliferation was present on the outer layer of the peritoneum, and an infiltrating lesion with continuous restiform or solid-like structures was noted. WDPM was believed to have undergone malignant transformation. Compared to DMM, WDPM has a good prognosis and is considered a benign or borderline neoplasm. Our findings suggest that WDPM does have malignant potential, however, because histological findings indicated a malignant transformation of WDPM to DMM.

[429]

TÍTULO / TITLE: - Subtyping of nonsmall cell lung cancer on cytology specimens: Reproducibility of cytopathologic diagnoses on sparse material.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Silje Haukali O; Henrik H; Olsen EK; Birthe T; Guldhammer SB
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Denmark.
RESUMEN / SUMMARY: - Cytologic examination of fine-needle aspiration (material is increasingly used in diagnosing lung cancer. High interobserver agreement in distinguishing small-cell lung cancer from nonsmall-cell lung cancer (NSCLC) on cytologic material has been demonstrated. Because of new treatment-modalities, subclassification of NSCLC into squamous cell carcinoma (SQC) and non-SQC has clinical impact. Subclassification based on morphology alone may be difficult, but applying immunohistochemistry (IHC) to
clot-material has proved helpful. When insufficient material is available to make a clot from the aspirate, cytoscrape (CS) can convert cytologic material into tissue fragments useful for IHC. The purpose of this study was to test the reproducibility of pulmonary malignant diagnoses, in particular distinction between subgroups of NSCLC, based on smeared material and IHC on CS. A consecutive series of May-Grunwald-Giemsa (MGG) stained smears and CS with IHC on material from 79 patients suspected of having lung cancer was included. The material was circulated twice to four pathologists. The diagnoses were categorized in five groups: SQC, adenocarcinoma of the lung, non-SQC, benign lesion and other forms of malignancy, including metastases. Reproducibility was analyzed using Kappa statistics. Interobserver reproducibility of the diagnoses in round 1 was good to very good (kappa 0.57-0.71) and very good in round 2 (0.63-0.80). Reproducibility of subclassification of NSCLC based on MGG stained smear and IHC on CS, was very good among experienced pathologists. With only sparse material available, CS should be used to achieve reproducible diagnoses, including subtyping of NSCLC. Diagn. Cytopathol. 2013. Esta es una cita bibliográfica que va por delante de la publicación en papel. La fecha indicada en la cita provista, NO corresponde con la fecha o la cita bibliográfica de la publicación en papel. La cita bibliográfica definitiva (con el volumen y su pagination) saldrá en 1 ó 2 meses a partir de la fecha de la emisión electrónica-online. *** This is a bibliographic record ahead of the paper publication. The given date in the bibliographic record does not correspond to the date or the bibliographic citation on the paper publication. The publisher will provide the final bibliographic citation (with the volume, and pagination) within 1 or 2 months from the date the record was published online. © 2013 Wiley Periodicals, Inc.
Epigenetics and Tumorigenesis, Tianjin Research Center of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China.

RESUMEN / SUMMARY: p66Shc, one of the SHC1 gene encoding proteins, promotes cell death and reports cell anchorage status, mediating anoikis in vitro and functioning as a metastasis suppressor in vivo. However, very little is known about p66Shc gene regulation in cancer cells. Here, we show that methylation of a specific CpG site in the early post-transcriptional region correlates with p66Shc repression in clinical human lung cancer samples and cancer cell lines. We also find that the stress related transcription factor Nrf2 associates with p66Shc gene promoter in the methylated region, and promotes p66Shc transcription. However, p66Shc induction by Nrf2 requires demethylation of the Nrf2 binding site in p66Shc promoter. Knock-down of p66Shc leads to a positive feedback upregulation of Nrf2 expression and accordingly, Nrf2 is found to be highly expressed in tumors with low p66Shc expression. Further, Nrf2 expression level positively correlates with tumor grade of patients. Thus, we propose that epigenetic repression of p66Shc in cancer cells might be a key factor leading to Nrf2 upregulation, increased cell survival, and tumor progression.

[431]


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


AUTORES / AUTHORS: Ye YZ; Zhang ZH; Fan XY; Xu XL; Chen ML; Chang BW; Zhang YB

INSTITUCIÓN / INSTITUTION: Department of Respiratory Medicine, Anhui Geriatric Institute, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, People’s Republic of China.

RESUMEN / SUMMARY: Notch3 receptor is one of the mammalian Notch family receptors (Notch1-4) which plays an important role in the regulation of cellular proliferation, differentiation, and apoptosis. Overexpression of Notch3 is associated with tumorigenesis. In order to assess the expression of Notch3 in Chinese non-small-cell lung cancer (NSCLC) patients and determine its association with prognosis, we designed a prospective study with five years of follow-up to evaluate Notch3 expression in NSCLC tissues and adjacent non-cancerous normal lung tissues from 131 patients undergoing surgical treatment by immunohistochemistry and western blot analysis. Notch3 had high expression in 67 of 131 cases of NSCLC (51.1 %), which was significantly
higher than in adjacent noncancerous lung tissues. Moreover, Notch3 overexpression was significantly correlated with TNM stage ($P = 5.41 \times 10^{-7}$ in squamous cell carcinoma, $P = 5.338 \times 10^{-7}$ in adenocarcinoma) and lymph node metastasis ($P = 0.00764$ in squamous cell carcinoma, $P = 0.01491$ in adenocarcinoma). Kaplan-Meier survival analysis showed that the overall survival times in patients expressing Notch3 in NSCLC were shorter. Multivariate analysis further demonstrated that Notch3 was an independent prognostic factor for patients with NSCLC. Therefore, Notch3 might be a useful biomarker to predict the prognosis of patients with NSCLC.

[432]

**TITULO / TITLE:** - The co-expression of ERbeta2 and IL-12Rbeta2 is better prognostic factor in non-small-cell lung cancer progression.

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


- Enlace al texto completo (gratuito o de pago) 1007/s12032-013-0592-x

**AUTORES / AUTHORS:** - Liu ZG; Lei YY; Li WW; Chen ZG

**INSTITUCIÓN / INSTITUTION:** - Department of General Thoracic Surgery First Affiliated Hospital, Sun-Yat Sen University, GuangZhou, 510089, China.

**RESUMEN / SUMMARY:** - Estrogens and IL-12 play a pivotal role in the development and progression of non-small-cell lung cancer (NSCLC); at the same time, estrogen receptor beta2 and (interleukin-12 receptor beta2)IL-12Rbeta2 are their important receptors, respectively. With the functions of ERbeta2 and IL-12Rbeta2 explored further in NSCLC, some questions on the relation between ERbeta2 and IL-12Rbeta2 expression need to be solved. In this study, our aim is to elucidate relationship and roles of ERbeta2 and IL-12Rbeta2 in NSCLC. The expression of estrogen receptors beta2 and IL-12Rbeta2 was confirmed by Western blot and RT-PCR analysis in frozen tissues. The correlation between their expression levels and clinical characteristics was evaluated by Mann-Whitney and Kruskal-Wallis test. Using Kaplan-Meier plots and Cox proportional hazard models analyses, overall survival (OS) was evaluated. In contrast to benign pulmonary, ERbeta2 and IL-12Rbeta2 were over-expressed in NSCLC ($P = 0.000$). IHC results showed significant correlation between ERbeta2 and IL-12Rbeta2 ($R = 0.382$, $P = 0.005$). By analyzing the relation between ERbeta2, IL-12Rbeta2 mRNA expression levels and clinical characteristics, it was revealed that ERbeta2 and IL-12Rbeta2 were significant correlated with regional lymph node metastasis, T stage and clinical stage ($P = 0.000/0.000; 0.001/0.000; 0.031/0.003$ respectively), and both protein expression levels were lower with TNM stage being higher. In a Kaplan-Meier analysis, compared to both ERbeta2 and IL-
12Rbeta2 or one low expression, high expression levels of ERbeta2 and IL-12Rbeta2 were identified in a group of patients with the longest overall survival (OS). Cox proportional hazard models revealed that ERbeta2 and IL-12Rbeta2 had longer OS. This is the first study to uncover that both ERbeta2 and IL-12Rbeta2 were over-expressed and further show that they were co-expressed in NSCLC. Moreover, we found that high expression levels of ERbeta2 and IL-12Rbeta2 may be positively correlated with OS and have prognostic values for the progression of NSCLC.

[433]

| TÍTULO / TITLE: | Comparing Histone Deacetylase Inhibitor Responses in Genetically Engineered Mouse Lung Cancer Models and a Window of Opportunity Trial in Lung Cancer Patients. |
| RESUMEN / SUMMARY: | Enlace al Resumen / Link to its Summary |
| AUTORES / AUTHORS: | Ma T; Galimberti F; Erkmen CP; Memoli V; Chinyengetere F; Sempere L; Beumer JH; Anyang BN; Nugent W; Johnstone D; Tsongalis GJ; Kurie JM; Li H; Direnzo J; Guo Y; Freemantle SJ; Dragnev KH; Dmitrovsky E |
| INSTITUCIÓN / INSTITUTION: | 1Departments of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth. |
| RESUMEN / SUMMARY: | Histone deacetylase inhibitor (HDACi, vorinostat) responses were studied in murine and human lung cancer cell lines and genetically-engineered mouse lung cancer models. Findings were compared with a window of opportunity trial in aerodigestive tract cancers. In human (HOP62, H522 and H23) and murine transgenic (ED-1, ED-2, LKR-13, and 393P, driven respectively by cyclin E, degradation-resistant cyclin E, KRAS, or KRAS/p53) lung cancer cell lines vorinostat reduced growth, cyclin D1 and cyclin E levels, but induced p27, histone acetylation and apoptosis. Other biomarkers also changed. Findings from transgenic murine lung cancer models were integrated with those from a window of opportunity trial that measured vorinostat pharmacodynamic responses in pre- versus post-treatment tumor biopsies. Vorinostat repressed cyclin D1 and cyclin E expression in murine transgenic lung cancers and significantly reduced lung cancers in syngeneic mice. Vorinostat also reduced cyclin D1 and cyclin E expression, but increased p27 levels in post- versus pre-treatment human lung cancer biopsies. Notably, necrotic and inflammatory responses appeared in post-treatment biopsies. These depended on intratumoral HDACi levels. Therefore, HDACi treatments of murine genetically-engineered lung cancer models exert similar responses (growth inhibition and changes in gene expression) as observed in lung cancer |
Moreover, enhanced pharmacodynamic responses occurred in the window of opportunity trial, providing additional markers of response that can be evaluated in subsequent HDACi trials. Thus, combining murine and human HDACi trials is a strategy to translate preclinical HDACi treatment outcomes into the clinic. This study uncovered clinically-tractable mechanisms to engage in future HDACi trials.

[434]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Maraz A; Furak J; Varga Z; Fodor E; Egyud Z; Borzasi E; Kahan Z; Palfoldi R; Tiszlavicz L; Hideghety K
INSTITUCIÓN / INSTITUTION: - Department of Oncotherapy, University of Szeged, Szeged, Hungary. dr.manna@freemail.hu
RESUMEN / SUMMARY: - BACKGROUND: Dosimetric data and acute oesophageal toxicity (AET) during chemoradiotherapy (CRT) were evaluated in patients with non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: Fifty patients were treated with paclitaxel-based conformal CRT with a mean +/− SD dose of 60.7 +/- 9.8 Gy. The oesophageal toxicity was prospectively registered and evaluated in relation to the maximal dose (Dmax), mean dose (D(mean)), length and volume of oesophagus irradiated with 35-60 Gy (V(35-60Gy)), and according to the seriousness of AET. RESULTS: Dmax and D(mean) to the oesophagus were 57.0 +/- 10.8 Gy and 24.9 +/- 9.0 Gy, respectively. AET of grade 1, 2 and 3 developed in 16 (32%), 14 (28%) and three (6%) cases, respectively. The Dmax, D(mean), length and the V(35-60Gy) were all related to dysphagia (p<0.001). V(45Gy) was the most reliable predictor of AET of grade 2 or more. CONCLUSION: Our results indicate that keeping oesophageal V(45Gy) below 32.5% can prevent severe AET during CRT of NSCLC.

[435]
TÍTULO / TITLE: - Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1093/ejcts/ezt195
AUTORES / AUTHORS: - Maniwa T; Okumura T; Isaka M; Nakagawa K; Ohde Y; Kondo H
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan.

RESUMEN / SUMMARY: - OBJECTIVES: The standard surgical treatment for patients with non-small-cell lung cancer (NSCLC) is lobectomy with systematic nodal dissection (SND). Lobe-specific patterns of nodal metastases have been recognized, and lobe-specific SND (L-SND) has been reported. We performed L-SND depending on patient-related factors, such as age or the presence of diabetes or respiratory dysfunction, or in the context of specific tumour-related factors, such as the presence of a tumour with a wide area of ground-glass opacity.

METHODS: Between September 2002 and December 2008, 335 consecutive patients with clinical and intraoperative N0 NSCLC underwent curative lobectomies at Shizuoka Cancer Center Hospital. Among these 335 patients, 206 underwent SND (Group A) and 129 underwent L-SND. Of the 129 patients undergoing L-SND, 98 underwent L-SND due to patient-related factors (Group B) and 31 underwent L-SND due to tumour-related factors (Group C).

RESULTS: There were no significant differences in morbidity or blood loss between patients undergoing SND or L-SND, but there was a significant difference in the mean operative times. The 5-year disease-free survival (5-DFS) and 5-year overall survival (5-OS) of patients in Group C were 100%.

Although the patients in Group B showed no significant difference in 5-DFS and 5-OS compared with Group A, patients in Group B had significantly more initial recurrence of mediastinal node cancer than did the Group A patients (P = 0.0050).

CONCLUSION: The recurrence of mediastinal node cancer in patients undergoing L-SND was significantly greater than that in those undergoing SND.

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CASTELLANO

TÍTULO / TITLE: Bronchogene Zyste des Magens: 2 Fallberichte und Übersicht über die englischsprachige Literatur.


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


AUTORES / AUTHORS: - Yang X; Guo K

INSTITUCIÓN / INSTITUTION: - Department of Pancreatic Surgery, No.1 Affiliated Hospital of China Medical University, 155 Nanjing North Street, Heping District, 110001, Shenyang, Liaoning, China, xingyang2001@163.com.

RESUMEN / SUMMARY: - Bronchogenic cysts (BCs) are a rare clinical entity because of anomalism of foregut in the embryonic stage. They have been
described mostly within the mediastinum and are uncommon reported arising from the stomach. In this article, we report two cases of BC of stomach identified by pathological examination after surgical resection. It is extremely difficult to make a definitive diagnosis preoperatively just based on imaging findings. Surgical resection may be indicated if malignancy is suspected, or the cyst is enlarging or infected or causing symptoms.

[437]
**TÍTULO / TITLE:** - Association between EGFR-TKI resistance and efficacy of radiotherapy for brain metastases from EGFR-mutant lung adenocarcinoma.

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


**AUTORES / AUTHORS:** - Hirata H; Nakamura K; Kunitake N; Shioyama Y; Sasaki T; Ohga S; Nonoshita T; Yoshitake T; Asai K; Inoue K; Nagashima A; Ono M; Honda H

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology, Kitakyushu Municipal Medical Center, Kitakyushu, Japan.

**RESUMEN / SUMMARY:** - AIM: To clarify how patients with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma with acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs) respond to radiotherapy (RT) for brain metastases. PATIENTS AND METHODS: Forty-seven patients were divided into the following three groups: a TKI-naive group with EGFR mutation (n=11), a TKI-resistant group with EGFR mutation (n=10), and an EGFR-wild-type group (n=26). Patients received stereotactic RT (n=23) or whole-brain RT (n=24). RESULTS: The response rate for patients with TKI-resistant tumor at three months after RT tended to be lower (11%) than that of those who were TKI-naive (82%, p=0.006) and for patients with wild-type EGFR (48%, p=0.10). On univariate analysis, central nervous system progression-free and overall survival were significantly shorter for patients with TKI-resistant tumors than for those who were TKI-naive (p=0.018 and p=0.005, respectively). Multivariate analysis showed that TKI resistance was an independent predictor of poorer overall survival (p=0.011). CONCLUSION: Acquired resistance to TKIs appears to be associated with low efficacy of brain RT.

[438]
**TÍTULO / TITLE:** - Involvement of intermediate filament nestin in cell growth of small-cell lung cancer.

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

BACKGROUND: Nestin is a class VI intermediate filament protein expressed in stem/progenitor cells during the development of the central nervous system. Nestin is detected in various types of tumors and is involved in malignant processes. This study investigated the expression and function of nestin in small-cell lung cancer (SCLC). METHODS: Expression of nestin and achaete-scute homolog 1 (ASH1) was studied in 21 lung cancer cell lines. To assess the function of nestin, a short hairpin RNA (shRNA) targeting nestin was transfected into two SCLC cell lines (DMS53 and SBC3), and cloned cells that showed apparent down-regulation of nestin were obtained. Nestin expression was also studied immunohistochemically in surgically resected SCLC primary tumors and metastatic SCLC tumors obtained from autopsy cases. RESULT: Nestin was expressed in nine of 10 SCLC cell lines. The nestin expression level was significantly higher in SCLC cell lines than in NSCLC cell lines (P<0.01). There was a statistically significant positive correlation between the expression levels of nestin and ASH1 in SCLC cell lines. Nestin knock-down cells created by transfection with shRNA exhibited decreased invasion and cell proliferation capabilities. Furthermore, nestin was detected in SCLC tumor cells and tumor vessels in all clinical tumor specimens. CONCLUSION: Nestin is expressed in SCLC in association with neuroendocrine features and participates in malignant phenotypes, including cell growth. Therefore, nestin may be a novel therapeutic target for SCLC.
RESUMEN / SUMMARY: - La incidencia de cáncer de pulmón ha aumentado dramáticamente en diez años, siendo ahora el más comúnmente diagnosticado en varones y el cuarto más comúnmente diagnosticado en mujeres. Considerando la evolución social y científica, el objetivo del estudio presentado por el Colegio Francés de Médicos de la Respiration en el Hospital General (CPHG) fue comparar las características del paciente y del cáncer de pulmón a un intervalo de diez años. Dos estudios epidemiológicos, KBP-2000-CPHG y KBP-2010-CPHG, fueron realizados en un intervalo de diez años. Estos estudios prospectivos multicéntricos incluyeron a todos los pacientes ≥18 años con cáncer de pulmón primario diagnosticado entre el 1 de enero y 31 de diciembre de 2000 o 2010, y manejado en las secciones respiratorias de uno de los hospitales participantes. Se completó un formato estándar para cada paciente. Un comité de dirección comprobó la exhaustividad de la recogida de datos. Respectivamente, en 2000 y 2010, 137 y 104 centros incluyeron 5667 y 7051 pacientes. Comparado con 2000, los pacientes en 2010 fueron significativamente mayores (65.5+-11.3 vs. 64.3+/-11.5 años, p<0.0001), más frecuentemente mujeres (24.3% vs. 16.0%, p<0.0001) y nunca fumadores (10.9% vs. 7.2%, p<0.0001). En 2010, el adenocarcinoma fue el cáncer más común (45.4%, vs. 29.0% en 2000, p<0.0001). El riesgo relativo del adenocarcinoma aumentó independientemente del sexo, la edad, o el estado de fumador (relativo riesgo [RR] antes y después del ajuste, RR=2.07 [1.92-2.24], p<0.0001 y 2.06 [1.90-2.23], p<0.0001). En diez años, las características del cáncer de pulmón han cambiado: más mujeres, más nunca fumadores, y más adenocarcinomas. El incremento particularmente alto de la tasa de adenocarcinoma merece un análisis adicional.

[440]
TÍTULO / TITLE: - Un caso raro de cáncer de pulmón no pequeñocelular metastatizando al glande pituitario: detección con 18F-FDG PET-CT.

RESUMEN / SUMMARY: - Enlace al resumen / Link to its summary


AUTORES / AUTHORS: - Agarwal KK; Sharma P; Singla S; Suman Kc S; Bal C; Kumar R

INSTITUCIÓN / INSTITUTION: - Del Departamento de Medicina Nuclear, Instituto All India de Ciencias Médicas, New Delhi, India.

RESUMEN / SUMMARY: - Las metástasis al glande pituitario son raras. Presentamos el caso de un hombre de 52 años con cáncer de pulmón no pequeñocelular donde la metástasis pituitaria fue detectada en el PET-CT de seguimiento F-FDG, caracterizada con MRI y confirmada en histología. Demostrando un sitio de metástasis tan raro, el PET-CT con F-FDG puede tener un impacto significativo en el manejo de los pacientes con cáncer.
Different mechanisms for metal-induced adaptation to cadmium in the human lung cell lines A549 and H441.

Sensitivity to Cd and Zn as well as the capacity to develop tolerance were characterized in human lung cells A549 and H441. In the A549 cells, a 2-fold lower LC50 was obtained for Cd compared to Zn, whereas H441 cells were similarly sensitive to both metals. H441 cells were twice as resistant to Cd as the A549 cells. Higher HSP70, but not metallothionein (MT) or glutathione (GSH) levels, could contribute to this better resistance. A 1.5- and 2-fold increase in the LC50 for Cd was obtained in the A549 cells pre-exposed to non-cytotoxic concentrations of Cd (20 μM) or Zn (40 μM) for 24 h. On the other hand, only Zn increased H441 cells’ resistance to Cd. Maximum Zn- and Cd-induced tolerances were reached as early as 3 and 12 h, respectively. Increases in MT-IIa and HSP70 messenger RNA levels were higher in A549 cells, but cycloheximide eliminated the induction of tolerance only in the H441 cells. Protein synthesis is a prerequisite for metal-induced tolerance to Cd in the H441 cells but not the A549 cells. Results obtained with L-buthionine sulfoximine revealed that GSH synthesis is not responsible for the acquired tolerance in both cell lines. However, GSH plays a critical role against Cd toxicity, and pro-oxidant conditions sensitized cells to Cd with different impacts on the metal-induced mechanisms of acquired tolerance. GSH and catalase both provide antioxidative protection, but only the stress related to low GSH content, not that resulting from catalase inhibition, may be alleviated with Zn.
ABSTRACT Background: EML4-ALK fusion oncogene has emerged as a novel molecular target in non-small cell lung cancer (NSCLC). Although break-apart fluorescent in situ hybridization (FISH) is the standard method for diagnosis, it is expensive, not readily available and sometimes difficult to interpret. In addition, ALK immunohistochemistry (IHC) may miss the diagnosis because of relatively low level of ALK transcription. Methods: In situ proximity ligation assay (PLA) originally developed for precise detection and quantification of proteins by dual recognition and amplification process was used for sensitive detection of EML4-ALK fusion oncprotein in NSCLC cell lines (ALK negative cell: PC-9 and H460, ALK positive cell: H3122 and H2228). EML4-ALK oncogene and protein in lung cancer cells were confirmed by multiplex RT-PCR and Western blots. Results: We detected 117 kDa variant 1 of EML4-ALK in H3122 and 90 kDa variant 3 of EML4-ALK in H2228. These cells were more sensitive to crizotinib, an ALK inhibitor compared with PC-9 and H460 cells without EML4-ALK rearrangement. After fixing on glass slides by cytopin centrifuge, in situ PLA test was performed. Among four cell lines, distinct, tiny spots were visible only in H3122 and H2228 cell lines with ALK rearrangement. The same results were also obtained when paraffin-embedded cell blocks were used. Conclusions: Highly specific and sensitive detection of EML4-ALK fusion oncprotein is possible by in situ PLA method suggesting its clinical application.
myocardial perfusion imaging. This case serves as a reminder that although the appearance of pathology on a nuclear medicine imaging study is typically what is seen (specifically, increased radiopharmaceutical uptake), it can just as importantly be what is not seen.

[444]

TÍTULO / TITLE: Angiotensin-converting enzyme 2 attenuates the metastasis of non-small cell lung cancer through inhibition of epithelial-mesenchymal transition.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Qian YR; Guo Y; Wan HY; Fan L; Feng Y; Ni L; Xiang Y; Li QY
INSTITUCIÓN / INSTITUTION: Respiratory Department, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, PR China.
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RESUMEN / SUMMARY: Angiotensin-converting enzyme 2 (ACE2) is a key enzyme of the renin-angiotensin system (RAS). ACE2 plays a critical counterbalancing role by degrading angiotensin II (Ang II) to Ang 1-7. Recent studies suggest that RAS influences tumor growth and development by its paracrine effects on the tumor microenvironment. Epithelial mesenchymal transition (EMT) is now thought to be a process that plays a fundamental role in tumor progression and metastasis. In the present study, we investigated the role of ACE2 in lung cancer metastasis and the mechanism of EMT. This is the first study to elucidate the mechanism through which the overexpression of ACE2 in the A549 lung cancer cell line decreases metastasis formation in vivo and upregulates the expression of E-cadherin both in vitro and in vivo. We also observed the downregulation of vimentin, which supports a role of ACE2 in influencing EMT in lung cancer. Further analysis indicated that ACE2 abrogated the upregulation of TGF-beta1-induced EMT markers, such as vimentin and alpha-smooth muscle actin (alphaSMA) in vitro in A549 cells. Finally, exposing A549 cells stably expressing ACE2 to DX600, an inhibitor of ACE2, recovered the sensitivity of lung cancer cells to TGF-beta1-mediated induction of EMT. Our study demonstrated that ACE2 attenuated the metastasis of lung cancer and may serve as a target for new strategies to inhibit EMT in cancer cells.

[445]

TÍTULO / TITLE: Crizotinib may be used in lewis lung carcinoma: A novel use for crizotinib.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 3892/or.2013.2424
AUTORES / AUTHORS: - Xia P; Gou WF; Zhao S; Zheng HC
INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Institute of Pathology and Pathophysiology, School of Basic Medical Science, China Medical University, Shenyang, Liaoning 110001, P.R. China.
RESUMEN / SUMMARY: - Lung cancer accounts for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths in 2008. Crizotinib (PF-02341066) is identified as an ATP competitive small-molecular inhibitor for anaplastic lymphoma kinase (ALK). The US Food and Drug Administration (FDA) approved crizotinib to be used for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC in 2011. In the present study, the side population (SP) and main population (MP) cells were obtained from Lewis lung carcinoma cells (LLC) and analyzed by DNA dye (Hoechst 33342) and flow cytometry. LLC SP and MP cells were confirmed as no ALK fusion gene by fluorescence in situ hybridization. The effects of crizotinib on LLC SP and MP cells both in vivo and in vitro were identified. Our results indicate that crizotinib can induce apoptosis and G1 phase arrest in LLC MP cells. Crizotinib used in combination with verapamil can inhibit proliferation of LLC SP cells. Moreover, crizotinib decreased tumor size and weight and inhibited angiogenesis in established xenografted tumors. To analyze the signaling pathway involved, computer simulation, Affymetrix microarray analysis and western blot analysis were performed. In these assays, crizotinib was found to dock into Smad3 and activate the Smad signaling pathway. Overall, these studies demonstrate the antitumor activity of crizotinib in LLC cell line, and provide a novel use for crizotinib.

[446]
TÍTULO / TITLE: - MAPK inhibitors augment gallic acid-induced A549 lung cancer cell death through the enhancement of glutathione depletion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 3892/or.2013.2447
AUTORES / AUTHORS: - Park WH; Kim SH
INSTITUCIÓN / INSTITUTION: - Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju 561-180, Republic of Korea.
RESUMEN / SUMMARY: - Gallic acid (GA) is involved in various biological processes such as cell growth inhibition and apoptosis through changes in
reactive oxygen species (ROS). In the present study, we investigated the effects of MAPK (MEK, JNK or p38) inhibitors on cell death in GA-induced A549 lung cancer cells in relation to ROS and glutathione (GSH). Treatment with 100 microM GA inhibited the growth of A549 cells and induced apoptosis and/or necrosis, which was accompanied by the loss of mitochondrial membrane potential (MMP; Psim). GA increased ROS levels as well as GSH depletion in A549 cells at 24 h. MEK inhibitor seemed to enhance cell growth inhibition by GA. This inhibitor also increased cell death, MMP (Psim) loss and GSH depletion in GA-treated A549 cells. Both JNK and p38 inhibitors intensified growth inhibition, cell death, MMP (Psim) loss and GSH depletion by GA. However, none of the MAPK inhibitors significantly altered ROS levels in GA-treated A549 cells. In conclusion, MAPK inhibitors enhanced growth inhibition and death in GA-treated A549 cells, which were correlated with GSH depletion rather than ROS levels.

[447]

TÍTULO / TITLE: - Overexpression of Numb suppresses tumor cell growth and enhances sensitivity to cisplatin in epithelioid malignant pleural mesothelioma.

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


AUTORES / AUTHORS: - Kang Y; Ding M; Tian G; Guo H; Wan Y; Yao Z; Li B; Lin D

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Shandong Provincial Hospital, Shandong University, Jinan, Shandong 250021, P.R. China.

RESUMEN / SUMMARY: - Malignant pleural mesothelioma (MPM) is a highly aggressive and conventional treatment-resistant tumor with a dismal prognosis. Among the three histological subtypes of MPM, the epithelioid is the most common type. Numb is considered as a tumor suppressor playing a critical role in controlling asymmetric cell division, maintenance of stem cell compartments, ubiquitination of specific substrates and regulating Notch-, Hedgehog- and TP53-activated pathways. The present study was designed to analyze the role of Numb in epithelioid MPM. We investigated the expression of Numb in 39 epithelioid MPM and 22 normal pleural tissues by immunohistochemistry. Furthermore, we overexpressed Numb in NCI-H2452, an epithelioid human MPM cell line, and investigated the effect of Numb overexpression on the proliferation, apoptosis and sensitivity to cisplatin in cells. The expression of Numb was significantly lower in MPM compared to the control group and Numb had an inverse correlation with the ki-67 labeling index. Loss of Numb expression was associated with poor prognosis in epithelioid MPM. Overexpression of Numb in NCI-H2452 cells significantly inhibited proliferation,
promoted apoptosis and enhanced sensitivity to cisplatin. Moreover, Numb overexpression activated caspase-9 and caspase-3 through release of cytochrome c as well as downregulation of XIAP and survivin. We speculate that cytochrome c/caspase signaling is a possible mechanism through which Numb enhances the apoptosis of NCI-H2452 cells. These results suggest that Numb may be involved in epithelioid MPM development, and its upregulation may confer sensitivity to cisplatin, suggesting potential therapeutic options for MPM.

[448]

TÍTULO / TITLE: - Evaluating consistency in the interpretation of NTP rodent cancer bioassays: An examination of mouse lung tumor effects in the 4-MEI study.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Haseman JK
INSTITUCIÓN / INSTITUTION: - J.K. Haseman Consulting, 1054 Tacketts Pond Drive, Raleigh, NC 27614, United States. Electronic address: hasemanjk@aol.com.
RESUMEN / SUMMARY: - The potential carcinogenicity of 4-methylimidazole (4-MEI) was evaluated in a National Toxicology Program (NTP) rodent cancer bioassay in Fischer 344 rats and B6C3F1 mice (NTP, 2007; Chan et al., 2008). The NTP concluded that there was “clear evidence of carcinogenic activity” in male and female mice, based on an increased incidence of lung tumors. The “category of evidence” that the NTP assigns to a rodent cancer bioassay outcome can have significant regulatory implications. This is especially important for 4-MEI, which forms in caramel colorings and other foods during cooking, with potential widespread human exposure in a broad spectrum of food and beverage products. A detailed analysis of all NTP mouse-lung-tumor-only carcinogens reveals that the proper call for lung tumors in the 4-MEI study should have been “some evidence” rather than “clear evidence” of carcinogenic activity for both male and female mice in order to be consistent with the NTP’s interpretation of other mouse lung carcinogens showing a similar strength of response. Suggestions are given as to measures the NTP should consider in the preparation of some or all future Technical Reports in order to enhance consistency of interpretation of experimental results.

[449]
INTRODUCTION:: No clear data are available on the high rate of tobacco-independent lung cancer in women. We hypothesize that genetic events or hormonal factors may be partly involved. METHODS:: We aimed to compare clinical, pathological, and biological characteristics of lung cancer in two cohorts of women: smokers and never-smokers. A total of 140 women (63 never-smokers and 77 former/current smokers) with adenocarcinoma, were included in this study. RESULTS:: The never-smokers were characterized by a higher age (67 versus 58.7 years; p < 0.0001) and a higher frequency of lepidic features (60.3% versus 37.7%; p = 0.008) compared with smokers. We observed differential genetic alteration repartition in women according to their tobacco status: 50.8% of never-smokers displayed an epidermal growth factor receptor (EGFR) mutation versus 10.4% of smokers (p < 0.001). In contrast, K-Ras was more frequently mutated in smokers (33.8%) than in never-smokers (9.5%; p = 0.001). We also observed a higher percentage of estrogen receptors (ER) alpha expression (p = 0.03; and p = 0.008 with two different antibodies) in patients who never smoked when compared with smokers. There was no significant difference in ERbeta and progesterone receptors between the groups. Finally, ERalpha expression was correlated with the presence of an EGFR mutation. CONCLUSIONS:: This study suggests that when lung cancer occurs in women who have never smoked, it is more frequently associated with an EGFR mutation and ERalpha expression, with a correlation between both markers. These findings underline the possibility of treating women who have never smoked by targeting both hormonal factors and genetic abnormalities.
Small cell carcinoma of the colon arising in a carcinoid tumor.

Small cell carcinomas of the gastrointestinal tract are rare and clinically aggressive tumors. A case is presented of a 70 year-old woman who presented with small bowel obstruction and was found to have a cecal mass. She underwent right hemicolectomy, and histopathology showed a small cell carcinoma arising in the background of a carcinoid tumor. Although small cell carcinomas of the colon have frequently been found in association with colonic adenomas, this appears to be the first report of a low-grade carcinoid tumor in combination with a small cell carcinoma.

Results of T4 Surgical Cases in the Japanese Lung Cancer Registry Study: Should Mediastinal Fat Tissue Invasion Really be Included in the T4 Category?

Results of T4 Surgical Cases in the Japanese Lung Cancer Registry Study: Should Mediastinal Fat Tissue Invasion Really be Included in the T4 Category?
RESUMEN / SUMMARY: - INTRODUCTION:: T4 lung cancer is a heterogeneous group of locally advanced disease. We hypothesized that patients in whom T4 lung cancer invaded only mediastinal fat tissue would show better prognosis after surgery than patients in whom T4 disease invaded other organs. The present study aimed to investigate how different invasive features of T4 disease impacted prognosis, and what types of patients with T4 disease could benefit most from surgical treatment. METHODS:: A nationwide registry study on lung cancer surgical cases during 2004 was conducted by the Japanese Joint Committee of Lung Cancer Registry, including registries of 11,663 cases within Japan. The present study analyzed 215 of these cases involving T4 structures or with ipsilateral nonprimary lobe pulmonary metastasis (PM).

RESULTS:: Reasons for T4 classification included invasion of only mediastinal tissue in 32 cases (15%), invasion of other structures in 96 cases (45%), and ipsilateral different lobe PM in 87 cases (40%); among these three groups, there were no significant differences in survival, nodal status, and patterns of first recurrence. Multivariate analysis showed an age of 70 years or above (p = 0.022) and nodal status (p = 0.004) to be significant prognostic factors. T4N0 patients less than 70 years of age showed significantly better prognosis than those who were T4N1-2 and 70 years of age or older (p = 0.0001; 5-year survival rate 50.3 versus 19.9%). CONCLUSIONS:: There was no significant difference in survival between T4 patients with only mediastinal fat invasion and those with other T4 organ invasion and ipsilateral different lobe PM, demonstrating appropriateness of the T4 category definition in the current tumor, node, metastasis staging system. Age and nodal status were significant independent prognostic factors in T4 patients, and the best surgical candidates were shown to be T4N0 patients who were less than 70 years of age and had a 5-year survival rate of more than 50%.

[452]

TITULO / TITLE: - Basaloid large cell lung carcinoma presenting as cutaneous metastasis at the colostomy site after abdominoperineal resection for rectal carcinoma.

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


●●Enlace al texto completo (gratuito o de pago) 1111/cup.12145

AUTORES / AUTHORS: - Sabater-Marcos V; Garcia-Garcia JA; Roig-Vila JV

INSTITUCIÓN / INSTITUTION: - Department of Pathology, University General Hospital, Valencia, España.

RESUMEN / SUMMARY: - The occurrence of a tumor at the colostomy site after abdominoperineal resection for rectal carcinoma is rare and it may be related to a previously resected carcinoma or another primary tumor. We report a 61-year-old man who developed an ulcerated skin nodule at her colostomy site 6 years
after resection of a rectal adenocarcinoma. Histopathologically, the skin nodule was composed of atypical large and pleomorphic cells with high mitotic rate and they were arranged in nests and within lymphatic channels in the dermis. The neoplastic cells were immunoreactive for cytokeratin (CK) AE1/3, CK7, CK34E12, epithelial membrane antigen and vimentin while detection of human papillomavirus and Epstein-Barr virus DNA was negative. A diagnosis of basaloid large cell carcinoma of pulmonary origin was suggested and it was confirmed by computed tomography-guided fine needle aspiration of a right subpleural mass. A metastatic tumor at the colostomy site is an exceptional finding and may be the first manifestation of lung cancer, especially if it consist of pleomorphic large cells with high mitotic rate and basaloid immunophenotype.

[453]
**TÍTULO / TITLE:** "When roscius was an actor in rome-" care for the elderly with n2-positive non-small-cell lung cancer.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1097/JTO.0b013e31828f5b51
**AUTORES / AUTHORS:** Osarogiagbon RU
**INSTITUCIÓN / INSTITUTION:** Thoracic Oncology Research (ThOR) Group, Multidisciplinary Thoracic Oncology Program, Baptist Cancer Center, Memphis, Tennessee.

[454]
**TÍTULO / TITLE:** The apoptosis of non-small cell lung cancer induced by cisplatin through modulation of STIM1.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1016/j.etp.2013.04.003
**AUTORES / AUTHORS:** Li W; Zhang M; Xu L; Lin D; Cai S; Zou F
**INSTITUCIÓN / INSTITUTION:** Department of Occupational Health and Occupational Medicine, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, Guangdong Province 510515, China.
**RESUMEN / SUMMARY:** Cis-diamminedichloroplatinum (II) (cisplatin) is one of the most active antitumor agents used in human chemotherapy of non-small cell lung cancer. Cisplatin forms crosslinked DNA adducts and its cytotoxicity has been shown to be mediated by propagation of DNA damage recognition signals...
to downstream pathways prompting apoptosis. The steps involved in the process include changes in Ca2+ signaling with dysregulated tumor cell turnover. Stromal interaction molecules 1 (STIM1), as one of the most potent tumor suppressor genes, are identified as the endoplasmic-reticulum (ER) Ca2+ sensor controlling store-operated Ca2+ entry (SOCE) in non-excitable cells, which is main pathway to extracellular Ca2+ influx. Its role in STIM1 cisplatin-induced apoptosis of non-small cell lung cancer was the focus of study with focus on SOCE inhibitors 2-APB- and SKF96365-cisplatin-induced apoptosis in the non-small cell lung cancer (NSCLC) cell lines A549 and H460. In this experimental model, cisplatin-induced apoptosis and decreased concentration of intracellular Ca2+ was demonstrated. The expression of STIM1 was significantly higher in carcinoma tissue than in the adjacent non-neoplastic lung tissue. These findings support the conclusion that STIM1 may play an important role in the development of NSCLC which makes drugs that repress the expression of STIM1 to be a potential target for lung cancer therapy.

[455]

TÍTULO / TITLE: - When and Why to Perform Nodal Dissection in Early-Stage Non-Small Cell Lung Cancer?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Baisi A; De Simone M; Cioffi U
INSTITUCIÓN / INSTITUTION: - Thoracic Surgery Unit, Azienda Ospedaliera San Paolo, University of Milan, Milano, Italy.

[456]

TÍTULO / TITLE: - Artemisinin induces A549 cell apoptosis dominantly via a reactive oxygen species-mediated amplification activation loop among caspase-9, -8 and -3.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Gao W; Xiao F; Wang X; Chen T
INSTITUCIÓN / INSTITUTION: - MOE Key Laboratory of Laser Life Science & Institute of Laser Life Science, College of Biophotonics, South China Normal University, Guangzhou, 510631, China.
RESUMEN / SUMMARY: - This report is designed to explore the roles of caspase-8, -9 and -3 in artemisinin (ARTE)-induced apoptosis in non-small cell lung cancer cells (A549 cells). ARTE induced reactive oxygen species (ROS)-
mediated apoptosis in dose- and time-dependent fashion. Although ARTE treatment did not induce Bid cleavage and significant loss of mitochondrial membrane potential, it induced release of Smac and AIF but not cytochrome c from mitochondria, and silencing of Bak but not Bax significantly prevented ARTE-induced cytotoxicity. Moreover, ARTE treatment induced ROS-dependent activation of caspase-9, -8 and -3. Of the utmost importance, silencing or inhibiting any one of caspase-8, -9 and -3 almost completely prevented ARTE-induced activation of all the three caspases and remarkably abrogated the cytotoxicity of ARTE, suggesting that ARTE triggered an amplification activation loop among caspase-9, -8 and -3. Collectively, our data demonstrate that ARTE induces a ROS-mediated amplification activation loop among caspase-9, -8 and -3 to dominantly mediate the apoptosis of A549 cells.

[457]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1186/1756-9966-32-29
AUTORES / AUTHORS: - Mo ML; Chen Z; Zhou HM; Li H; Hirata T; Jablons DM; He B
INSTITUCIÓN / INSTITUTION: - School of Life Sciences, Tsinghua University, Beijing 10084, China. zhm-dbs@mail.tsinghua.edu.cn.
RESUMEN / SUMMARY: - BACKGROUND: E2A-PBX1 fusion gene caused by t(1;19)(q23;p13), has been well characterized in acute lymphoid leukemia (ALL). There is no report on E2A-PBX1 fusion transcripts in non-small-cell lung cancer (NSCLC). METHODS: We used polymerase chain reaction (PCR) to detect E2A-PBX1 fusion transcripts in human NSCLC tissue specimens and cell lines. We analyzed correlation of E2A-PBX1 fusion transcripts with clinical outcomes in 76 patients with adenocarcinoma in situ (AIS) and other subgroups. We compared mutation status of k-ras, p53 and EGFR in 22 patients with E2A-PBX1 fusion transcripts. RESULTS: We detected E2A-PBX1 transcripts in 23 of 184 (12.5%) NSCLC tissue specimens and 3 of 13 (23.1%) NSCLC cell lines. Presence of E2A-PBX1 fusion transcripts correlated with smoking status in female patients (P = 0.048), AIS histology (P = 0.006) and tumor size (P = 0.026). The overall survival was associated with gender among AIS patients (P = 0.0378) and AIS patients without E2A-PBX1 fusion transcripts (P = 0.0345), but not among AIS patients with E2A-PBX1 fusion transcripts (P = 0.6401). The overall survival was also associated with status of E2A-PBX1 fusion transcripts among AIS stage IA patients (P = 0.0363) and AIS stage IA female patients (P = 0.0174). In addition, among the 22 patients with E2A-PBX1
fusion transcripts, 12 (54.5%) patients including all four non-smokers, showed no common mutations in k-ras, p53 and EGFR. CONCLUSIONS: E2A-PBX1 fusion gene caused by t(1;19)(q23;p13) may be a common genetic change in AIS and a survival determinant for female AIS patients at early stage.
Carcinoid is a rare lung cancer that typically presents with a relatively indolent clinical behavior. We present the case of a 32-year-old male with progressive respiratory symptoms, which resulted in the diagnosis of typical bronchial carcinoid. This case shows a novel imaging technique for staging a bronchial carcinoid for determination of optimal management. This case also shows the multidisciplinary approach required for management of patients with carcinoid tumors.
their usual method, and to submit results within a 4-week time frame. According to a predefined scoring system, two points were assigned to correct genotype and zero points to false-negative or false-positive results. The threshold to pass the EQA was set at higher than 18 of 20 points. Two rounds were preplanned.

RESULTS: All participating centers submitted the results within the time frame. Polymerase chain reaction (PCR)/sequencing was the main methodology used (n = 37 laboratories), although a few centers did use pyrosequencing (n = 8) or real-time PCR (n = 2). A significant number of analytical errors were observed (n = 20), with a high frequency of false-positive results (n = 16). The lower scores were obtained for the small biopsies. Fourteen of 47 centers (30%) that did not pass the first round, having a score less than or equal to 18 points, used PCR/sequencing, whereas 10 of 10 laboratories, using pyrosequencing or real-time PCR, passed the first round. Eight laboratories passed the second round. Overall, 41 of 47 centers (87%) passed the EQA.

CONCLUSION: The results of the EQA for EGFR testing in non-small-cell lung cancer suggest that good quality EGFR mutational analysis is performed in Italian laboratories, although differences between testing methods were observed, especially for small biopsies.

[461]
TÍTULO / TITLE: - Phase II Trial of Erlotinib for Japanese Patients With Previously Treated Non-small-cell Lung Cancer Harboring EGFR Mutations: Results of Lung Oncology Group in Kyushu (LOGiK0803).
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1093/jjco/hyt056
AUTORES / AUTHORS: - Yamada K; Takayama K; Kawakami S; Saruwatari K; Morinaga R; Harada T; Aragane N; Nagata S; Kishimoto J; Nakanishi Y; Ichinose Y
INSTITUCIÓN / INSTITUTION: - *Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume City, Fukuoka 830-0011, Japan.
kayamada@med.kurume-u.ac.jp.
RESUMEN / SUMMARY: - OBJECTIVE: Erlotinib has been reported to be useful for treatment of non-small-cell lung cancer harboring mutation of the epidermal growth factor receptor gene EGFR-mt. However, no prospective trial has yet assessed the utility of erlotinib in Japanese patients. METHODS: Patients with EGFR-mt (exon 19/21) non-small-cell lung cancer who had previously received one to two chemotherapy regimens were enrolled in this trial. Erlotinib was initially administered at a dose of 150 mg/day orally until disease progression or unacceptable toxicities occurred. The primary endpoint was the objective
response rate. RESULTS: Twenty-six patients were enrolled between February 2009 and January 2011. Objective response was observed in 14 patients (53.8%, 95% confidence interval: 33.4-73.4%), and the disease control rate reached 80.8% (95% confidence interval: 60.7-93.5%). After a median follow-up time of 17.3 months (range: 5.8-29.5 months), the median progression-free survival was 9.3 months (95% confidence interval: 7.6-11.6 months). The median survival time is yet to be determined. Major toxicities were skin disorder and liver dysfunction; most episodes were grade 2 or less, and all were tolerable. Only one patient with grade 3 skin rash discontinued the study. No patients developed interstitial lung disease, and there were no treatment-related deaths. CONCLUSIONS: This prospective study is the first to have investigated the usefulness of erlotinib in Japanese patients with previously treated EGFR-mt non-small-cell lung cancer. Although this trial could not meet the primary endpoint, erlotinib was well tolerated and showed clinical benefit such as promising disease control rate or progression-free survival in this population, similar to gefitinib.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Kim YS; Zerin T; Song HY
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RESUMEN / SUMMARY: Ellagic acid (EA) is a natural dietary polyphenol whose benefits in a variety of diseases shown in epidemiological and experimental studies involve anti-inflammation, anti-proliferation, anti-angiogenesis, anti-carcinogenesis and anti-oxidation properties. This study aimed to evaluate the effect of EA against paraquat (PQ)-induced oxidative stress. PQ decreased the viability of A549 cells in dose- and time-dependent manners, which was associated with the massive generation of reactive oxygen species (ROS). However, cell viability was significantly recovered by the treatment of EA, from 47.01+/−1.59% to 66.04+/−2.84%. The release of lactate dehydrogenase (LDH) was also decreased with the treatment of EA in PQ-treated A549 cells. EA induced the level of expression and activation of nuclear factor-erythroid 2-related factor (Nrf2) and its target cytoprotective and antioxidant genes, heme oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO1). The antioxidant potential of EA might be directly correlated with the increased expression of HO-1 and NQO1, whose expression may have surmounted the oxidative stress generated by PQ. Notably, EA treatment significantly reduced the levels of
biochemical markers as lipid peroxidation, reduced the intracellular ROS level, and surmounted total glutathione level in A549 cells. Data indicate that the antioxidant and cytoprotective properties of EA reduce PQ-induced cytotoxicity in human alveolar A549 cells.

[463]
**TITULO / TITLE:** - Thoracoscopic lobectomy for type I pleuropulmonary blastoma in an infant.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
**REVISTA / JOURNAL:** - Pediatr Surg Int. 2013 Apr 16.
  - [Enlace al texto completo (gratuito o de pago) 1007/s00383-013-3310-z](#)
**AUTORES / AUTHORS:** - Fingeret A; Garcia A; Borczuk AC; Rothenberg SS; Aspelund G
**INSTITUCIÓN / INSTITUTION:** - Division of Pediatric Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons and Morgan Stanley Children’s Hospital of New York-Presbyterian, 177 Fort Washington Avenue, MHB 7GS-313, New York, NY, 10032, USA, af2451@columbia.edu.
**RESUMEN / SUMMARY:** - Pleuropulmonary blastoma (PPB) is a rare, aggressive, intrathoracic mesenchymal neoplasm associated with cystic lung lesions. The authors describe an 8-month-old male who underwent thoracoscopic left upper lobectomy for a cystic lung lesion initially diagnosed as congenital pulmonary airway malformation. Pathology revealed type I PPB.

[464]
**TITULO / TITLE:** - Lymph Node Ratio May Predict the Benefit of Postoperative Radiotherapy in Non-Small-Cell Lung Cancer.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
**REVISTA / JOURNAL:** - J Thorac Oncol. 2013 May 20.
  - [Enlace al texto completo (gratuito o de pago) 1097/JTO.0b013e318292c53e](#)
**AUTORES / AUTHORS:** - Urban D; Bar J; Solomon B; Ball D
**INSTITUCIÓN / INSTITUTION:** - *Department of Medical Oncology, Peter MacCallum Cancer Centre, Ramat Gan, Israel; daggerInstitute of Oncology, Chaim Sheba Medical Center, Israel; double daggerDepartment of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia; and section signSir Pater MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia.
**RESUMEN / SUMMARY:** - INTRODUCTION:: The use of postoperative radiotherapy (PORT) after resection of non-small-cell lung cancer (NSCLC) is controversial, with some evidence suggesting a benefit in patients with N2
disease. We assessed lymph node ratio (LNR) as a predictor of PORT benefit. **METHODS:** By using the Surveillance, Epidemiology and End Results database, we analyzed resected, node-positive (N1-N2) NSCLC patients diagnosed between 1998 and 2009. LNR, (number of positive nodes/number of resected nodes) was categorized into four groups: LNR less than 12.5%, 12.5 to 24.9%, 25 to 49.9%, and 50% or more. **RESULTS:** Of 11,324 node-positive NSCLC patients identified, 6551 (57.9%) had N1 disease. The LNR was prognostic for survival in the entire cohort and within each nodal stage. The median survival in LNR groups 1, 2, 3, and 4 was 43, 40, 32, 27, and 22 months in N1 disease and 40, 32, 27, and 22 months in N2 disease, respectively. PORT was associated with a worse survival on univariate analysis (hazard ratio [HR] =1.09; confidence interval [CI] 1.03-1.15; p = 0.002) but no effect on multivariate analysis (HR = 0.96; CI 0.90-1.02; p = 0.201). When analyzed by nodal stage, the benefit of PORT was limited to N2 disease (HR = 0.9; CI 0.84-0.99; p= 0.026) with no benefit in N1 disease (HR = 1.06; CI 0.97-1.15; p=0.2). After stratifying by LNR, the survival benefit of PORT was limited to those with N2 disease and an LNR of 50% or more. **CONCLUSION:** A high LNR is associated with a poorer survival in resected, node-positive NSCLC. The survival benefit associated with PORT in this disease seems to be limited to those with an LNR of 50% or more. This warrants further investigation in other cohorts and prospective studies.
in radiation therapy planning, monitoring of treatment (surgery/chemotherapy) response and prognosis assessment.

[466]
TÍTULO / TITLE: - Solitary fibrous tumor of the pleura.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Marak CP; Dorokhova O; Guddati AK
INSTITUCIÓN / INSTITUTION: - Division of Pulmonary and Critical Care Medicine, Montefiore Hospital, Albert Einstein College of Medicine, Yeshiva University, New York, NY, USA.
RESUMEN / SUMMARY: - Solitary fibrous tumor of the pleura (SFTP) is a rare tumor of mesenchymal origin which can grow to a large size and present with symptoms of cough and pleuritic chest pain. No specific etiological factors for SFTPs are known and they may grow undetected for several years. These tumors are usually benign and may mimic a variety of malignancies. SFTPs are often detected as peripheral opacities on chest X-ray. Unfortunately, fine needle aspiration rarely provides adequate information for a definitive diagnosis. Imaging with computed tomography provides details about the size and extent of any invasion into adjacent tissues. Surgical resection is the mainstay of treatment, and immunohistochemistry of the resected tumor often provides confirmation of the diagnosis. Some SFTPs have been observed to be malignant, and surgical intervention is often lifesaving. There is no adequate data to support the usage of radiotherapy and chemotherapy in the treatment of SFTPs. This tumor exemplifies malignancies which require surgical resection to preempt worse outcomes. Awareness of their presentation and clinical course may help the clinician provide a prompt referral to the thoracic surgeon for resection.

[467]
TÍTULO / TITLE: - Delayed paraplegia due to “surgiceloma” following thoracotomy for a Pancoast tumor.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Schatlo B; Eger AF; Schaller K; Tessitore E
TÍTULO / TITLE: - ALK rearrangements in EBUS-derived transbronchial needle aspiration cytology in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Neat MJ; Foot NJ; Hicks A; Breen R; Wilkins B; McLean E; Santis G
INSTITUCIÓN / INSTITUTION: - Cytogenetics Unit, GSTS Pathology, Guy’s & St Thomas’ NHS Foundation Trust, London, UK.
RESUMEN / SUMMARY: - OBJECTIVES: Patients with non-small cell lung cancer (NSCLC) positive for anaplastic lymphoma kinase (ALK) gene rearrangements may be treated successfully with the ALK inhibitor crizotinib. ALK copy-number abnormalities have also been described. In this study, we evaluated the suitability of fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) to determine ALK status in endobronchial ultrasound (EBUS)-derived cytology samples. METHODS: Samples were obtained from 55 consecutive patients with NSCLC who had undergone EBUS-transbronchial needle aspiration (TBNA) according to our standard clinical protocols. All tumours had been screened previously for epithelial growth factor receptor (EGFR) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. FISH, using commercially available ALK rearrangement-specific probes, was employed to assess ALK status. IHC using the ALK-1 monoclonal antibody (DAKO) was also performed. RESULTS: FISH analysis was successful in 52 of 55 samples (94.5%); ALK rearrangement was demonstrated in 3 of 52 samples from patients with NSCLC (5.7%). ALK amplification was observed in 3 of 52 patient samples (5.7%) and an increase in ALK copy number was found in 28 of 52 patient samples (53.8%). IHC on cell blocks demonstrated ALK expression in one of three samples with ALK rearrangement. One patient sample had concomitant ALK rearrangement and KRAS mutation. CONCLUSIONS: We found FISH to be superior to IHC using the ALK-1 monoclonal antibody for the detection of ALK rearrangement in EBUS-TBNA cytology specimens in NSCLC, and also that ALK rearrangement can co-exist with KRAS mutation in the same tumour.

TÍTULO / TITLE: - Use of cidofovir in recurrent respiratory papillomatosis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1007/s00405-013-2456-6
AUTORES / AUTHORS: - Carifi M
INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology, A.O.R.N Azienda Ospedaliera Cardarelli, Via Antonio Cardarelli, 9, 80131, Naples, Italy, marco.carifi@gmail.com.

CASTELLANO

TÍTULO / TITLE: Les promesses de la radiotherapie. Focus sur les tumeurs pulmonaires.

TÍTULO / TITLE: - Radiotherapy promises: focus on lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1684/bdc.2013.1760
AUTORES / AUTHORS: - Jouin A; Durand-Labrunie J; Leroy T; Pannier D; Wagner A; Rault E; Lartigau E
INSTITUCIÓN / INSTITUTION: - Centre Oscar-Lambret, universite Lille 2, departement universitaire de radiotherapie, 3, rue Frederic-CombeMale, 59000 Lille, France.

RESUMEN / SUMMARY: - Radiotherapy is a key cancer treatment, which greatly modified its practice in recent years thanks to medical imaging and technical improvements. The systematic use of computed tomography (CT) for treatment planning, the imaging fusion/co-registration between CT/magnetic resonance imaging (MRI) or CT/positron emission tomography (PET) improve target identification/selection and delineation. New irradiation techniques such as image-guided radiotherapy (IGRT), stereotactic radiotherapy or hadron therapy offer a more diverse therapeutic armamentarium to patients together with lower toxicity. Radiotherapy, as well as medical oncology, tends to offer a personalized treatment to patients thanks to the IGRT, which takes into account the inter- or intra-fraction anatomic variations. IGRT leads to adaptive radiotherapy (ART) with a new planification in the treatment course in order to decrease toxicity and improve tumor control. The use of systemic therapies with radiations needs to be studied in order to improve efficiency without increasing toxicities from these multimodal approaches. Finally, radiotherapy advances were impacted by radiotherapy accidents like Epinal. They led to an increased quality control with the intensification of identity control, the emergence of in vivo dosimetry or the experience feedback committee in radiotherapy. We will illustrate through the example of lung cancer.
TÍTULO / TITLE: - Human immunodeficiency virus-associated lung malignancies.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lambert AA; Merlo CA; Kirk GD
INSTITUCIÓN / INSTITUTION: - Department of Medicine, Johns Hopkins School of Medicine, 1830 Monument Street, Baltimore, MD, USA; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA.
RESUMEN / SUMMARY: - This review of lung malignancies in human immunodeficiency virus (HIV) briefly highlights key epidemiologic and clinical features in the pulmonary involvement of AIDS-defining malignancies of Kaposi sarcoma and non-Hodgkin lymphoma. Then, focusing on non-AIDS defining lung cancer, the epidemiology and mechanisms, clinical presentation, pathology, treatment and outcomes, and prevention of HIV-associated lung cancer are discussed. Finally, the important knowledge gaps and future directions for research related to HIV-associated lung malignancies are highlighted.

[472]
TÍTULO / TITLE: - A combination of two electrophoretical approaches for detailed proteome-based characterization of SCLC subtypes.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Poschmann G; Lendzian A; Uszkoreit J; Eisenacher M; Borght AV; Ramaekers FC; Meyer HE; Stuhler K
INSTITUCIÓN / INSTITUTION: - Molecular Proteomics Laboratory, BMFZ, Universitat Dusseldorf, Germany.
RESUMEN / SUMMARY: - Abstract Context: Small cell lung cancers (SCLC) are heterogeneous and tumours differ in growth characteristics and treatment resistance. Objective: To get insight into the underlying protein profiles responsible for this heterogeneity, two subtypes of SCLC cells mutually differing in chemo resistance properties and growth characteristics are analysed. Materials and methods: Two different electrophoresis approaches in combination with mass spectrometry were used to detect differences between the SCLC cell lines GLC1 and GLC1M13: IEF/SDS-PAGE as well as
cetyltrimethylammonium bromide (CTAB)-SDS-PAGE. Results: Altogether 60 non redundant differentially expressed proteins were found of which 5 were verified by Western Blot analysis. Discussion: Most of these proteins identified are involved in processes of tumour progression. Therefore, these proteins are interesting candidates for further functional analysis. Conclusion: Additional CTAB-SDS page is a complementary method to IEF-SDS page revealing a complete new subset of proteins differentially expressed between GLC1 and GLC1 M13 cells SCLC subtypes.

[473]

TÍTULO / TITLE: SOX7 is down-regulated in lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Hayano T; Garg M; Yin D; Sudo M; Kawamata N; Shi S; Chien W; Ding LW; Leong G; Mori S; Xie D; Tan P; Koeffler HP
INSTITUCIÓN / INSTITUTION: Genomic Oncology Programme, Cancer Science Institute of Singapore, NUS, Singapore, 14 Medical Drive, #12-01, Singapore 117599, Singapore. csimg@nus.edu.sg.

RESUMEN / SUMMARY: BACKGROUND: SOX7 is a transcription factor belonging to the SOX family. Its role in lung cancer is unknown. METHODS: In this study, whole genomic copy number analysis was performed on a series of non-small cell lung cancer (NSCLC) cell lines and samples from individuals with epidermal growth factor receptor (EGFR) mutations using a SNP-Chip platform. SOX7 was measured in NSCLC samples and cell lines, and forced expressed in one of these lines. RESULTS: A notable surprise was that the numerous copy number (CN) changes observed in samples of Asian, non-smoking EGFR mutant NSCLC were nearly the same as those CN alterations seen in a large collection of NSCLC from The Cancer Genome Atlas which is presumably composed of predominantly Caucasians who often smoked. However, four regions had CN changes fairly unique to the Asian EGFR mutant group. We also examined CN changes in NSCLC lines. The SOX7 gene was homozygously deleted in one (HCC2935) of 10 NSCLC cell lines and heterozygously deleted in two other NSCLC lines. Expression of SOX7 was significantly downregulated in NSCLC cell lines (8/10, 80%) and a large collection of NSCLC samples compared to matched normal lung (57/62, 92%, p= 0.0006). Forced-expression of SOX7 in NSCLC cell lines markedly reduced their cell growth and enhanced their apoptosis. CONCLUSION: These data suggest that SOX7 is a novel tumor suppressor gene silenced in the majority of NSCLC samples.
Surgical approach to locally advanced non-small cell lung cancer.

Treatment for locally advanced non-small cell lung cancer is complex. It may best be described as chemotherapy-based multimodality therapy, but there is little consensus on the optimal approach for local therapy. With the integration of the 7th edition of the staging system, the role for surgery in stage IIIB is limited to only biopsies and staging procedures. Surgery plays a more important role in stage IIIA disease, when the extent of mediastinal lymph node involvement is the principal factor dictating the benefit that can be derived from resection. In N2-negative, stage IIIA patients (T4N0, T3N1, T4N1), surgery is the primary therapy. These tend to be large and complex resections that include removal of neighboring involved structures. In the larger cohort of N2-positive, stage IIIA patients, surgery is reserved for those with occult or resectable N2 involvement and not used for bulky mediastinal disease. Significant controversy exists regarding which patients with potentially resectable N2 should receive surgery and how to best integrate a resection with chemotherapy and radiation.

Antitumor effect of blister beetles: An ethnomedicinal practice in Karbi community and its experimental evaluation against a murine malignant tumor model.

ETHNOPHARMACOLOGICAL IMPORTANCE: The blister beetles Epicauta hirticornis and Mylabris cichorii are used as a folk medicine by the Karbi tribe in Karbi Anglong district of Assam, India for the...
AIM OF THE STUDY: It includes field survey related to zoo-therapeutic aspects of two blister beetles in Karbi community, isolation of bio-active compound and evaluation of its antitumor potential with possible mode of action against murine Ehrlich ascites carcinoma (EAC). MATERIALS AND METHODS: The main bio-active compound of blister beetles was isolated from ethyl acetate extract and the structure was confirmed as cantharidin using NMR, IR, Mass and X-ray diffractometer. The effect of cantharidin on apoptosis, necrosis, autophagy and the apoptosis related signaling pathways were determined using different bioassays, including cell cycle analysis, mitochondrial membrane potential, western blot analysis of cytochrome c, caspases 9, 3/7 assays, and lactate dehydrogenase (LDH) assay. RESULTS: Cantharidin induced apoptosis, necrosis and autophagy cell death in EAC cells. The decrease in mitochondrial membrane potential was observed, which may help to release cytochrome c from mitochondria to cytosol. Cantharidin treatment caused up-regulation of caspases 9 and -3/7 and a decrease in LDH activity in EAC cells. CONCLUSION: The major bioactive compound of these blister beetles is cantharidin which induces severe apoptosis in EAC cells involving mitochondrial intrinsic pathway. Cantharidin-mediated inhibition of LDH activity may lead to short supply of NAD+ and cut off energy and anabolic supply to cancer cells.

[476]

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

AUTORES / AUTHORS: - Weng Y; Cai M; Zhu J; Geng J; Zhu K; Jin X; Ding W
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, The Fourth People's Hospital of Wuxi, The Fourth Affiliated Hospital of Suzhou University, Jiangsu, China.

RESUMEN / SUMMARY: - Background: The matrix metalloproteinases (MMPs)-2, -9 and -7 are thought to be associated with tumor invasion, metastasis, and angiogenesis. However, their possible roles in early-stage lung cancer are not clear. We measured the activity of MMP-2, -7 and -9 in early-stage lung cancer tissues. Material and Methods: Normal lung tissues and cancer tissues were collected from 60 consecutive stage-I non-small cell lung cancer (NSCLC) patients. The activities of MMP-2 and MMP-9 were determined by gelatin zymography, and the activity of MMP-7 was determined by casein zymography. Furthermore, the ratio of the active form of MMP-2 in tumor tissue (T) compared with normal tissue (N) was determined, and the survival in the groups with different MMP-2 T:N ratio was compared. Results: The activity of both MMP-2
and MMP-9 was detected in all cancer and normal tissues. Interestingly, MMP-9 activity was significantly reduced, whereas MMP-2 activity was significantly increased, in cancer tissues compared to normal tissues. The survival rate of the MMP-2 T:N ratio > 2.5 group was 57.45%, which was significantly reduced compared with that of the T:N ratio ≤ 2.5 group (86.78%). Conclusion: Our findings suggest that MMP-2, but not MMP-9 and MMP-7, may be implicated in early-stage tumor invasion, metastasis, and angiogenesis in NSCLC.

[477]

TÍTULO / TITLE: Exposing a deadly alliance: Novel insights into the biological links between COPD and lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Vermaelen K; Brusselle G
INSTITUCIÓN / INSTITUTION: Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. Electronic address: karim.vermaelen@ugent.be.
RESUMEN / SUMMARY: Chronic obstructive pulmonary disease (COPD) affects more than 200 million people worldwide and is expected to become the third leading cause of death in 2020. COPD is characterized by progressive airflow limitation, due to a combination of chronic inflammation and remodeling of the small airways (bronchiolitis) and loss of elastic recoil caused by destruction of the alveolar walls (emphysema). Lung cancer is the most important cause of cancer-related death in the world. (Cigarette) smoking is the principal culprit causing both COPD and lung cancer; in addition, exposure to environmental tobacco smoke, biomass fuel smoke, coal smoke and outdoor air pollution have also been associated with an increased incidence of both diseases. Importantly, smokers with COPD - defined as either not fully reversible airflow limitation or emphysema - have a two- to four-fold increased risk to develop lung cancer. In this review, we highlight several of the genetic, epigenetic and inflammatory mechanisms, which link COPD and carcinogenesis in the lungs. Elucidating the biological pathways and networks, which underlie the increased susceptibility of lung cancer in patients with COPD, has important implications for screening, prevention, diagnosis and treatment of these two devastating pulmonary diseases.

[478]

RESUMEN / SUMMARY: Infection with high-risk types of human papillomavirus (hrHPV) is associated with cervical, anogenital, and oropharyngeal cancers. Since a causal contribution of hrHPV infection to lung cancer (LC) is still a matter of debate, a comprehensive study was performed to delineate hrHPV involvement in LC, using a Dutch study population.

METHODS: Archival tissue specimens from 223 patients (145 men, 78 women, median age 65 years, range 27-87 years), who presented with cancer in the lungs, were subjected to GP5+/6+ polymerase chain reaction and p16 immunohistochemistry. The series included primary lung carcinomas of patients without a history of cancer (n = 175), primary lung carcinomas of patients with an unrelated cancer in the past (n = 36), and carcinomas with primary presentation in the lungs of which the origin (i.e., primary or metastasis) was equivocal at the time of diagnosis (n = 12). GP5+/6+ polymerase chain reaction/p16 double-positive carcinomas were subjected to HPV genotyping, HPVE7 transcript analysis, loss of heterozygosity analysis, and array-comparative genomic hybridization. RESULTS: Whereas all primary lung carcinomas were hrHPV-negative (211 of 211, 100%), three hrHPV-positive equivocal carcinomas (3 of 12, 25%) were identified. These patients (1 male, 2 females) had a history of hrHPV-associated disease; one tonsillar and two cervical carcinomas. A clonal relationship between individual tumor pairs was supported by identical hrHPV genotype, pattern of p16 expression, HPVE7 mRNA expression, and genomic aberrations. CONCLUSIONS: hrHPV presence in a tumor with primary presentation in the lungs signifies pulmonary metastasis from a primary hrHPV-positive cancer elsewhere in the body. No support was found for an attribution of hrHPV infection to the development of primary LC.
TÍTULO / TITLE: - From the guest editors: management of locally advanced lung cancer.

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


AUTORES / AUTHORS: - Carbone DP; Chakravarti A

INSTITUCIÓN / INSTITUTION: - From the *James Thoracic Center and James Cancer Center, The Ohio State University Medical Center; and the daggerDepartment of Radiation Oncology, Brain Tumor Program, Arthur G. James Comprehensive Cancer Center and Richard L. Solove Research Institute, The Ohio State University Medical School, Columbus, Ohio.

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[480]

TÍTULO / TITLE: - Locally advanced lung cancer: an optimal setting for vaccines and other immunotherapies.

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


AUTORES / AUTHORS: - Iyengar P; Gerber DE

INSTITUCIÓN / INSTITUTION: - From the Departments of *Radiation Oncology and daggerInternal Medicine (Hematology-Oncology) and double daggerThe Harold C. Simmons Cancer Center; University of Texas Southwestern Medical Center, Dallas, TX.

RESUMEN / SUMMARY: - Lung cancer has traditionally been considered relatively resistant to immunotherapies. However, recent advances in the understanding of tumor-associated antigens, anti-tumor immune responses, and tumor immunosuppression mechanisms have resulted in a number of promising immunomodulatory therapies such as vaccines and checkpoint inhibitors. Locally advanced non-small cell lung cancer is an optimal setting for these treatments because standard therapies such as surgery, radiation, and chemotherapy may enhance anti-tumor immune effects by debulking the tumor, increasing tumor antigen presentation, and promoting T-cell response and trafficking. Clinical trials incorporating immunomodulatory agents into combined modality therapy of locally advanced non-small cell lung cancer have shown promising results. Future challenges include identifying biomarkers to predict those patients most likely to benefit from this approach, radiographic assessment of treatment effects, the timing and dosing of combined modality
treatment including immunotherapies, and avoidance of potentially overlapping toxicities.

[481]

**TÍTULO / TITLE:** - Comparison of endobronchial ultrasound and/or endoesophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small-cell lung cancer.

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


**AUTORES / AUTHORS:** - Zielinski M; Szlubowski A; Kolodziej M; Orzechowski S; Laczynska E; Pankowski J; Jakubiak M; Obrochta A

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland. marcinz@mp.pl

**RESUMEN / SUMMARY:** - BACKGROUND: To compare the diagnostic yield of endobronchial ultrasound (EBUS) and/or endoesophageal ultrasound (EUS) with transcervical extended mediastinal lymphadenectomy (TEMLA) for primary staging and repeated staging (restaging) of non-small-cell lung cancer (NSCLC). METHODS: In this retrospective study, all consecutive patients undergoing primary staging and restaging after neoadjuvant chemoradiotherapy for NSCLC with EBUS, EUS, or EBUS combined with EUS (CUS) with fine needle aspiration biopsy and cytological examination and subsequent TEMLA from January 1, 2007 to December 31 2010, were included. RESULTS: Primary staging was performed in 623 patients: EBUS in 351, EUS in 72, and CUS in 200 patients. TEMLA was performed for primary staging in 276 patients. There was no mortality and morbidity after EBUS or EUS. One patient died after TEMLA and morbidity rate after TEMLA was 7.2%. There was a significant difference between EBUS or EUS and TEMLA for sensitivity (87.8% and 96.2%; p < 0.01) and negative predictive value (82.5% and 99.6%; p < 0.01) in favor of TEMLA. In the restaging group, endoscopic staging was performed in 88 patients and TEMLA in 78 patients. There was a significant difference between EBUS or EUS and TEMLA for sensitivity (64.3% and 100%; p < 0.01) and negative predictive value (82.1% and 100%; p < 0.01) in favor of TEMLA. CONCLUSIONS: The results of this largest reported series comparing the endoscopic and surgical primary staging and restaging of NSCLC showed a significantly higher diagnostic yield of TEMLA when compared with that of EBUS or EUS.

[482]
TÍTULO / TITLE: - An unusual manifestation of a rare pleuropulmonary blastoma presenting with spinal cord compression and its neurosurgical implications.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fayeye O; Volpon M; George J; Hobin D; Solanki G
INSTITUCIÓN / INSTITUTION: - Department of Paediatric Neurosurgery, Department of Paediatric Oncology, Birmingham Children’s Hospital, Steelhouse Lane, Birmingham B4 6NH, UK.
RESUMEN / SUMMARY: - Pleuropulmonary blastomas (PPB) are rare and biologically aggressive paediatric tumours. Although central nervous system metastatic dissemination is a recognised complication of PPB, to our knowledge, spinal cord compression has been described only in six patients. We report a 5-year-old boy with a diagnosis of recurrent type III PPB that was initially thought to be an empyema, who developed features of thoracic spinal cord compression secondary to local tumour infiltration. Although PPB demonstrate significant biologically aggressive behaviour, aggressive surgical resections together with adjuvant chemotherapy can help limit disease progression without impacting on the quality of life. Spinal metastatic disease should also be treated vigorously. In this paper we discuss the treatment strategies available in the management of PPB.

[483]
TÍTULO / TITLE: - Sarcomatoid Lung Carcinomas Show High Levels of Programmed Death Ligand-1 (PD-L1).
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Velcheti V; Rimm DL; Schalper KA
INSTITUCIÓN / INSTITUTION: - Departments of Medical Oncology and Pathology, Yale School of Medicine, New Haven, Connecticut.
RESUMEN / SUMMARY: - Programmed death-1 (PD-1) is a co-inhibitory inducible receptor present on T-cells and macrophages. Tumor cells with increased programmed death ligand-1 (PD-L1) are believed to escape immunity through activation of PD-1/PD-L1 pathway and suppression of effector-immune responses. Recent strategies targeting the PD-1/PD-L1 axis have shown promising results in patients with several tumors types, including lung carcinomas. Preliminary data suggest that PD-L1 protein expression might have predictive response to such therapies. Sarcomatoid carcinomas (SCs) of the
lung include rare subtypes of poorly differentiated non-small-cell lung carcinomas of high grade and aggressive behavior. The biology of these neoplasms is poorly understood and they frequently show increased local inflammatory and lymphocytic infiltration. Here, we report the expression of PD-L1 in 13 SCs from two large retrospective lung cancer cohorts. Using automated quantitative immunoflorescence and a mouse monoclonal antibody directed against the extracellular domain of PD-L1, we show that 9 of 13 patients (69.2%) with SCs are positive for PD-L1 and their levels are higher than in conventional non-small-cell lung carcinoma. These results provide rationale for the potential use of targeted immunotherapy in lung SCs.

[484]

**Título / Title:** Management of malignant pleural mesothelioma: have we made any progress?

**Resumen / Summary:** As the incidence of malignant pleural mesothelioma (MPM) is increasing in the next decades, treatment is a challenge. The past 2 years have seen a number of promising achievements in the management of patients with MPM. Treatment of a symptomatic malignant pleural effusion through indwelling pleural catheter (IPC) may allow for an individualized treatment. Advances in the systemic treatment with targeted agents will undoubtedly gain by the discovery of a driver mutation which may be selectively targeted. In the meantime, the addition of monoclonal antibodies to a standard chemotherapy backbone might result in a modest improvement in outcome in patients selected for the presence of the ligand. New techniques in radiation therapy, pleural intensity-modulated radiotherapy, helical tomography and proton-therapy are exciting advances in multimodality treatment enhancing local control and therefore improving overall survival. The role of surgery remains controversial and should be further explored. Surgical procedures consist of extrapleural pneumonectomy or lung sparing operations like debulking of the parietal and visceral pleura by (extended) pleurectomy/decortication. Where the treatment in multimodality therapy may lead to improved disease-free survival and overall survival, the type of cytoreductive procedure should be selected on institutional and surgeon’s experience. The increase in mesothelioma incidence is matched only by the increasing number of researchers and studies. It is up to the clinicians to...
support these efforts by stimulating their patients to participate in this clinical research.

RESUMEN / SUMMARY: - INTRODUCTION:: Lung cancer is often diagnosed by cytology, necessitating predictive molecular marker analyses on cytological specimens. The gold standard for detection of predictive anaplastic lymphoma kinase (ALK)-rearrangements is fluorescence in situ hybridization (FISH), but FISH is both expensive and often challenging to interpret. The aim of our study was to investigate the accuracy of ALK immunocytochemistry (ICC) on cytological specimens of non-small-cell lung cancers (NSCLCs). METHODS:: Forty-one cytological specimens with available ALK FISH results were retrospectively analyzed with the 5ª4 monoclonal antibody (Novocastra; Leica Biosystems) on a fully automated slide stainer. The specimens were enriched for ALK FISH-positive NSCLCs (14 of 41; 34.1%). Evaluation of the ICC staining was performed blinded to the FISH results. The staining intensity and the percentage of stained cancer cells were recorded. Any ICC staining was regarded as a positive result. The ALK ICC results were compared with the FISH results. In case of a discrepancy the ICC-stained slide and the FISH signals were reviewed. RESULTS:: ICC was evaluable on 40 of 41 specimens. Fifteen of 40 NSCLCs (37.5%) were ALK ICC-positive, with staining of the majority of cancer cells (median 100%; mean 82.3%). Twelve of the ICC-positive NSCLCs (80.0%) showed an intense staining (3+). Compared with the ALK FISH results, only one NSCLC was false-negative, and one false-positive by ICC, respectively. The sensitivity, specificity, and positive and negative predictive values for ALK ICC compared with ALK FISH were 93.3%, 96.0%, 93.3%, and 96%, respectively. CONCLUSION:: ALK ICC is highly accurate for detecting ALK-rearranged NSCLCs.
Interobserver Agreement in the Nuclear Grading of Primary Pulmonary Adenocarcinoma.

INTRODUCTION:: Nuclear grading involves an evaluation of the size and shape of nuclei and the percentage of tumor cells that are in the mitotic phase. To estimate the degree of aggressiveness, this approach has been applied to various types of carcinomas, such as breast carcinoma and pulmonary adenocarcinoma (Nakazato et al.). In the present study, we estimated and evaluated the interobserver variability of nuclear grading in primary pulmonary adenocarcinomas. METHODS:: We selected 122 primary pulmonary adenocarcinomas measuring 2 cm or less in diameter. Eight pathologists independently evaluated the nuclear factors, using the nuclear grading system reported previously by Nakazato et al. The same pathologists also used both the international multidisciplinary classification of pulmonary adenocarcinoma (2011 International Association for the Study of Lung Cancer classification) and Noguchi’s classification, and assessed the extent of the lepidic pattern in the largest cut surface of the tumor. Interobserver agreement was evaluated using the kappa statistic. The disease-free survival curves of the patients were obtained using the Kaplan-Meier method and analyzed with the
RESULTS:: The mean (+/-SD) kappa values for the two histological classifications, the extent of the lepidic pattern, and nuclear grading were 0.46 +/- 0.09, 0.48 +/- 0.09, 0.45 +/- 0.16, and 0.58 +/- 0.09, respectively. The cases judged as negative on the basis of nuclear grading showed a significantly better prognosis (5-year disease-free survival rate; 91.8% +/- 2.7) than the positive cases did (68.6% +/- 3.1). CONCLUSION:: Nuclear grading is practical for prognostic evaluation of pulmonary adenocarcinoma. The interobserver agreement for nuclear grading is significantly higher than for histological classifications and the extent of the lepidic pattern. Nuclear grading is a reliable prognostic indicator for small adenocarcinomas.
TÍTULO / TITLE: - Lung Cancer Detection with Digital Chest Tomosynthesis: Baseline Results from the Observational Study SOS.

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


AUTORES / AUTHORS: - Terzi A; Bertolaccini L; Viti A; Comello L; Ghirardo D; Priotto R; Grosso M

INSTITUCIÓN / INSTITUTION: - *Thoracic Surgery Unit, Department of Surgery, and daggerDepartment of Radiology, S. Croce City Hospital, Cuneo Italy.

RESUMEN / SUMMARY: - INTRODUCTION: Observational studies consistently support strategies for early cancer diagnosis and treatment. Owing to its high prevalence, mortality rate, and easily identifiable at-risk population groups, lung cancer seems ideal for early detection programs. We present the baseline results of the SOS study, a single-arm observational study of digital chest tomosynthesis for lung cancer detection in an at-risk population. METHODS: Accrual of study participants started in December 2010 and ended in December 2011. Participants considered eligible were smokers or former smokers aged 45 to 75 years, with a smoking history of at least 20 pack-years, without malignancy in the 5 years before the start of the study. A tomosynthesis examination was performed at baseline and another the year after. RESULTS: Of the 1919 candidates assessed, 1843 (96%) were enrolled into the study: the mean age was 61 years (range, 48-73 years); 1419 (77%) were current smokers. The most prevalent comorbidities were hypertension, chronic obstructive pulmonary disease, and cardiovascular diseases. A total of 1843 tomosynthesis studies were obtained. Pulmonary abnormalities were detected in 268 subjects (14.5%). First-line basal computed tomography (CT) was subsequently carried out in 132 subjects (7.2%), 68 (4.9%) of which were referred for follow-up CT. Positron-emission tomography/CT was performed on 27 individuals (1.46%), and lung cancer was detected in 18 (0.98%) of them. CONCLUSION: The detection rate of noncalcified lung nodules for tomosynthesis was comparable with rates reported for CT. A small subgroup underwent low-dosage CT and entered a follow-up program. Overall, lung cancer was detected in approximately 1% of cases. Digital chest tomosynthesis holds promise as a first-line lung cancer screening tool.

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TÍTULO / TITLE: - Detection of ALK Rearrangement by Immunohistochemistry in Lung Adenocarcinoma and the Identification of a Novel EML4-ALK Variant.

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

INTRODUCTION:: The echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion gene has been identified as a potent oncogenic driver in non-small-cell lung cancer, in particular adenocarcinoma (ADC). It defines a unique subgroup of lung ADC, which may be responsive to ALK inhibitors. Detection of ALK rearrangement by fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) is considered to be the standard procedure, but each with its own limitation. We evaluated the practical usefulness of immunohistochemistry (IHC) to detect ALK expression as a reliable detection method of ALK rearrangement in lung ADC.

METHODS:: We tested 373 lung ADCs for ALK rearrangement by IHC and FISH. Multiplex RT-PCR was performed to confirm the fusion variants. RESULTS:: Twenty-two of 373 lung ADCs (5.9%) were positive for ALK immunoreactivity. ALK-positive tumor cells demonstrated strong and diffused granular staining in the cytoplasm. All the ALK IHC-positive cases were confirmed to harbor ALK rearrangement, either by FISH, or RT-PCR. Two cases with positive ALK protein expression, but negative for breakapart FISH signal were shown to harbor EML4-ALK variant 1 by RT-PCR. None of the ALK IHC-negative cases were FISH-positive. In addition, we identified a novel EML4-ALK fusion variant (E3:ins53A20), and its potent transformation potential has been confirmed by in vivo tumorigenicity assay. CONCLUSION:: IHC can effectively detect ALK rearrangement in lung cancer. It might provide a reliable and cost-effective diagnostic approach in routine pathologic laboratories for the identification of suitable candidates for ALK-targeted therapy.
INTRODUCTION: Although positron emission tomography computed tomography (PET-CT) has been widely used for small-cell lung cancer (SCLC) staging, no study has examined the clinical impact of PET staging in limited-stage (LS) SCLC. METHODS: We identified patients with LS-SCLC treated definitively with concurrent chemoradiation. Outcomes were assessed using the Kaplan-Meier approach, Cox regression, and competing risks method. RESULTS: We treated 54 consecutive LS-SCLC patients with concurrent chemoradiation from January 2002 to August 2010. Forty underwent PET, 14 did not, and all underwent thoracoabdominopelvic CT and magnetic resonance imaging neuroimaging. Most patient characteristics were balanced between the comparison groups, including age, race, sex, bone scanning, median dosage, and performance status. More number of PET-staged patients presented with nodal metastases (p = 0.05). Median follow-up was similar for PET-staged and non-PET-staged patients (p = 0.59). Median overall survival from diagnosis in PET-staged patients was 32 versus 17 months in patients staged without PET (p = 0.03), and 3-year survival was 47% versus 19%. Median time-to-distant failure was 29 versus 12 months (p = 0.04); median time-to-local failure was not reached versus 16 months (p = 0.04). On multivariable analysis, PET staging (odds ratio [OR] = 0.24; p = 0.04), performance status (OR = 1.89; p = 0.05), and N-stage (OR = 4.94; p < 0.01) were associated with survival. CONCLUSION: LS-SCLC patients staged with PET exhibited improved disease control and survival when compared with non-PET-staged LS-SCLC patients. Improved staging accuracy and better identification of intrathoracic disease may explain these findings, underscoring the value of PET-CT in these patients.
AUTORES / AUTHORS: - Davies HE; Lee YC

INSTITUCIÓN / INSTITUTION: - aDepartment of Respiratory Medicine, University Hospital of Wales, Cardiff, UK bDepartment of Respiratory Medicine, Sir Charles Gairdner Hospital cSchool of Medicine and Pharmacology, CAARR, University of Western Australia, Perth, Western Australia, Australia.

RESUMEN / SUMMARY: - PURPOSE OF REVIEW: Malignant pleural effusion (MPE) is common. However, regardless of the differences between patients, their underlying cancer type, and pleural fluid characteristics, management options are often limited. These have not advanced significantly over the last 80 years since pleurodesis was first described. Correspondingly, patient-related outcome measures have been neglected. The evidence (or lack of) behind the current treatment recommendations is reviewed and key research questions are described. RECENT FINDINGS: Talc continues to be the most effective sclerosant available for pleurodesis in MPE. A recent randomized controlled trial comparing talc pleurodesis and indwelling pleural catheter insertion as first-line therapy suggests these approaches are equally effective, and utilized a patient-based symptom score as the primary outcome. The need to acknowledge the advances in translational medicine and oncological therapies to measure patient-related trial outcomes and to target pleural fluid formation in MPE is discussed. SUMMARY: Pulmonologists should be aware of the staggering lack of progress in the evidence that supports the current 'recommended' management of MPE. The need for a re-think about MPE management with a focus on alternative therapeutic targets and treatment objectives should be appreciated, in order to optimize future patient care.

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TÍTULO / TITLE: - Disease Flare After EGFR Tyrosine Kinase Inhibitor Cessation Predicts Poor Survival in Patients with Non-small Cell Lung Cancer.

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


AUTORES / AUTHORS: - Chen HJ; Yan HH; Yang JJ; Chen ZH; Su J; Zhang XC; Wu YL

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, People’s Republic of China.

RESUMEN / SUMMARY: - Available study revealed non-small cell lung cancer (NSCLC) patients faced a risk of disease flare after cessation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. There was no data concerning the prognostic value of disease flare. This study aimed to investigate the prevalence of disease flare in a Chinese cohort, and analyzed
A cohort of 227 NSCLC patients with acquired resistance to EGFR TKI was retrospectively analyzed. Prevalence and clinical features of disease flare after TKI cessation were reviewed. Survival data were analyzed between patients with flare and those without flare. EGFR gene mutations in tumors were detected. Twenty of 227 (8.8%) patients were determined with disease flare after TKI cessation. The median interval from TKI cessation to disease flare was 7 days (range 3-18). Forty percent of patients complained of deteriorated dyspnea attributable to malignant effusion. Thirty percent of patients had progressive lesions in the brain. After TKI cessation 35% of flare patients died before challenge of subsequent treatment. No response was observed in 30% of flare patients undergoing subsequent chemotherapy. When compared with the non-flare group, patients with disease flare demonstrated comparable progression-free survival (10.1 vs. 9.9 months; P = 0.973), shorter post-TKI survival (4.1 vs. 6.1 months; P < 0.001), and a significantly poor overall survival (16.6 vs. 21.6 months; P = 0.002). Disease flare after cessation of EGFR TKI occurred in Chinese NSCLC population and predicted a poor survival.
that the variant genotypes of XPA23 (A/G+G/G) were associated with significantly longer progression-free survival (PFS) (6.0 m vs. 10.6 m, log-rank P = 0.001) and overall survival (OS) (11.2 m vs. 20.8 m, log-rank P = 0.001). In Cox proportional hazards model, the hazard ratio (HR) for death in patients with G allele was 0.65 (P = 0.049). While no significant differences were observed in PFS or OS according to XPD Lys751Gln genotypes (log-rank P > 0.05). In combination with our previous short-term clinical results, this study further confirmed that by detecting the SNPs in blood cells, XPA A23G polymorphic variants might be a promising biomarker in predicting a favorable prognosis of NSCLC patients and be helpful towards designing individualized treatments.
AUTORES / AUTHORS: - Nogueira A; Assis J; Catarino R; Medeiros R
INSTITUCIÓN / INSTITUTION: - Portuguese Institute of Oncology, Molecular Oncology Group - Cl, Edificios Laboratorios - Piso 4, Rua Dr. Ant. Bernardino Almeida, 4200-072 Porto, Portugal.
RESUMEN / SUMMARY: - Many of the cytotoxic drugs used in the treatment of non-small-cell lung carcinoma patients can interfere with DNA activity and the definition of an individual DNA repair profile could be a key strategy to achieve better response to chemotherapeutic treatment. Although DNA repair mechanisms are important factors in the prevention of carcinogenesis, these molecular pathways are also involved in therapy response. RAD51 is a crucial element in DNA repair by homologous recombination and has been shown to interfere with the prognosis of patients treated with chemoradiotherapy. There is increasing evidence that genetic polymorphisms in repair enzymes can influence DNA repair capacity and, consequently, affect chemotherapy efficacy. We conducted this review to show the possible influence of the RAD51 genetic variants in damage repair capacity and treatment response in non-small-cell lung carcinoma patients.

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TÍTULO / TITLE: - Metabolic response evaluated by F-FDG PET/CT as a potential screening tool in identifying a subgroup of patients with advanced non-small cell lung cancer for immediate maintenance therapy after first-line chemotherapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Moon SH; Cho SH; Park LC; Ji JH; Sun JM; Ahn JS; Park K; Choi JY; Ahn MJ
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: Among patients with advanced non-small cell lung cancer (NSCLC), identification of a subgroup of patients for immediate maintenance treatment after first-line chemotherapy has great importance in improving survival. The purpose of this study was to investigate whether the metabolic responses evaluated by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) may be a potential screening tool for identifying patients with early disease progression who may benefit from immediate maintenance treatment. METHODS: A total of 52 patients with advanced NSCLC (36 men and 16 women, mean age 57.2 +/- 10.6 years) who
underwent baseline and follow-up 18F-FDG PET/CT after four cycles of first-line chemotherapy were enrolled. Maximum standardized uptake value (SUVmax), SUVpeak, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) of the tumour lesions were measured and percentage decrease of the parameters was calculated. The prognostic significance of percentage decrease of these parameters and other clinical variables related to progression-free survival (PFS) and overall survival (OS) were assessed by Cox proportional hazards regression analysis. Receiver-operating characteristic (ROC) curve analysis was used to define the optimal cut-off value of percentage decrease of the parameters that could distinguish between early (PFS < 6 months) and late (PFS ≥ 6 months) disease progression groups. RESULTS: Multivariate analysis showed that percentage decrease of TLG [hazard ratio per 10 % decrease = 1.030, 95 % confidence interval (CI) = 1.012-1.048, p = 0.001] was a significant predictor of PFS and OS. ROC curves identified a 50.0 % decrease in TLG as the optimal cut-off value to distinguish disease progression groups. Positive and negative predictive values of the optimal TLG value for selecting patients with late disease progression were 36.4 and 100.0 %, respectively. CONCLUSION: The percentage decrease in TLG of measurable tumour lesions may be a potential parameter to appropriately identify a subgroup of patients for immediate maintenance treatment after first-line chemotherapy in patients with advanced NSCLC.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Maftouh M; Avan A; Galvani E; Peters GJ; Giovannetti E
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands.
RESUMEN / SUMMARY: - Non-small cell lung cancer (NSCLC) is one of the deadliest types of cancer. One explanation for this poor prognosis is the failure of most chemotherapeutic regimens, which prompted the development of new, rationally designed, targeted antitumor agents, such as inhibitors of the epidermal growth factor receptor (EGFR) and downstream pathways. However, most of these targeted therapies also fail, and studies on the mechanisms underlying resistance toward targeted agents might provide critical findings for NSCLC research and treatment. Some of these studies showed that drug resistance can emerge not only from genetic aberrations, but also from epigenetic changes, including regulation of different signaling pathways by microRNAs (miRNAs), which act as key post-transcriptional regulators of gene
expression. There is accumulating evidence that specific miRNAs correlated with drug sensitivity and can be used as prognostic markers in NSCLC. However, a greater knowledge of miRNAs might also provide novel insights in several drug-resistance mechanisms; hence, suggesting their potential in novel therapeutic interventions, by sensitizing tumor cells to drug-induced apoptosis as well as by inhibiting tumor proliferation and invasive capabilities. Therefore, this review highlights several recent and clinically relevant aspects of the regulation of drug resistance by miRNAs from the perspective of current anti-EGFR-targeted therapies in NSCLC.
% (p = 0.013), respectively, was indicative of an increased risk of disease-specific death. CONCLUSION: PET/CT performed 1 year after SBRT can reliably identify local recurrence and therefore help to clarify unclear CT findings. As posttherapeutic glucose metabolism also correlates with disease-specific survival, PET/CT may help to stratify lung cancer patients for additional treatment 1 year after SBRT.

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TÍTULO / TITLE: - Relationship between 18 FDG PET-CT findings and the survival of 177 patients with malignant pleural mesothelioma.

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


AUTORES / AUTHORS: - Abakay A; Komek H; Abakay O; Palanci Y; Ekici F; Tekbas G; Tanrikulu AC

INSTITUCIÓN / INSTITUTION: - Department of Chest Disease, School of Medicine, Dicle University, Diyarbakir, Turkey. arahmanabakay@hotmail.com.

RESUMEN / SUMMARY: - BACKGROUND AND OBJECTIVES: Malignant pleural mesothelioma (MPM) is a fatal malignancy. Radiological imaging is necessary for the diagnosis, staging, and clinical management of patients with MPM. The 18 fluorodeoxyglucose positron emission tomography (18 FDG-PET) scan has proven useful in preoperative staging and as a prognostic tool in MPM. We aimed to investigate the relationship between the pre-treatment 18 FDG PET/CT results, together with other known clinical parameters, and the survival of patients with MPM in our region. PATIENTS AND METHODS: A retrospective analysis was performed on the data of 177 patients with MPM between April 2007 and April 2011. Pre-treatment 18 FDG PET/CT scans were done on all patients. Survival time was calculated by the Kaplan-Meier method. RESULTS: The mean age was 55.40 years. There were 56% male patients and 44% female patients. The mean survival time was 11 months from time of diagnosis. According to multivariate analysis results, being of male gender increased the poor prognosis 5.30 times, a Karnofsky performance score (KPS) < 60 increased a poor prognosis 2.18 times, being on “best supportive care” increased a poor prognosis 25.40 times, the stage III-IV increased a poor prognosis 11.13 times, and a level of maximum standardized uptake value (SUVmax) > 5 increased a poor prognosis 4.34 times. CONCLUSIONS: MPM remains a fatal prognosis. Significant predictors of survival include KPS, stage of disease, gender, treatment regimen and level of SUVmax. An understanding of the importance of these markers for MPM prognosis should allow targeted treatments to be developed.

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[500]
- CASTELLANO -


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


AUTORES / AUTHORS: - Schroder C; Ivo M; Buchali A

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RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: The present analysis compares two palliative treatment concepts for lung cancer in terms of overall survival. PATIENTS AND METHODS: Survival data from 207 patients were used in a retrospective analysis. All patients received palliative treatment comprising either 25 Gy applied in 5 fractions or 50 Gy in 20 fractions. A subgroup analysis was performed to compare patients with a good-fair vs. poor overall condition. RESULTS: Median survival times were 21 weeks (range 6-26 weeks) for patients treated with 25 Gy in 5 fractions and 23 weeks (range 14.5-31.5 weeks) for patients treated with 50 Gy in 20 fractions (95 % confidence interval, CI; p = 0.334). For patients with a good-fair overall condition, median survival times were 30 weeks (21.8-39.2 weeks) for 25 Gy in 5 fractions and 28 weeks (14.2-41.8 weeks) for 50 Gy in 20 fractions (CI 95 %, p = 0.694). In patients with a poor overall condition, these values were 18 weeks (14.5-21.5 weeks) and 21 weeks (13.0-29.0 weeks), respectively (CI 95 %, p = 0.248). CONCLUSION: The palliative treatment concept of 25 Gy applied in 5 fractions is sufficient for radiation of lung cancer, given that there was no obvious survival improvement in patients treated with the higher total dose regimen.

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


AUTORES / AUTHORS: - Abd-El-Fattah AA; Sadik NA; Shaker OG; Aboulftouh ML

INSTITUCIÓN / INSTITUTION: - Biochemistry Department, Faculty of Pharmacy, Cairo University, Kasr El-Einy Street, Cairo, Egypt.
RESUMEN / SUMMARY: - MicroRNAs (miRNAs) play critical regulatory roles in the physiological and pathological processes. The high stability of miRNAs in human serum represents attractive novel diagnostic biomarkers of clinical conditions. Several studies have shown that aberrant expression of miRNAs in human cancer including lung cancer, but little is known about their effects on some infectious lung diseases such as pulmonary tuberculosis (TB) and pneumonia. In this study, we investigated miRNA expression pattern in serum of Egyptian patients with lung cancer, TB, and pneumonia compared with matched healthy controls. Using microarray-based expression profiling followed by real-time quantitative polymerase chain reaction validation, we compared the levels of a series of circulating miRNAs (miR-21, miR-155, miR-182, and miR-197) in serum from patients with lung cancer (n = 65), pulmonary tuberculosis (n = 29), pneumonia (n = 29), and transudate (n = 16) compared with matched healthy controls (n = 37). MiRNA SNORD68 was the housekeeping endogenous control. We found that the serum levels of miR-21, miR-155, and miR-197 were significantly elevated in the patients with lung cancer and pneumonia whereas miR-182 and miR-197 levels were increased only in patients with lung cancer and TB, respectively, compared with controls. Receiver operating characteristic analysis revealed that miR-182, miR-155, and miR-197 have superior diagnostic potential in discriminating patients with lung cancer, pneumonia, and TB, respectively, from controls. Our results conclude that the differential expression of the four studied miRNAs can be potential non-invasive biomarkers for patients with lung cancer, TB and pneumonia.

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


AUTORES / AUTHORS: - Malik FA; Gysels M; Higginson IJ

INSTITUCIÓN / INSTITUTION: - The Department of Palliative Care, Policy & Rehabilitation, King’s College School of Medicine, Cicely Saunders Institute, London, UK.

RESUMEN / SUMMARY: - Background: Breathlessness is a common, distressing symptom in patients with advanced disease. With increasing focus on home death for patients, carers are expected to support breathless people at home. Little is known about how carers experience breathlessness and the differences in caring for someone with breathlessness and malignant or non-malignant disease. Aim: To compare experiences of caring for a breathless patient with lung cancer versus those with heart failure and to examine factors associated
with caregiver burden and positive caring experiences. Design: Cross-sectional survey of caregivers of breathless patients. Setting/participants: Participants were recruited from two London hospitals. Inclusion criteria: caregivers of patients with breathlessness and heart failure or lung cancer. Measures included self-completion of Short Form version of Zarit Burden Interview, a ‘positive caring experiences’ scale and Palliative Care Outcome Scale. We compared caregiver reports between heart failure and lung cancer. Multiple regression analyses were used to examine factors related to burden and positive caring experiences.

Results: In total, 51 heart failure and 50 lung cancer caregivers were recruited. Most were spouses (72%) and women (80%). Severity of patient breathlessness was similar in both groups. Caregiver concerns were mostly similar across conditions. Higher burden was associated with poorer ‘quality of patient care’ and worse carer psychological health ($R^2 = 0.37$, $F = 12.2$, $p = 0.01$). Caregiver depression and looking after more breathless patients were associated with fewer positive caring experiences ($R^2 = 0.15$, $F = 4.4$, $p = 0.04$).

Conclusions: Those who care for breathless patients report high levels of unmet needs and burden, equally severe for heart failure and lung cancer caregivers. Caregivers of patients with more severe breathlessness report fewer positive caring experiences and should be targeted by services with increased support in managing this symptom.
the management of patients with cerebral metastasis from melanoma and non-small cell lung cancer (NSCLC). Expert opinion: FTM is a third-generation nitrosourea that has proved its efficacy on brain metastases of melanoma and showed promising results for the treatment of brain metastasis of NSCLC because of its ability to pass the blood-brain barrier.

[504]


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


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AUTORES / AUTHORS: - Herbert C; Kwa W; Nakano S; James K; Moiseenko V; Wu J; Schellenberg D; Liu M

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, British Columbia Cancer Agency, 600 West 10th Avenue, Vancouver, BC, V5Z 4E6 Canada. christopher.herbert@UHBristol.nhs.uk.

RESUMEN / SUMMARY: - Stereotactic body radiotherapy (SBRT) is a treatment option for patients with early stage lung cancer. Treatment duration can be >30 minutes per fraction with non-coplanar 3D-conformal radiotherapy (3D-CRT). Whilst this is generally well tolerated, faster delivery techniques are desirable. Volumetric modulated arc therapy (VMAT) allows for fast delivery of radiation treatment. The purpose of this planning study was to compare SBRT with 3D-CRT and VMAT, with VMAT plans generated using both single arc and 3 non-coplanar partial arcs. Ten patients who previously underwent SBRT (48 Gy in 4 fractions) with 3D-CRT were selected. VMAT plans were generated to treat the PTV while limiting doses to organs at risk. Cumulative dose volume histogram (DVH) parameters were compared between the 3 techniques using the Wilcoxon matched pairs test. Treatment delivery time was also assessed. Both VMAT techniques covered target volumes more conformally than 3D-CRT with a mean V48/VPTV of 1.21 for 3D-CRT, 1.03 for 3 arc plans and 1.01 for single arc plans (p = 0.005). Dose constraints to organs at risk were met using all three techniques. Mean lung doses were 2.93 Gy for 3D-CRT, 2.87 Gy for single arc and 2.73 Gy for the 3 arc technique (3-arc vs. 3D-CRT: p = 0.009). Lung V20 for 3D-CRT, 1 arc and 3 arcs were 3.24%, 2.89% and 2.73%, respectively (3 arc vs. 3D-CRT: p 5 0.028). Mean time to deliver a single fraction was 13 minutes for 3D-CRT, 9.2 minutes for 3 arcs and 5.5 minutes for 1 arc. VMAT resulted in improved conformity compared to 3D-CRT. The 3 arc technique appears to have the lowest dose to lung although the magnitude is unlikely to be clinically significant. The main advantage of VMAT over 3D-CRT is faster treatment delivery time. Shortened treatment times are anticipated to
improve tolerability of this treatment and reduce the chance of error due to intra-fraction motion.

[505]

TÍTULO / TITLE: Diagnosis of chronic obstructive pulmonary disease in lung cancer screening Computed Tomography scans: independent contribution of emphysema, air trapping and bronchial wall thickening.

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


AUTORES / AUTHORS: Mets OM; Schmidt M; Buckens CF; Gondrie MJ; Isgum I; Oudkerk M; Vliegenthart R; de Koning HJ; van der Aalst CM; Prokop M; Lammers JW; Zanen P; Hoesein FA; Mali WP; van Ginneken B; van Rikxoort EM; de Jong PA

RESUMEN / SUMMARY: BACKGROUND: Beyond lung cancer, screening CT contains additional information on other smoking related diseases (e.g. chronic obstructive pulmonary disease, COPD). Since pulmonary function testing is not regularly incorporated in lung cancer screening, imaging biomarkers for COPD are likely to provide important surrogate measures for disease evaluation. Therefore, this study aims to determine the independent diagnostic value of CT emphysema, CT air trapping and CT bronchial wall thickness for COPD in low-dose screening CT scans. METHODS: Prebronchodilator spirometry and volumetric inspiratory and expiratory chest CT were obtained on the same day in 1140 male lung cancer screening participants. Emphysema, air trapping and bronchial wall thickness were automatically quantified in the CT scans. Logistic regression analysis was performed to derive a model to diagnose COPD. The model was internally validated using bootstrapping techniques. RESULTS: Each of the three CT biomarkers independently contributed diagnostic value for COPD, additional to age, body mass index, smoking history and smoking status. The diagnostic model that included all three CT biomarkers had a sensitivity and specificity of 73.2% and 88.8%, respectively. The positive and negative predictive value were 80.2% and 84.2%, respectively. Of all participants, 82.8% was assigned the correct status. The C-statistic was 0.87, and the Net Reclassification Index compared to a model without any CT biomarkers was 44.4%. However, the added value of the expiratory CT data was limited, with an increase in Net Reclassification Index of 4.5% compared to a model with only inspiratory CT data. CONCLUSION: Quantitatively assessed CT emphysema, air trapping and bronchial wall thickness each contain independent diagnostic information for COPD, and these imaging biomarkers might prove useful in the absence of lung function testing and may influence lung cancer screening strategy. Inspiratory CT biomarkers alone may be sufficient to identify patients with COPD in lung cancer screening setting.
Iododerma following serial computed tomography scans in a lung cancer patient.

Resumen / Summary: Nine cases of iododerma following intravenous contrast have been reported in the English-language literature, typically in patients with renal insufficiency. We report a case of iododerma in a patient with relatively unimpaired renal function who underwent serial computer tomography (CT) scans with intravenous contrast. An 81-year-old woman with stage IV lung cancer developed fever and rash following serial CT scans with ioxithalamate contrast media. On examination, we noted conjunctival injection, enlarged glands, oral ulcers, and erythematous papules and plaques on her forehead, arms, and legs. Random urine iodine was elevated to 106,767 μg/L (normal range, 26-705 μg/L). Skin biopsy revealed diffuse predominantly neutrophilic dermal infiltrate. The patient’s clinical presentation, laboratory findings, and biopsy results were consistent with iododerma. Iododerma can occur in patients with adequate kidney function, and its presentation can include ocular and glandular symptoms, as in this case. Withdrawal of the source of iodine typically leads to resolution of symptoms.

Therapeutic implications of the warburg effect assessing the survival of MRC5 and a549 cell lines upon exposure to honey and d glucose.

Resumen / Summary: Lung cancer is one of the most prevalent and deadly cancers in United States. Experimental evidence support that cancer cells do exhibit higher glycolytic rates than normal cells. To exploit this unique cancer-dependent ATP generation phenomenon, we hypothesize that exposure of cancer cells to organic inhibitors of glycolysis would negatively impact their survival and alter their growth and viability resulting from the vast decrease in their essential glycolytic ATP production; no negative consequences will be
seen on normal lung cells. The human lung fibroblast cell line MRC-5 and the human lung alveolar epithelial cancer cell line A549 were used in this study as models for normal lung and lung cancer respectively. Using standard methods, both cell lines were maintained and exposed to honey and D-glucose reagents at concentration levels ranging from 31.3-2,000 microg/ml in 96 well plates in quadruplets and experiments repeated at least three times using MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide), and cell counting (T4 Cellometer; automated cell counting system) assays as well as phase-contrast photo-imaging. Our results indicate that exposure of both cell lines to these organics lead to concentration dependent cell destruction/cell survival depending on the cell line exposed. Honey and D-glucose showed statistically significant (p<0.05) differential negative effects on the A549 line in comparison to its unexposed control as well as to their effects on the MRC-5 cell line. These findings show a promising role for honey and D-glucose as biotherapeutic metabolites of interest for selective management of cancerous cells.
the translocation of RARalpha to the plasma membrane, where it colocalizes with Akt. Immunoprecipitation assays showed that ATRA promotes Akt activation mediated by RARalpha-Akt interaction. Activation of the PI3k-Akt pathway by ATRA promotes invasion through Rac-GTPase, whereas pretreatment with 15e (PI3k inhibitor) or over-expression of the inactive form of Akt blocks ATRA-induced invasion. We also found that treatment with ATRA induces cell survival, which is inhibited by 15e or over-expression of an inactive form of Akt, through a subsequent increase in the levels of the active form of caspase-3. Finally, we showed that over-expression of the active form of Akt significantly decreases expression levels of the tumor suppressors RARbeta2 and p53. In contrast, over-expression of the inactive form of Akt restores RARbeta2 expression in cells treated with ATRA, indicating that activation of the PI3k-Akt pathway inhibits the expression of ATRA target genes.

CONCLUSION: Our results demonstrate that rapid activation of Akt blocks transcription-dependent mechanism of ATRA, promotes invasion and cell survival and confers resistance to retinoic acid treatment in lung cancer cells. These findings provide an incentive for the design and clinical testing of treatment regimens that combine ATRA and PI3k inhibitors for lung cancer treatment.

[509]
TITULO / TITLE: The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials.

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


AUTORES / AUTHORS: Cui J; Cai X; Zhu M; Liu T; Zhao N

INSTITUCIÓN / INSTITUTION: Department of Biostatistics, Fudan University, Shanghai, People’s Republic of China; Key Laboratory of Public Health Safety, Fudan University, Ministry of Education, Shanghai, People’s Republic of China.

RESUMEN / SUMMARY: BACKGROUND: The extent of the benefit of bevacizumab combined with chemotherapy in the treatment of advanced non-small-cell lung cancer (NSCLC) is still unclear. We performed this meta-analysis to compare the efficacy of bevacizumab with other commonly used targeted drugs for different patients with advanced NSCLC. METHODS: We searched PubMed, Cochrane Library, EMBASE and abstracts from the proceedings of the American Society of Clinical Oncology (ASCO), and identified 30 randomized controlled clinical trials published within 1999 to 2011 for meta-analysis.

RESULTS: The outcomes of treatment efficacy included response rate, PFS
and OS. Comparing bevacizumab (15 mg/kg) with chemotherapy to standard chemotherapy alone, for chemotherapy-naive patients, the pooled OR of response rate was 2.741 (95% CI: 2.046, 3.672), the pooled HR for disease progression was 0.645 (95% CI: 0.561, 0.743), and the pooled HR for death was 0.790 (95% CI: 0.674, 0.926), respectively. In addition, the adjusted HR for previously-treated patients was 0.680 (95% CI: 0.492, 0.942) comparing bevacizumab combined with chemotherapy to standard chemotherapy alone.

CONCLUSIONS: Bevacizumab accompanied by chemotherapy was found to significantly improve patients’ response rate, progression free survival (PFS), and overall survival (OS) among chemotherapy-naive patients compared to other targeted drugs in the treatment of non-small cell lung carcinoma (NSCLC).

[510]
**TÍTULO / TITLE:** - Lung cancer - a comorbidity in chronic obstructive pulmonary disease.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** - Roca M; Roca IC; Mihaescu T
**INSTITUCIÓN / INSTITUTION:** - University of Medicine and Pharmacy, Grigore T. Popa - Iasi, Faculty of Medicine.
**RESUMEN / SUMMARY:** - Chronic Obstructive Pulmonary Disease (COPD) is an important public health challenge, representing the fourth leading cause of death in the world. A very important characteristic of COPD is represented by the coexistence of comorbidities. Lung cancer, a major cause of morbidity and mortality throughout the world, is also a frequent comorbidity in COPD. Cigarette smoking represents the best-known risk factor in both COPD and lung cancer, causing common pathogenic mechanisms like oxidative stress and inflammation. However, the etiopathogenic link between COPD and lung cancer implies a common underlying genetic susceptibility, acting in addition to environmental risk factors. These trigger more complex cellular and molecular mechanisms, represented by immune dysfunction, abnormal activation of transcription factors, altered signaling pathways, epithelial to mesenchymal transition. A better understanding of the etiopathogenic link between COPD and lung cancer at the molecular level will allow the discovery of more sensitive diagnostic methods and also new molecular targets for an efficient treatment.

[511]
**TÍTULO / TITLE:** - The novel BH3 alpha-helix mimetic JY-1-106 induces apoptosis in a subset of cancer cells (lung cancer, colon cancer and
mesothelioma) by disrupting Bcl-xL and Mcl-1 protein-protein interactions with Bak.

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


AUTORES / AUTHORS: - Cao X; Yap JL; Newell-Rogers MK; Peddaboina C; Jiang W; Papaconstantinou HT; Jupiter D; Rai A; Jung KY; Tubin RP; Yu W; Vanommeslaeghe K; Wilder PT; Mackerell AD Jr; Fletcher S; Smythe RW

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Scott & White Memorial Hospital and Clinic, The Texas A&M University System, Health Science Center, College of Medicine, 702 SW HK Dodgen Loop, Temple, Texas 76504, USA. rsmythe@sw.org.

RESUMEN / SUMMARY: - BACKGROUND: It has been shown in many solid tumors that the overexpression of the pro-survival Bcl-2 family members Bcl-2/Bcl-xL and Mcl-1 confers resistance to a variety of chemotherapeutic agents. We designed the BH3 alpha-helix mimetic JY-1-106 to engage the hydrophobic BH3-binding grooves on the surfaces of both Bcl-xL and Mcl-1. METHODS: JY-1-106-protein complexes were studied using molecular dynamics (MD) simulations and the SILCS methodology. We have evaluated the in vitro effects of JY-1-106 by using a fluorescence polarization (FP) assay, an XTT assay, apoptosis assays, and immunoprecipitation and western-blot assays. A preclinical human cancer xenograft model was used to test the efficacy of JY-1-106 in vivo. RESULTS: MD and SILCS simulations of the JY-1-106-protein complexes indicated the importance of the aliphatic side chains of JY-1-106 to binding and successfully predicted the improved affinity of the ligand for Bcl-xL over Mcl-1. Ligand binding affinities were measured via an FP assay using a fluorescently labeled Bak-BH3 peptide in vitro. Apoptosis induction via JY-1-106 was evidenced by TUNEL assay and PARP cleavage as well as by Bax-Bax dimerization. Release of multi-domain Bak from its inhibitory binding to Bcl-2/Bcl-xL and Mcl-1 using JY-1-106 was detected via immunoprecipitation (IP) western blotting. At the cellular level, we compared the growth proliferation IC50s of JY-1-106 and ABT-737 in multiple cancer cell lines with various Bcl-xL and Mcl-1 expression levels. JY-1-106 effectively induced cell death regardless of the Mcl-1 expression level in ABT-737 resistant solid tumor cells, whilst toxicity toward normal human endothelial cells was limited. Furthermore, synergistic effects were observed in A549 cells using a combination of JY-1-106 and multiple chemotherapeutic agents. We also observed that JY-1-106 was a very effective agent in inducing apoptosis in metabolically stressed tumors. Finally, JY-1-106 was evaluated in a tumor-bearing nude mouse model, and was found to effectively repress tumor growth. Strong TUNEL signals in the tumor cells demonstrated the effectiveness of JY-1-106 in this animal model. No significant side effects were observed in mouse organs after multiple injections.
CONCLUSIONS: Taken together, these observations demonstrate that JY-1-106 is an effective pan-Bcl-2 inhibitor with very promising clinical potential.

[512]
**TÍTULO / TITLE:** - High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR.

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

**REVISTA / JOURNAL:** - J Transl Med. 2013 Apr 4;11(1):90.

**AUTORES / AUTHORS:** - Wang F; Fu S; Shao Q; Zhou YB; Zhang X; Zhang X; Xue C; Lin JG; Huang LX; Zhang L; Zhang WM; Shao JY

**RESUMEN / SUMMARY:** - BACKGROUND: This study was designed to determine whether advanced non-small-cell lung cancer (NSCLC) patients with high copy number of epidermal growth factor receptor (EGFR) can benefit from treatment with EGFR-tyrosine kinase inhibitors (TKIs). METHODS: EGFR gene copy number was assessed by fluorescence in situ hybridization (FISH) and EGFR mutations was tested using Luminex xTAG technology in 502 TKI-treated NSCLC patients. The association between both biomarkers and clinical benefit from EGFR-TKI were analyzed. RESULTS: EGFR FISH + and EGFR mutations were significantly associated with higher response rates (37.2% and 43.7%, respectively), superior progression-free survival (PFS) (FISH+, 11.2 months; hazard ratio [HR], 0.51; 95% CI, 0.42 to 0.62; p < 0.001; mutation+, 11.7 months; HR, 0.37; 95% CI, 0.31 to 0.45; p < 0.001) and overall survival (OS) (FISH+, 30.2 months; HR, 0.51; 95% CI, 0.40 to 0.65; p < 0.001; mutation+, 30.2 months; HR, 0.45; 95% CI, 0.36 to 0.58; p < 0.001). In patients with wild-type EGFR, EGFR FISH + correlated with longer PFS than EGFR FISH- status (4.4 months vs. 2.0 months; HR, 0.56; 95% CI, 0.41 to 0.75; p < 0.001), so did amplification (5.0 months vs. 2.0 months; HR, 0.43; 95% CI, 0.24 to 0.76; p = 0.003). However, FISH+ had no association with improved PFS in EGFR-mutated patients (HR, 0.77; 95% CI, 0.57 to 1.03; p = 0.076). CONCLUSIONS: A combined analysis of EGFR FISH and mutation is an effective predictor of EGFR-TKI therapy. Specifically, a high EGFR copy number may predict benefit from TKIs treatment for NSCLC patients with wild-type EGFR.

[513]
**TÍTULO / TITLE:** - There is no Significant Association Between Death Receptor 4 (DR4) Gene Polymorphisms and Lung Cancer in Turkish Population.

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

**REVISTA / JOURNAL:** - Pathol Oncol Res. 2013 May 10.

**Enlace al texto completo (gratuito o de pago) 1007/s12253-013-9643-Z**
AUTORES / AUTHORS: - Tastemir-Korkmaz D; Demirhan O; Kuleci S; Hasturk S

INSTITUCIÓN / INSTITUTION: - Vocational School of Health Services, Adiyaman University, TR-02040, Adiyaman, Turkey, deniz-tbio@hotmail.com.

RESUMEN / SUMMARY: - Death receptor 4 (DR4) gene is a candidate tumor suppressor gene that has a role in apoptotic pathway. It was reported in literature that polymorphisms in DR4 gene lead to susceptibility to many cancers. In accordance with this information, we aimed to investigate the association between G422A, C626G, A683C and A1322G polymorphisms in DR4 gene and lung cancer. We selected 60 patients with lung cancer (LC) and 30 healthy, sex and age matched volunteers randomly. Four polymorphisms, G422A, C626G, A683C and A1322G, in DR4 gene were analyzed with Polymerase Change Reaction (PCR) - Restriction Fragment Lenght Polymorphism (RFLP) and Amplification Refraactory Mutation System (ARMS) techniques in both groups. Our results showed that there are no statistically significances between the patients and controls in terms of the G422A, C626G, A683C and A1322G polymorphisms in DR4 gene (p > 0,05). Our findings showed no role of DR4 gene polymorphisms in susceptibility to LC and provide a plausible explanation for DR4 genetic heterogeneity in LC susceptibility.

[514]

TÍTULO / TITLE: - Multiple therapeutic peptide vaccines consisting of combined novel cancer testis antigens and anti-angiogenic peptides for patients with non-small cell lung cancer.

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


AUTORES / AUTHORS: - Suzuki H; Fukuhara M; Yamaura T; Mutoh S; Okabe N; Yaginuma H; Hasegawa T; Yonechi A; Osugi J; Hoshino M; Kimura T; Higuchi M; Shio Y; Ise K; Takeda K; Gotoh M

RESUMEN / SUMMARY: - BACKGROUND: Vaccine treatment using multiple peptides derived from multiple proteins is considered to be a promising option for cancer immune therapy, but scientific evidence supporting the therapeutic efficacy of multiple peptides is limited. METHODS: We conducted phase I trials using a mixture of multiple therapeutic peptide vaccines to evaluate their safety, immunogenicity and clinical response in patients with advanced/recurrent NSCLC. We administered two different combinations of four HLA-A24-restricted peptides. Two were peptides derived from vascular endothelial growth factor receptor 1 (VEGFR1) and 2 (VEGFR2), and the third was a peptide derived from up-regulated lung cancer 10 (URLC10, which is also called lymphocyte antigen 6 complex locus K [LY6K]). The fourth peptide used was derived from TTK protein kinase (TTK) or cell division associated 1 (CDCA1). Vaccines were administered weekly by subcutaneous injection into the axillary...
region of patients with montanide ISA-51 incomplete Freund’s adjuvant, until the disease was judged to have progressed or patients requested to be withdrawn from the trial. Immunological responses were primarily evaluated using an IFN-gamma ELISpOT assay. RESULTS: Vaccinations were well tolerated with no severe treatment-associated adverse events except for the reactions that occurred at the injection sites. Peptide-specific T cell responses against at least one peptide were observed in 13 of the 15 patients enrolled. Although no patient exhibited complete or partial responses, seven patients (47%) had stable disease for at least 2 months. The median overall survival time was 398 days, and the 1- and 2-year survival rates were 58.3% and 32.8%, respectively. CONCLUSION: Peptide vaccine therapy using a mixture of four novel peptides was found to be safe, and is expected to induce strong specific T cell responses. Trial registration: These studies were registered with ClinicalTrials.gov NCT00633724 and NCT00874588.
the LC-2/ad cells. CCDC6-RET was constitutively active, and the introduction of a siRNA targeting the RET 3’ region decreased cell proliferation by downregulating RET and ERK1/2 phosphorylation. Moreover, treatment with RET-inhibitors, including vandetanib, reduced cell viability, which was accompanied by the downregulation of the AKT and ERK1/2 signaling pathways. Vandetanib exhibited anti-tumor effects in the xenograft model. Endogenously expressing CCDC6-RET contributed to cell growth. The inhibition of kinase activity could be an effective treatment strategy for LAD. LC-2/ad is a useful model for developing fusion RET-targeted therapy.

[516]

**TÍTULO / TITLE:** IGF-1R targeting increases the antitumor effects of DNA damaging agents in SCLC model: an opportunity to increase the efficacy of standard therapy.

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

**REVISTA / JOURNAL:** Mol Cancer Ther. 2013 May 2.

**AUTORES / AUTHORS:** Ferte C; Loriot Y; Clemenson C; Commo F; Gombos A; Bibault JE; Fumagalli I; Hamama S; Auger N; Lahon B; Chargari C; Calderaro J; Soria JC; Deutsch E

**INSTITUCIÓN / INSTITUTION:** 1INSERM U1030, Paris XI University, Institut Gustave Roussy.

**RESUMEN / SUMMARY:** Insulin-like growth factor receptor-1 (IGF-1R) inhibition could be a relevant therapeutic approach in small cell lung cancer (SCLC) given the importance of an IGF-1R autocrine loop and its role in DNA damage repair processes. We assessed IGF-1R and pAkt protein expression in 83 SCLC human specimens. The efficacy of R1507 (a monoclonal antibody directed against IGF-1R) alone or combined with cisplatin or ionizing radiation (IR) was evaluated in H69, H146 and H526 cells in vitro and in vivo. Innovative genomic and functional approaches were conducted to analyze the molecular behavior under the different treatment conditions. A total of 53% and 37% of human specimens expressed IGF-1R and pAkt, respectively. R1507 demonstrated single agent activity in H146 and H526 cells but not in H69 cells. R1507 exhibited synergistic effects with both Cisplatin and IR in vitro. The triple combination R1507-Cisplatin-IR led to a dramatic delay in tumor growth compared to Cisplatin-IR in H526 cells. Analyzing the apparent absence of antitumoral effect of R1507 alone in vivo, we observed a transient reduction of IGF-1R staining intensity in vivo, concomitant to the activation of multiple cell surface receptors and intracellular proteins involved in proliferation, angiogenesis and survival. Finally, we identified that the nucleotide excision repair pathway (NER) was mediated after exposure to R1507-CDDP and
R1507-IR in vitro and in vivo. In conclusion, adding R1507 to the current standard Cisplatin-IR doublet reveals remarkable chemo- and radiosensitizing effects in selected SCLC models and warrants to be investigated in the clinical setting.

[517]

**TITULO / TITLE:** - Src mediates cigarette smoke-induced resistance to tyrosine kinase inhibitors in NSCLC cells.

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

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 17.

**AUTORES / AUTHORS:** - Filosto S; Baston DS; Chung S; Becker CR; Goldkorn T

**INSTITUCION / INSTITUTION:** - 1Internal Medicine, UC Davis School of Medicine.

**RESUMEN / SUMMARY:** - The EGF Receptor (EGFR) is a proto-oncogene commonly dysregulated in several cancers including non-small cell lung cancer (NSCLC) and, thus, is targeted for treatment using tyrosine kinase inhibitors (TKIs) such as Erlotinib. However, despite the efficacy observed in NSCLC patients harboring oncogenic variants of the EGFR, general ineffectiveness of TKIs in NSCLC patients who are current and former smokers necessitates identification of novel mechanisms to overcome this phenomenon. Previously, we showed that NSCLC cells harboring either wild-type (WT) EGFR or oncogenic mutant (MT) L858R EGFR become resistant to the effects of TKIs when exposed to cigarette smoke (CS), evidenced by their auto-phosphorylation and prolonged downstream signaling. Here, we present Src as a target mediating CS-induced resistance to TKIs in both WT EGFR and L858R MT EGFR expressing NSCLC cells. First, we show that CS exposure of A549 cells leads to time-dependent activation of Src which then abnormally binds to the WT EGFR causing TKI resistance, contrasting previous observations of constitutive binding between inactive Src and TKI-sensitive L858R MT EGFR. Next, we demonstrate that Src inhibition restores TKI sensitivity in CS-exposed NSCLC cells, preventing EGFR auto-phosphorylation in the presence of Erlotinib. Furthermore, we show that over-expression of a dominant-negative Src (Y527F/K295R) restores TKI sensitivity to A549 exposed to CS. Importantly, the TKI resistance that emerges even in CS-exposed L858R EGFR expressing NSCLC cells could be eliminated with Src inhibition. Together, these findings offer new rationale for using Src inhibitors for treating TKI-resistant NSCLC commonly observed in smokers.

[518]
**TÍTULO / TITLE:** Role of p38 and JNK MAPK signaling pathways and tumor suppressor p53 on induction of apoptosis in response to Ad-eIF5A1 in A549 lung cancer cells.

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


**AUTORES / AUTHORS:** Taylor CA; Zheng Q; Liu Z; Thompson JE

**INSTITUCIÓN / INSTITUTION:** Department of Biology, University of Waterloo, 200 University Ave, W., Waterloo, ON N2L 3G1, Canada.

**RESUMEN / SUMMARY:** BACKGROUND: The eukaryotic translation initiation factor 5A1 (eIF5A1) is a highly conserved protein involved in many cellular processes including cell division, translation, apoptosis, and inflammation. Induction of apoptosis is the only function of eIF5A1 that is known to be independent of post-translational hypusine modification. In the present study, we investigated the involvement of mitogen- and stress-activated protein kinases during apoptosis of A549 lung cancer cells infected with adenovirus expressing eIF5A1 or a mutant of eIF5A1 that cannot be hypusinated (eIF5A1K50A). METHODS: Using adenoviral-mediated transfection of human A549 lung cancer cells to over-express eIF5A1 and eIF5A1K50A, the mechanism by which unhypusinated eIF5A1 induces apoptosis was investigated by Western blotting, flow cytometry, and use of MAPK and p53 inhibitors. RESULTS: Phosphorylation of ERK, p38 MAPK, and JNK was observed in response to adenovirus-mediated over-expression of eIF5A1 or eIF5A1K50A, along with phosphorylation and stabilization of the p53 tumor suppressor protein. Synthetic inhibitors of p38 and JNK kinase activity, but not inhibitors of ERK1/2 or p53 activity, significantly inhibited apoptosis induced by Ad-eIF5A1. Importantly, normal lung cells were more resistant to apoptosis induced by eIF5A1 and eIF5A1K50A than A549 lung cancer cells. CONCLUSIONS: Collectively these data indicate that p38 and JNK MAP kinase signaling are important for eIF5A1-induced cell death and that induction of apoptosis was not dependent on p53 activity.

[519]

**TÍTULO / TITLE:** Urban vs. rural patients. Differences in stage and overall survival among patients treated surgically for lung cancer.

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


**AUTORES / AUTHORS:** Rybojad P; Dluski D; Rybojad B; Kedra M; Sawicki M; Skoczylas P; Tabarkiewicz J
INTRODUCTION: Besides the undoubted influence of risk factors on morbidity and survival time, there are also other environmental factors, such as awareness of the prevalence of risk factors and the availability of modern diagnosis and treatment methods. OBJECTIVE: To evaluate differences in lung cancer 5-year overall survival rates between urban and rural patients hospitalized in the Department of Thoracic Surgery of the Medical University in Lublin, Poland, and possible influence of several risk factors on these rates. MATERIALS AND METHODS: The analysis was based on 125 lung cancer patients who underwent surgical procedures in years 2006-2007 and who agreed to take part in the survey. The study aimed at recognition of the health situation and selected demographic traits of people who had been treated surgically for lung cancer. The differences were evaluated between rural and urban inhabitants in gender, age, lung function, smoking habits, exposure to risk factors at work, family history of cancer, staging of the disease, histological type of cancer, post-surgical treatment, and their possible influence on overall survival. RESULTS: The results showed that the only noted differences between urban and rural population were in tobacco smoking and lung function. Survival rates were very similar and did not differ from the European average. CONCLUSIONS: The assumption that Polish rural patients are presenting with later cancer stages at the time of diagnosis, and have worse chances for survival, has become invalid in modern times.

TÍTULO / TITLE: - The role of vascular endothelial growth factor in the pathogenesis, diagnosis and treatment of malignant pleural effusion.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Bradshaw M; Mansfield A; Peikert T
INSTITUCIÓN / INSTITUTION: - Mayo Medical School, Mayo Clinic, Rochester, MN, USA.
RESUMEN / SUMMARY: - Malignant pleural effusions (MPEs) are a significant source of cancer-related morbidity. Over 150,000 patients in the United States suffer from breathlessness and diminished quality of life due to MPE each year. Current management strategies are of mostly palliative value and focus on symptom control; they do not address the pathobiology of the effusion, nor do they improve survival. Further elucidation of the pathophysiological mechanisms, coupled with the development of novel treatments such as
intrapleural chemotherapeutics targeting this process, has the potential to greatly improve the efficacy of our current management options. Vascular endothelial growth factor-A (VEGF-A) has been implicated as a critical cytokine in the formation of malignant pleural effusions. Elevated levels of VEGF produced by tumor cells, mesothelial cells, and infiltrating immune cells result in increased vascular permeability, cancer cell transmigration, and angiogenesis. Therefore antiangiogenic therapies such as Bevacizumab, a monoclonal antibody targeting VEGF-A, may have a potential role in the management of malignant pleural effusions. Herein we review the pathogenesis and potential treatment strategies of malignant pleural effusions, with a focus on angiogenesis and antiangiogenic therapeutics.

[521]
TITULO / TITLE: - Assessing the survival of MRC5 and a549 cell lines upon exposure to pyruvic Acid, sodium citrate and sodium bicarbonate - biomed 2013.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Farah IO; Lewis VL; Ayensu WK; Cameron JA
INSTITUCION / INSTITUTION: - Jackson State University.
RESUMEN / SUMMARY: - Lung cancer is among the most prevalent and deadly cancers in United States. In general, cancer cells are known to exhibit higher rates of glycolysis in comparison to normal cells. In attempting to exploit this unique cancer-dependent ATP generation phenomenon, it was our hypothesis that upon exposure to organic inhibitors of glycolysis, cancer cells would not survive normally and that their growth and viability would be vastly decreased; essential glycolytic ATP production will be exhausted to the point of collapsing energy utilization. Furthermore, we hypothesize that no negative effect would be seen with exposures to organic inhibitors for normal lung cells. The human lung fibroblast MRC-5 and the human A549 alveolar epithelial cell lines were used as in vitro models of normal lung and lung cancers respectively. Using standard methods, both cell lines were maintained and exposed to pyruvic acid, sodium citrate and sodium bicarbonate reagents at concentration levels ranging from 31.3-2,000 microg/ml in 96 well plates in quadruplets and experiments repeated at least three times using MTT, and cell counting (T4 Cellometer) assays as well as phase-contrast photo-imaging for parallel morphological displays of any changes in the course of their vitality and metabolic activities. Our results indicate that exposure of both cell lines to these organics resulted in concentration dependent cell destruction/cell survival depending on the cell line exposed. Pyruvic acid, sodium citrate and sodium bicarbonate showed statistically significant (p<0.05) differential negative effects on the A549 cell line.
in comparison to its unexposed control as well as to their effects on the MRC-5 cell line, presenting a potential promise for their use as cancer biotherapeutics.

[522]
TÍTULO / TITLE: - Outcome and prognosis for patients younger than thirty with primary lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Duan L; You Q; Chen X; Wang H; Zhang H; Xie D; Xu X; Jiang G
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery Shanghai Pulmonary Hospital Tongji University School of Medicine Shanghai, China - jianggengen@163.com.
RESUMEN / SUMMARY: - Aim: Aim of the present study was to investigate the clinical and pathological features of surgical treatment for primary bronchogenic carcinoma in adolescent patients. Patients: We retrospectively reviewed the clinico-pathological records documenting surgical outcomes and prognostic factors in 68 lung cancer patients aged less than 30 years old enrolled in our hospital between March 1980 and December 2009. Results: Sixty-eight patients were identified (38 male, 30 female) with a mean age of 22+/−5 years (range 8 to 29 years). Preoperative clinical manifestations were present in 82.4% (56/68) of the patients and 26.5% (16/68) of patients were initially misdiagnosed. Fifty-two patients had undergone radical surgery, 4 palliative surgery, 9 had exploratory thoracotomies, and 3 had thoracoscopic lung biopsies. Eight patients were classified (TNM) stage Ia, 7 stage Ib, 9 stage IIa, 13 stage IIb, 17 stage IIIa, 10 stage IIIb, and 4 stage IV. Postoperative atelectasis was observed in 4.41% (3/68) of the patients, and 1.47% (1/68) died of respiratory failure 5 days after exploratory thoracotomy. The overall 5-year survival rate in very young people was 31%, while those who underwent radical surgery was slightly higher at 36.7%. Five-year survival rates were correlated with the surgical procedures and pTNM stage (P <0.05). Multivariate analysis indicated that the TNM stage is the only independent prognostic factor (P=0.000). Conclusion: We conclude that radical surgeries, the predominant comprehensive therapies are the best choice for primary lung cancer patients younger than 30 years of age.

[523]
TÍTULO / TITLE: - Anaplastic lymphoma kinase: a glimmer of hope in lung cancer treatment?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Anaplastic lymphoma kinase (ALK) rearrangements (ALK-Rs) have been identified in 3-7% of all non-small-cell lung cancers (NSCLCs) and represent an important molecular target for NSCLC treatment. The authors discuss the role of ALK-Rs in the prediction of clinical-pathological features of NSCLCs and the technical problems related to their determination in specimens. The authors also describe the preclinical and clinical results derived from the use of ALK inhibitors. ALK-R is generally detected in patients with specific clinical-pathological features: never-smokers, young males, adenocarcinoma histotype and EGF receptor/KRAS wild-type. The diagnosis of ALK-R remains a challenge, implicating the need of a careful filtering of patients. NSCLC patients harboring ALK-R have shown sensitivity to ALK inhibitors even if their activity is limited at the time by the occurrence of mechanisms of resistance. The authors summarize the strategies that in the future could overcome these mechanisms of escape.

[524]

**TITULO / TITLE:** CD146 and insulin-like growth factor 2 mRNA-binding protein 3 predict prognosis of asbestos-induced rat mesothelioma.

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


**AUTORES / AUTHORS:** Okazaki Y; Nagai H; Chew SH; Li J; Funahashi S; Tsujimura T; Toyokuni S

**INSTITUCIÓN / INSTITUTION:** Department of Pathology and Biological Responses, Nagoya University Graduate School of Medicine, Aichi, Japan.

**RESUMEN / SUMMARY:** Malignant mesothelioma (MM), which is associated with asbestos exposure, is one of the most deadly tumors in humans. Early MM is concealed in the serosal cavities and lacks specific clinical symptoms. For better treatment, early detection and prognostic markers are necessary. Recently, CD146 and insulin-like growth factor 2 mRNA-binding protein 3 (IMP3) were reported as possible positive markers of MM to distinguish from reactive mesothelia in humans. However, their application on MM of different species and its impact on survival remain to be elucidated. To disclose the utility of these molecules as early detection and prognostic markers of MM, we injected chrysotile or crocidolite intraperitoneally to rats, thus obtaining 26 peritoneal MM and establishing 11 cell lines. We immunostained CD146 and IMP3 using paraffin-embedded tissues and cell blocks and found CD146 and
IMP3 expression in 58% (15/26) and 65% (17/26) of MM, respectively, but not in reactive mesothelia. There was no significant difference in both immunostainings for overexpression among the three histological subtypes of MM and the expression of CD146 and IMP3 was proportionally associated. Furthermore, the overexpression of CD146 and/or IMP3 was proportionally correlated with shortened survival. These results suggest that CD146 and IMP3 are useful diagnostic and prognostic markers of MM.

[525]
TÍTULO / TITLE: Surgical results and survival of older patients with unsuspected N2 (stage IIIA) non-small cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Dell’amore A; Monteverde M; Caroli G; Sanna S; Stella F; Bini A

RESUMEN / SUMMARY: Purposes. The optimal treatment of N2 non-small cell lung cancer (NSCLC) in older patients is still debate and represent an important treatment and ethical problem. Patients and methods. Between January 2000 to December 2010, 273 older patients underwent lung resection for (NSCLC). Results. The overall-operative mortality was 9.5%. Risk factors for in-hospital mortality were pneumonectomy and poli-vasculopathy. One, 3 and 5-year survival were 73%, 23% and 16% respectively. Conclusions. In potentially operable older patients with NSCLC we need to make every effort to exclude N2 involvement because very poor long-term survival. Pneumonectomy in older patients gains prohibitive in-hospital mortality.

[526]
TÍTULO / TITLE: The Role of Radiation Therapy in Small Cell Lung Cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Videtic GM
INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, Taussig Cancer Institute, The Cleveland Clinic, 9500 Euclid Avenue, Mailroom T28, Cleveland, OH, 44195, USA, videtig@ccf.org
RESUMEN / SUMMARY: Radiotherapy (RT) is fundamental to the care of patients diagnosed with small-cell lung cancer (SCLC). In the setting of limited stage disease (LS-SCLC), the addition of thoracic RT to chemotherapy (CHT) improves survival and local control, as demonstrated in decades-worth of randomized clinical trials and subsequent meta-analyses. In extensive stage...
disease (ES-SCLC), thoracic RT is invaluable in the palliation of chest symptoms but there are suggestions that its use in selected patients may potentially improve overall survival. Prophylactic cranial irradiation (PCI) also improves outcomes in SCLC. For LS-SCLC patients, it reduces brain metastases rates by half and improves overall survival with minimal impact on quality-of-life. Recently, favorable results for PCI with respect to survival and prevention of symptomatic brain disease have been observed for ES-SCLC patients with any response to CHT. Current phase III trials in SCLC RT include studies looking at the optimal dose and target for limited disease and the role of thoracic RT in extensive disease.

[527]

Title: - Sensing Biophysical Alterations of Human Lung Epithelial Cells (A549) in the Context of Toxicity Effects of Diesel Exhaust Particles.

Summary: - Enlace al Resumen / Link to its Summary


Authors: - Wu Y; McEwen GD; Tang M; Yu T; Dimmick JT; Zhou A; Gilbertson TA; Coulombe RA Jr; Stevens JR

Institution: - Department of Biological Engineering, Utah State University, 4105 Old Main Hill, Logan, UT, 84322-4105, USA, yzwu@uic.edu.

Resumen: - Diesel exhaust particles (DEP) in urban air are associated with numerous respiratory diseases. The role of underlying biomechanics in cytotoxicity of individual lung cells relating to DEP exposure is unclear. In this study, atomic force microscopy (AFM), confocal Raman microspectroscopy (RM), and fluorescence (FL) microscopy were used to monitor alterations of single A549 cells exposed to DEP. Results revealed a significant decrease in membrane surface adhesion force and a significant change in cell elasticity as a function of DEP-cell interaction time, and the dynamic changes in cellular biocomponents which were reflected by changes of characteristic Raman bands: 726 cm⁻¹ (adenine), 782 cm⁻¹ (uracil, cytosine, thymine), 788 cm⁻¹ (O-P-O), 1006 cm⁻¹ (phenylalanine), and 1320 cm⁻¹ (guanine) after DEP exposure. These findings suggest that the combination of multi-instruments (e.g., AFM/FL) may offer an exciting platform for investigating the roles of biophysical and biochemical responses to particulate matter-induced cell toxicity.

[528]

Title: - Prediction of Lung Cancer Histological Types by RT-qPCR Gene Expression in FFPE Specimens.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

Enlace al texto completo (gratuito o de pago)
1016/jjmoldx.2013.03.007

AUTORES / AUTHORS: Wilkerson MD; Schallheim JM; Hayes DN; Roberts PJ; Bastien RR; Mullins M; Yin X; Miller CR; Thorne LB; Geiersbach KB; Muldrew K; Funkhouser WK; Fan C; Hayward MC; Bayer S; Perou CM; Bernard PS

INSTITUCIÓN / INSTITUTION: Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

RESUMEN / SUMMARY: Lung cancer histologic diagnosis is clinically relevant because there are histology-specific treatment indications and contraindications. Histologic diagnosis can be challenging owing to tumor characteristics, and it has been shown to have less-than-ideal agreement among pathologists reviewing the same specimens. Microarray profiling studies using frozen specimens have shown that histologies exhibit different gene expression trends; however, frozen specimens are not amenable to routine clinical application. Herein, we developed a gene expression-based predictor of lung cancer histology for FFPE specimens, which are routinely available in clinical settings. Genes predictive of lung cancer histologies were derived from published cohorts that had been profiled by microarrays. Expression of these genes was measured by quantitative RT-PCR (RT-qPCR) in a cohort of patients with FFPE lung cancer. A histology expression predictor (HEP) was developed using RT-qPCR expression data for adenocarcinoma, carcinoid, small cell carcinoma, and squamous cell carcinoma. In cross-validation, the HEP exhibited mean accuracy of 84% and kappa = 0.77. In separate independent validation sets, the HEP was compared with pathologist diagnoses on the same tumor block specimens, and the HEP yielded similar accuracy and precision as the pathologists. The HEP also exhibited good performance in specimens with low tumor cellularity. Therefore, RT-qPCR gene expression from FFPE specimens can be effectively used to predict lung cancer histology.

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[529]


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

Enlace al texto completo (gratuito o de pago) 1038/aps.2013.19
AUTORES / AUTHORS: Li Y; Ma HL; Han L; Liu WY; Zhao BX; Zhang SL; Miao JY

414
INSTITUCIÓN / INSTITUTION: - Shandong Provincial Key Laboratory of Animal Cells and Developmental Biology, Institute of Developmental Biology, School of Life Science, Shandong University, Ji-nan 250100, China.

RESUMEN / SUMMARY: - Aim: To investigate the effects of 7 novel 1-ferrocenyl-2-(5-phenyl-1H-1,2,4-triazol-3-ylthio) ethanone derivatives on human lung cancer cells in vitro and to determine the mechanisms of action. Methods: A549 human lung cancer cells were examined. Cell viability was analyzed with MTT assay. Cell apoptosis and senescence were examined using Hoechst 33258 and senescence-associated-beta-galactosidase (SA-beta-gal) staining, respectively. LDH release was measured using a detection kit. Cell cycle was analyzed using a flow cytometer. Intracellular ROS level was measured with the 2',7'-dichlorodihydrofluorescein probe. Phosphorylation of p38 was determined using Western blot. Results: Compounds 5b, 5d, and 5e (40 and 80 mumol/L) caused significant decrease of A549 cell viability, while other 4 compounds had no effect on the cells. Compounds 5b, 5d, and 5e (80 mumol/L) induced G1-phase arrest (increased the G1 population by 22.6%, 24.23%, and 26.53%, respectively), and markedly increased SA-beta-gal-positive cells. However, the compounds did not cause nuclear DNA fragmentation and chromatin condensation in A549 cells. Nor did they affect the release of LDH from the cells. The compounds significantly elevated the intracellular ROS level, decreased the mitochondrial membrane potential, and increased p38 phosphorylation in the cells. In the presence of the antioxidant and free radical scavenger N-acetyl-L-cysteine (10 mmol/L), above effects of compounds 5b, 5d, and 5e were abolished. Conclusion: The compounds 5b, 5d, and 5e cause neither apoptosis nor necrosis of A549 cells, but exert anti-cancer effect via inducing G1-phase arrest and senescence through ROS/p38 MAP-kinase pathway.

[530]

TÍTULO / TITLE: - Pulmonary Artery Reconstruction Using Autologous Pericardium or Azygos Venae Substitute for Surgical Treatment of Central Non-Small Cell Lung Cancer.

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


AUTORES / AUTHORS: - Xuegang L; Chao S; Zhen T; Xiaojun L; Ge L; Lei Z

INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, 233004, China.

RESUMEN / SUMMARY: - We evaluated the clinico-surgical significance of pulmonary artery (PA) reconstruction using a patch of autologous pericardium/azygos venae substitute to treat central non-small cell lung cancer.
in 62 patients with pulmonary arteries invaded by tumor. According to TNM-classification, four patients were stage IIb, 46 were stage IIIa, and 12 were stage IIIb. Depending on tumor infiltration, surgical procedures included partial PA tangential resections/reconstructions by a patch of autologous azygos venae, a patch of autologous pericardium and complete PA sleeve resection and reconstruction by a custom-made autologous pericardial conduit interposition. 47 patients received postoperative chemotherapy and 19 received radiotherapy. There were 2 (3.2 %) postoperative early deaths due to bronchial anastomotic leakage. Postoperative complications occurred in 17.7 % (11/62) patients and all recovered uneventfully. Mean follow-up time after surgical resection was 49.5 (6-12) months and overall <=1-, 3-, 5-, and >10-year survival rates were 80.2, 44.7, 31.4, and 23.1 %, respectively. It was concluded that autologous pericardial patch and azygos vein patch reconstruction of PA were safe and effective. Regarding extended circumferential defects after sleeve resection in which end-to-end anastomosis is not feasible, autologous pericardial conduit interposition may be useful for reconstruction when a tumor extensively infiltrates full circumference of the PA.

[531]
TÍTULO / TITLE: - Inhibition of CK2alpha down-regulates Notch1 signalling in lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang S; Long H; Yang YL; Wang Y; Hsieh D; Li W; Au A; Stoppler HJ; Xu Z; Jablons DM; You L
INSTITUCIÓN / INSTITUTION: - Thoracic Oncology Laboratory, Department of Surgery, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; Department of Surgical Oncology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China.
RESUMEN / SUMMARY: - Protein kinase CK2 is frequently elevated in a variety of human cancers. The Notch1 signalling pathway has been implicated in stem cell maintenance and its aberrant activation has been shown in several types of cancer including lung cancer. Here, we show, for the first time, that CK2alpha is a positive regulator of Notch1 signalling in lung cancer cell lines A549 and H1299. We found that Notch1 protein level was reduced after CK2alpha silencing. Down-regulation of Notch1 transcriptional activity was demonstrated after the silencing of CK2alpha in lung cancer cells. Furthermore, small-molecule CK2alpha inhibitor CX-4945 led to a dose-dependent inhibition of Notch1 transcriptional activity. Conversely, forced overexpression of CK2alpha resulted in an increase in Notch1 transcriptional activity. Finally, the inhibition of
CK2alpha led to a reduced proportion of stem-like CD44+ /CD24- cell population. Thus, we report that the inhibition of CK2alpha down-regulates Notch1 signalling and subsequently reduces a cancer stem-like cell population in human lung cancer cells. Our data suggest that CK2alpha inhibitors may be beneficial to the lung cancer patients with activated Notch1 signalling.

[532]
**TÍTULO / TITLE:** - Uptake of cerium oxide nanoparticles and their influences on functions of A549 cells.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** - Zhou X; Wang B; Chen Y; Mao Z; Gao C
**INSTITUCIÓN / INSTITUTION:** - MOE Key Laboratory of Macromolecular Synthesis and Functionalization, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, China.
**RESUMEN / SUMMARY:** - The cerium oxide nanoparticles (NPs) have been widely used in the fields of fuel additives, cosmetics, commodities, pharmaceuticals and other industries. Exposure of the CeO2 NPs causes a public concern on their potential health risk. In this study, the interactions between two commercial CeO2 NPs and human bronchoalveolar carcinoma-derived A549 cells were investigated to provide a fast and in-depth understanding of the biological influences of the NPs. In the culture medium containing 10% fetal bovine serum, both of the D-CeO2 and PC-CeO2 NPs had an extremely small solubility (< 0.1 ng/mL) and were aggregated from 20 nm and 8 nm (in a dry state) to approximately 190 nm and approximately 60 nm, respectively. Both types of the CeO2 NPs showed slightly negative surface charge due to the adsorption of serum proteins. They had rather weak cytotoxicity even at the highest concentration of 200 microg/mL. Cellular uptake of the CeO2 NPs increased along with the increase of concentration and incubation time. The internalized CeO2 NPs were dispersed in vacuoles and cytoplasm. Uptake of the particles resulted in slight change of the cell cycles, i.e., more cells stayed in the G1 phase, and could suppress the production of reactive oxygen species but brought negligible influence on the mitochondrial membrane potential. However, the cytoskeleton organization and the cell adhesion ability were affected to some extent.

[533]
**TÍTULO / TITLE:** - Deubiquitinase Inhibition of 19S Regulatory Particles by 4-Arylidene Curcumin Analogue AC17 Causes NF-kappaB Inhibition and p53 Reactivation in Human Lung Cancer Cells.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
Proteasome inhibitors have been suggested as potential anti-cancer agents in many clinical trials. Recent evidence indicates that proteasomal deubiquitinase (DUB) inhibitors, bearing a different mechanism from that of traditional proteasome inhibitors, would be appropriate candidates for new anti-cancer drug development. In the present study, we describe the DUB inhibition of 19S regulatory particles (19S RP) by AC17, a 4-arylidene curcumin analogue synthesized in our laboratory. Although 4-arylidene curcumin analogues were reported to act as IkappaB kinase (IKK) inhibitors, AC17 instead induced a rapid and marked accumulation of ubiquitinated proteins without inhibiting proteasome proteolytic activities. In contrast to its parent compound curcumin that is a proteasome proteolytic inhibitor, AC17 serves as an irreversible DUB inhibitor of 19S RP, resulting in inhibition of NF-kappaB pathway and reactivation of pro-apoptotic protein p53. Additionally, in a murine xenograft model of human lung cancer A549, treatment with AC17 suppresses tumor growth in a manner associated with proteasome inhibition, NF-kappaB blockage, and p53 reactivation. These results suggest that 4-arylidene curcumin analogues are novel 19S DUB inhibitors with great potential for anti-cancer drug development.
and may therefore be functionally synonymous with minimal residual disease. Similar to other solid tumours, several putative surface markers for lung cancer stem cells have been identified, including CD133 and CD44. In addition, expression and/or activity of the cytoplasmic enzyme ALDH, and capacity of cells to exclude membrane permeable dyes (known as the “side population”) correlate with stem-like function in vitro and in vivo. Embryonic stem cell pathways such as Hedgehog, Notch and WNT may also be active in lung cancers stem cells, and therefore may be therapeutically targetable for maintenance therapy in patients achieving a complete response to surgery, radiotherapy or chemotherapy. This paper will review the evidence regarding the existence and function of lung cancer stem cells in the context of the experimental and clinical evidence and discuss some ongoing controversies regarding this model.

[535]
TITULO / TITLE: - Fluorescence backgroun d subtraction technique for hybrid fluorescence molecular tomography/x-ray computed tomography imaging of a mouse model of early stage lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1117/1.JBO.18.5.056006
AUTORES / AUTHORS: - Ale A; Ermolayev V; Deliolanis NC; Ntziachristos V
INSTITUCIÓN / INSTITUTION: - Technische Universität Munchen and Helmholtz Zentrum Munchen, Institute for Biological and Medical Imaging, Ingolstädter Landstrasse 1, D-85764 Neuherberg, Germany; Imperial College London, Division of Molecular Biosciences, Theoretical Systems Biology Group, London SW7 2AZ, United Kingdom.
RESUMEN / SUMMARY: - ABSTRACT. The ability to visualize early stage lung cancer is important in the study of biomarkers and targeting agents that could lead to earlier diagnosis. The recent development of hybrid free-space 360-deg fluorescence molecular tomography (FMT) and x-ray computed tomography (XCT) imaging yields a superior optical imaging modality for three-dimensional small animal fluorescence imaging over stand-alone optical systems. Imaging accuracy was improved by using XCT information in the fluorescence reconstruction method. Despite this progress, the detection sensitivity of targeted fluorescence agents remains limited by nonspecific background accumulation of the fluorochrome employed, which complicates early detection of murine cancers. Therefore we examine whether XCT CT information and bulk fluorescence detection can be combined to increase detection sensitivity. Correspondingly, we research the performance of a data-driven fluorescence
background estimator employed for subtraction of background fluorescence from acquisition data. Using mice containing known fluorochromes ex vivo, we demonstrate the reduction of background signals from reconstructed images and sensitivity improvements. Finally, by applying the method to in vivo data from K-ras transgenic mice developing lung cancer, we find small tumors at an early stage compared with reconstructions performed using raw data. We conclude with the benefits of employing fluorescence subtraction in hybrid FMT-XCT for early detection studies.

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[536]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - D’Arcangelo M; Cappuzzo F
INSTITUCIÓN / INSTITUTION: - Istituto Toscano Tumori, Ospedale Civile, Viale Alfieri 36, 57100, Livorno, Italy.
RESUMEN / SUMMARY: - Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths. In the last decade the EGF receptor (EGFR) signaling pathway has emerged as one of the most important molecular aberrations in NSCLC. Drugs interfering with the tyrosine kinase domain of the EGFR (EGFR-TKI), such as erlotinib or gefitinib, demonstrated efficacy in patients with advanced NSCLC irrespective of therapy line and particularly in patients harboring activating mutations of the EGFR gene. Results of large Phase III randomized trials clearly demonstrated that an EGFR-TKI is the best front-line option for patients with classical EGFR mutations, while in the EGFR wild-type or EGFR unknown population platinum-based chemotherapy remains the gold standard. In pretreated patients, EGFR-TKIs are considered more effective than standard chemotherapy in the EGFR-mutated population, with no difference in EGFR wild-type NSCLC. Although EGFR-TKIs are certainly particularly effective in patients with EGFR mutations, at present no biomarker, including KRAS mutations, can be recommended in clinical practice for precluding the therapy to any pretreated patient. In this article, the authors analyzed data of erlotinib in NSCLC, focusing on its role in front-line therapy.

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[537]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Introduction: Non-small cell lung cancer (NSCLC) is a major cause of cancer-related death worldwide. Although advanced NSCLC is still incurable, various anti-neoplastic agents have become available for the treatment of this disease. Pemetrexed, a multi-target folate antagonist, has improved the survival of non-squamous NSCLC patients. Currently, pemetrexed is approved for first-line treatment in combination with a platinum derivate, for second-line treatment as a single agent and, more recently, as maintenance treatment after first-line chemotherapy. Areas covered: The authors analyzed the state of the art of pemetrexed through a review of the literature. Clinical trials and meta-analyses involving pemetrexed in NSCLC were evaluated. Pemetrexed improved survival of non-squamous NSCLC in first-line, maintenance, and second-line treatments; this benefit is limited to non-squamous histology. Because pemetrexed has become part of the standard of care, current clinical trials are designed to compare it to other investigational combinations. Limited data on resectable disease are available, and additional clinical trials are being conducted. Expert opinion: Pemetrexed has shown effectiveness and a favorable toxicity profile. Histology-driven indications and the relationship of pemetrexed with thymidylate synthase expression suggest that a more precise definition of predictive biomarkers could be further investigated.

[538]

TITULO / TITLE: Acyl-CoA thioesterase 8 is a specific protein related to nodal metastasis and prognosis of lung adenocarcinoma.

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


AUTORES / AUTHORS: Jung WY; Kim YH; Ryu YJ; Kim BH; Shin BK; Kim A; Kim HK

INSTITUCIÓN / INSTITUTION: Department of Pathology, Korea University College of Medicine, Seoul, South Korea.

RESUMEN / SUMMARY: Metastasis is a major cause of cancer recurrence or death. This study attempted to quantitatively identify different proteins in metastatic lung adenocarcinoma. The N/T quotient [number of metastatic
lymph nodes (n)/tumor diameter (cm)] was used to select samples with an extreme metastatic phenotype. Among the six fresh frozen lung adenocarcinoma specimens, the three showing the highest N/T quotient represented the metastatic group, and others with the greatest tumor diameters without metastasis represented the non-metastatic group. After 2-dimensional electrophoresis, the significantly different protein spots were selected by image analysis and analyzed with MALDI-TOF mass spectrometry. Acyl-CoA thioesterase 8 isoform c (ACOT8) was one of most overexpressed proteins in the metastatic group, and it was validated by Western blot and immunohistochemical staining on 108 paraffin-embedded tumor samples. High ACOT8 expression was correlated with lymph node metastasis (p=0.002), recurrence (p=0.034), predominant histologic subtypes (p=0.007), and higher stage (p=0.005). In multivariate analysis, high ACOT8 expression was significantly associated with increased risks of lymph node metastasis (p=0.009) and cancer-related death (p=0.030), independent of clinical factors. ACOT8 may be a candidate prognostic biomarker and therapeutic target of lung adenocarcinoma.
protein composition, are still unknown. In this study we report the first global proteomic analysis of highly purified MVs derived from human non-small-cell-lung-cancer (NSCLC) pleural effusion. Using nano-LC-MS/MS following 1-D SDS-PAGE separation, we identified a total of 912 MV proteins with high confidence. Three independent experiments on three patients showed that MV proteins from PE were distinct from MV obtained from other malignancies. Bioinformatics analyses of the MS data identified pathologically relevant proteins and potential diagnostic makers for NSCLC, including lung-enriched surface antigens and proteins related to EGFR signaling. These findings provide new insight into the diverse functions of MVs in cancer progression and will aid in the development of novel diagnostic tools for NSCLC.

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TÍTULO / TITLE: - AD-1, a novel ginsenoside derivative, shows anti-lung cancer activity via activation of p38 MAPK pathway and generation of reactive oxygen species.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhang LH; Jia YL; Lin XX; Zhang HQ; Dong XW; Zhao JM; Shen J; Shen HJ; Li FF; Yan XF; Li W; Zhao YQ; Xie QM
INSTITUCIÓN / INSTITUTION: - Zhejiang Respiratory Drugs Research Laboratory of State Food and Drug Administration of China, Medical College of Zhejiang University, Hangzhou 310058, China; Medical and Pharmaceutical Institute, Medicine School of Yangzhou University, Yangzhou 225001, China.
RESUMEN / SUMMARY: - BACKGROUND: Ginseng is a traditional Chinese herb that has been used for thousands of years. In the present study, effects and mechanisms of AD-1 were evaluated for its development as a new anti-lung cancer drug. METHODS: The cytotoxic activity was evaluated by MTT assay. Flow cytometry was employed to detect cell cycle, apoptosis and ROS. Western blot and immunohistochemistry were used to analyze signaling pathways. Lung cancer xenograft models were established by subcutaneous implantation of A549 or H292 cells into nude mice. RESULTS: AD-1 concentration-dependently reduces lung cancer cell viability without affecting normal human lung epithelial cell viability. In A549 and H292 lung cancer cells, AD-1 induces G0/G1 cell cycle arrest, apoptosis and ROS production. The apoptosis can be attenuated by a ROS scavenger - N-acetylcysteine (NAC). In addition, AD-1 up-regulates the expression of p38 and ERK phosphorylation. Addition of a p38 inhibitor SB203580, suppresses the AD-1-induced decrease in cell viability. Furthermore, genetic silencing of p38 attenuates the expression of p38 and
decreases the AD-1-induced apoptosis. Treatment with NAC reduces AD-1-induced p38 phosphorylation, which indicates that ROS generation is involved in the AD-1-induced p38 activation. In mice, oral administration of AD-1 (10-40mg/kg) dose-dependently inhibited the growth of xenograft tumors without affecting body weight and decreases the expression of VEGF, MMP-9 and CD34 in tumor tissue. TUNEL staining confirms that the tumors from AD-1 treated mice exhibit a markedly higher apoptotic index. CONCLUSIONS AND GENERAL SIGNIFICANCE: These data support development of AD-1 as a potential agent for lung cancer therapy.

[542]

TÍTULO / TITLE: - Expression of HAb18G/CD147 and its localization correlate with the progression and poor prognosis of non-small cell lung cancer.

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


AUTORES / AUTHORS: - Xu XY; Lin N; Li YM; Zhi C; Shen H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou, PR China; Department of Pathology, School of Basic Medical Sciences, Southern Medical University, Guangzhou, PR China.

RESUMEN / SUMMARY: - This study was designed to investigate the association of HAb18G/CD147 expression and localization with clinicopathological parameters and prognosis in NSCLC. Two hundred and eight (208) specimens of surgically resected NSCLC were stained by immunohistochemistry utilizing mouse anti-human HAb18G/CD147 monoclonal antibody. High levels of HAb18G/CD147 expression were associated with male gender, smoking history, tumor position, distant metastasis status, and clinical stage (p<0.05) in squamous cell carcinoma. In adenocarcinomas, HAb18G/CD147 expression was associated with male gender, tumor diameter, differentiation, lymph node status, distant metastasis status, and clinical stage (p<0.05). HAb18G/CD147 expression with higher PU was predominantly localized in the tumor cell membranes rather than in cytoplasms. In squamous cell carcinomas, membranous localization of HAb18G/CD147 was linked to distant metastasis status and TNM stage (p<0.05). Cytoplasmic localization of HAb18G/CD147 was associated with male gender and smoking history. In adenocarcinomas, membranous localization of HAb18G/CD147 correlated with tumor diameter, differentiation and distant metastasis (p<0.05). Univariate analysis indicated that patients with high HAb18G/CD147 expression and membranous localization predicted poor prognosis in both squamous cell carcinomas and adenocarcinomas. Multivariate analysis showed that lymph node status
(HR=1.762, 95%CI 1.105-2.811, p=0.017), distant metastasis status (HR=3.789, 95%CI 2.196-6.539, p=0.000), expression (HR=6.632, 95%CI 2.457-17.904, p=0.000), and localization (HR=0.520, 95%CI 0.341-0.794, p=0.002) were good or excellent independent predictors of patient survival. HAb18G/CD147 is a biomarker characterizing progression and survival of NSCLC. More importantly, its cellular localizations should be considered in the analysis of clinicopathological characteristics and prognostic factors in NSCLC.

[543]
TITULO / TITLE: Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Srour N; Amjadi K; Forster A; Aaron S
RESUMEN / SUMMARY: BACKGROUND: Management of malignant pleural effusion typically involves insertion of an indwelling pleural catheter (IPC) or chemical pleurodesis with agents such as talc. OBJECTIVES: To compare these management strategies with regard to success of pleural effusion management. METHODS: A retrospective cohort study was designed comparing patients with malignant and paramalignant pleural effusions and Eastern Cooperative Oncology Group performance status <4 managed with IPC insertion or talc pleurodesis (TP) through tube thoracostomy during noncontemporary three-year periods at a single centre. Results: The IPC and TP groups comprised 193 and 167 patients, respectively. The pleural effusion control rate at six months was higher in the IPC group (52.7% versus 34.4% in the TP group; P<0.01), but the rate of freedom from catheter at 90 days and pleural effusion at 180 days was not significantly different (IPC 25.8% versus TP 34.4% [P=0.17]). Median effusion-free survival from the date of catheter insertion was significantly longer in the IPC group (101 days versus 58 days in the TP group; log-rank P=0.025). Both procedures were safe. DISCUSSION: While the results suggest better pleural effusion control and longer effusion-free survival with IPC insertion compared with TP, the present study had several limitations. Other recent studies have not shown one strategy to be clearly superior to the other. CONCLUSION: Both IPC insertion and TP remain acceptable options for the management of malignant pleural effusions.

[544]
TITULO / TITLE: Irregular breathing during 4DCT scanning of lung cancer patients: Is the midventilation approach robust?
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1016/j.ejmp.2013.03.003
AUTORES / AUTHORS: - Aznar MC; Persson GF; Kofoed IM; Nygaard DE; Korreman SS
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Niels Bohr Institute, Faculty of Sciences, University of Copenhagen, Denmark. Electronic address: marianne.aznar@regionh.dk,
RESUMEN / SUMMARY: - BACKGROUND: With 4DCT the risk of introducing positional systematic errors in lung cancer radiotherapy can be minimised. A common approach is to plan on the phase bin of the 4DCT best representing the tumour’s time-weighted mean position also called the midventilation scan. However breathing irregularities can introduce uncertainties and potentially misrepresent both the tumour trajectory and the determination of the midventilation phase. In this study we evaluated the robustness of the midventilation approach in the presence of irregular breathing patterns.
METHODS: A LEGO Mindstorms® phantom with compact balls simulating lung tumours was constructed. The breathing curves loaded in the phantom were either acquired from a human volunteer or constructed with various magnitudes (ranging from 12 to 29 mm) as well as various irregularities of motion pattern. Repeated 4DCT scans were performed while tumour trajectories were recorded with two motion tracking systems. RESULTS: The time-weighted mean tumour position is accurately represented in 4DCT scans, even for irregular breathing patterns: the position presentation in the midventilation scan was always within one standard deviation of the global position presentation (3 mm and 2 mm for regular and irregular breathing patterns, respectively). The displacement representation tended to be underestimated in 4DCT scans. CONCLUSION: The midventilation approach is robust even in the presence of breathing irregularity. The representation of the tumour trajectory in 4DCT scans is affected by breathing irregularity and the extent of tumour motion can be underestimated, which will affect the calculation of patient-individualised margins based on the 4DCT scan.

[545]
TÍTULO / TITLE: - Polymorphisms in thymidylate synthase and reduced folate carrier ( ) genes predict survival outcome in advanced non-small cell lung cancer patients treated with pemetrexed-based chemotherapy.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 3892/ol.2013.1175
AUTORES / AUTHORS: - Li WJ; Jiang H; Fang XJ; Ye HL; Liu MH; Liu YW; Chen Q; Zhang L; Zhang JY; Yuan CL; Zhang QY

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The Second People’s Hospital of Lianyungang (Lianyungang Hospital Affiliated to Bengbu Medical College), Jiangsu 222000, P.R. China.

RESUMEN / SUMMARY: - The aim of this study was to evaluate the association between thymidylate synthase (TS), methylenetetrahydrofolate reductase (MTHFR) and reduced folate carrier (SLC19A1) gene polymorphisms and the treatment efficacy of pemetrexed-based chemotherapy in advanced non-small cell lung cancer (NSCLC). Advanced NSCLC patients received pemetrexed and cisplatin every three weeks. Polymorphisms in the TS, MTHFR and SLC19A1 genes were detected in peripheral blood samples using DNA sequencing and Taqman PCR. An analysis of gene polymorphisms was performed with respect to the progression-free survival (PFS), response rate (RR) and overall survival (OS) of patients treated with pemetrexed. The median PFS times for patients with the TS 2R/2R, 2R/3C or 3C/3C genotypes were significantly longer than those of patients with the 2R/3G, 3C/3G or 3G/3G genotypes (P=0.036). Patients with the SLC19A1 CC genotype had a significantly longer median OS compared with individuals with the homozygous and heterozygous genotypes (12.2 vs. 8.9 and 7.3 months, respectively; P=0.022). The PFS and OS did not differ for the three genotypes of MTHFR assessed. The RR was higher in patients with the TS 2R/2R, 2R/3C or 3C/3C genotypes than in the other groups (P=0.044). The polymorphisms of the 5'-UTR of the TS gene and exon 6 (2522) C/T of the SLC19A1 gene predict the survival of advanced NSCLC patients treated with pemetrexed. However, a large scale clinical trial is required to validate these findings.

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TÍTULO / TITLE: - Is Alpha-B Crystallin an Independent Marker for Prognosis in Lung Cancer?

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


AUTORES / AUTHORS: - Campbell-Lloyd AJ; Mundy J; Deva R; Lampe G; Hawley C; Boyle G; Griffin R; Thompson C; Shah P

INSTITUCIÓN / INSTITUTION: - Princess Alexandra Hospital, Australia.

RESUMEN / SUMMARY: - BACKGROUND: Alpha B-crystallin (CRYAB) is an oncogene that increases tumour survival by promoting angiogenesis and preventing apoptosis. CRYAB is an independent prognostic marker in epithelial tumours including head and neck squamous cell carcinoma and breast cancer where it is predictive of nodal status and associated with poor outcome. We explored the role of CRYAB in non-small-cell lung cancer (NSCLC). METHODS:
Immunohistochemical analysis was performed on 50 samples. Following staining with anti-alpha-B crystallin antibody, a blinded pathologist scored samples for nuclear (N) and cytoplasmic © staining intensity. Analysis was performed using Cox’s proportional hazards model. RESULTS: There were 32 adenocarcinomas and 18 squamous cell carcinomas. The median tumour size was T2, grade 2 moderately differentiated, and 10 patients had nodal spread. Recurrence was seen in 22 patients (46%). Mortality was 48%, with median time to mortality 871 days. N staining was detected in eight samples (16%), and C staining in 20 (40%), with both N and C staining positive in five (10%). Staining for CRYAB predicted neither recurrence (N stain p=0.78, C stain p=0.38) nor mortality (N stain p=0.86, C stain p=0.66). CONCLUSION: CRYAB did not predict outcomes in patients treated for NSCLC. Larger studies are required to validate this finding.

[547]

**TITULO / TITLE:** - Real-World Effectiveness of Systemic Agents Approved for Advanced Non-Small Cell Lung Cancer: A SEER-Medicare Analysis.

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


●●Enlace al texto completo (gratis o de pago)
1634/theoncologist.2012-0480

**AUTORES / AUTHORS:** - Owonikoko TK; Ragin C; Chen Z; Kim S; Behera M; Brandes JC; Saba NF; Pentz R; Ramalingam SS; Khuri FR

**INSTITUCIÓN / INSTITUTION:** - Department of Hematology and Medical Oncology, Emory University, Atlanta, Georgia, USA;

**RESUMEN / SUMMARY:** - Disparity exists between patients with lung cancer enrolled in clinical trials and patients treated in the community setting. This study assessed the real-world effectiveness of cytotoxic agents that became available for the treatment of non-small cell lung cancer (NSCLC) in the last 2 decades. Methods. We employed the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database for patients diagnosed with stage IIIB/IV NSCLC between 1988 and 2005 to assess the effectiveness of newly approved agents. Effectiveness of specific agents was assessed at time periods immediately following the approval of the agent for NSCLC: baseline, 1988-1994; platinum, 1995-1999; docetaxel, 1999-2003; pemetrexed and bevacizumab, 2004-2005. Significant associations between specific drug treatment and survival improvement were determined using the Kaplan-Meier method, Cox proportional hazard model, and propensity score analyses. Significant differences were established by log-rank test. Results. This analysis employed data from 143,548 patients by sex (58% male, 42% female), cancer stage (35% stage IIIB, 65% stage IV), and age (12% 20-64 years, 22% 65-69
years, 45% 70-79 years, 22% 80 years and older). There was temporal improvement in survival for patients treated with newly approved chemotherapy (1-year survival rates: 32.41% in 1988-1994, 32.95% in 1995-1998, 37.40% in 1999-2003, and 39.55% in 2004-2005). Patients treated with a newly approved drug during the relevant treatment era had a significant reduction in the risk of death when compared with patients treated with chemotherapy other than the newly approved agent (hazard ratios [95% confidence interval] were 0.76 [0.71-0.81] for platinum, 0.73 [0.70-0.75] for docetaxel, 0.40 [0.37-0.44] for pemetrexed, and 0.33 [0.27-0.40] for bevacizumab; p < .001). Propensity score adjustment did not significantly alter the results. Conclusions. Currently approved drugs for the treatment of advanced NSCLC are associated with improved survival in the U.S. Medicare patient population. Our findings support the effectiveness of these agents in the real-world oncology practice.

[548]
TITULO / TITLE: Expression of SIRT1 and cortactin is associated with progression of non-small cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Noh SJ; Baek HA; Park HS; Jang KY; Moon WS; Kang MJ; Lee DG; Kim MH; Lee JH; Chung MJ
INSTITUCIÓN / INSTITUTION: Department of Pathology, Chonbuk National University, Medical School and Research Institute for Endocrine Sciences, Jeonju 561-180, Republic of Korea.
RESUMEN / SUMMARY: Cortactin is an F-actin binding protein involved in cell migration and tumor metastasis. Recent reports suggest that silent mating-type information regulation 2 homologue 1 (sirtuin1; SIRT1) enhances the function of cortactin and promotes cell migration. We investigated SIRT1 and cortactin expression in 144 invasive non-small cell lung cancers (NSCLC) and 19 adenocarcinomas in situ (AIS) by immunohistochemistry and evaluated their clinicopathological significance in NSCLC. Positive SIRT1 and cortactin expression was observed in 67% (96 of 144) and 58% (84 of 144) of patients with invasive NSCLC, respectively. SIRT1 and cortactin expression was significantly associated with unfavorable clinicopathological factors, including high pathological T stage, lymph node metastasis, and advanced tumor invasion (AIS vs. invasive adenocarcinoma). Cortactin was significantly associated with high pathological T stage and lymph node metastasis in SIRT1-positive tumors. Cytoplasmic SIRT1 was significantly associated with high pathological T stage and large tumor size compared to that of nuclear SIRT1. Large tumor size, high pathological T stage, lymph node metastasis, and
cytoplasmic SIRT1 expression were significantly associated with shorter overall survival in a univariate analysis. Our findings suggest that SIRT1 and cortactin may play a role in the progression of NSCLC and may cooperate during tumor progression in NSCLC.

[549]

**TÍTULO / TITLE:** Primary small cell carcinoma of the esophagus: review of 64 cases from a single institution.

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


**AUTORES / AUTHORS:** Zhu Y; Qiu B; Liu H; Li Q; Xiao W; Hu Y; Liu M

**INSTITUCIÓN / INSTITUTION:** Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; Guangdong Esophageal Cancer Research Institute, Guangzhou, Guangdong, China.

**RESUMEN / SUMMARY:** Primary small cell carcinoma of esophagus (SCCE) is a rare disease with poor prognosis. The aims of this study are to review the clinical characteristics, treatment modalities, and outcomes of SCCE and to investigate the prognostic factors and optimal treatment options. Sixty-four patients diagnosed as SCCE in Sun Yat-sen University Cancer Center from 1990 to 2011 were retrospectively reviewed. There were 46 patients with limited disease (LD) and 18 with extensive disease. The median survival time (MST) and overall survival rate were calculated and compared by the Kaplan-Meier method and log-rank test, respectively. The prognostic factors were calculated by Cox hazards regression model. With a median follow up of 11.6 months, the MST of all the 64 patients was 12.6 months, 16.5 months for LD and 9.0 months for extensive disease. The 1-, 3-, and 5-year overall survivals were 52.5%, 20.9%, and 7.5%, respectively. In univariate analysis, patients with ECOG performance score <2 (P = 0.009), lesion length <=5 cm (P = 0.009), T stage <=2 (P = 0.004), LD (P = 0.000), and multimodality treatment (P = 0.016) had significant associations with MST. Multivariate analysis showed that ECOG performance score (P = 0.001), T stage (P = 0.023), limited-extensive stage (P = 0.007), and treatment modality (P = 0.008) were independent prognostic factors. Locoregional treatment combined with chemotherapy had a trend to increase MST from 15.3 to 20.0 months in LD patients (P = 0.126), while combined chemotherapy had a significant impact on MST in extensive disease patients (P = 0.000). SCCE is a highly malignant disease with poor prognosis. Patients might obtain survival benefit from the combination of locoregional treatment and systemic therapy. Prospective studies are needed to validate these factors.
Control of Alveolar Differentiation by the Lineage Transcription Factors GATA6 and HOPX Inhibits Lung Adenocarcinoma Metastasis.

Molecular programs that mediate normal cell differentiation are required for oncogenesis and tumor cell survival in certain cancers. How cell-lineage-restricted genes specifically influence metastasis is poorly defined. In lung cancers, we uncovered a transcriptional program that is preferentially associated with distal airway epithelial differentiation and lung adenocarcinoma (ADC) progression. This program is regulated in part by the lineage transcription factors GATA6 and HOPX. These factors can cooperatively limit the metastatic competence of ADC cells, by modulating overlapping alveolar differentiation and invasogenic target genes. Thus, GATA6 and HOPX are critical nodes in a lineage-selective pathway that directly links effectors of airway epithelial specification to the inhibition of metastasis in the lung ADC subtype.

Right ventricular metastasis of lung cancer: Persistent ST-segment elevation and constrictive physiology.

Department of Cardiology, Marmara University Faculty of Medicine, Istanbul, Turkey, acincin@yahoo.com.
TÍTULO / TITLE: - Corticotropin secreting bronchial carcinoid diagnosed after 22 years.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hadj Ali S; Chihaoui M; Kanoun F; Lamine F; Ayadi A; El Mezni F; Kchir MN; Kilani T; Slimane H

[553]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Li B; Lu Q; Song ZG; Yang L; Jin H; Li ZG; Zhao TJ; Bai YF; Zhu J; Chen HZ; Xu ZY
INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai, China. chenhezhongchh@hotmail.com
RESUMEN / SUMMARY: - OBJECTIVES: We aimed to explore the DNA methylation difference between lung cancer samples and non-cancer lung samples, and to investigate the role of DNA methylation in the mechanism of lung cancer development. Besides, we analyzed the transcriptional regulation network of DNA methylation and the miRNAs regulated by DNA methylation. This study provides a framework for DNA methylation in other tumors or diseases. MATERIALS AND METHODS: DNA methylation and gene expression profiles used were obtained from Gene Expression Omnibus. Firstly, we identified differentially methylated genes (DMGs) by Student’s t-test. Then we detected the biological processes and pathways changed in lung cancer by Gene Ontology (GO) and KEGG pathway enrichment analysis. The transcriptional factors in differential genes were identified and the microRNAs regulated by them were also obtained in TransmiR. RESULTS: We obtained 108 DMGs between lung cancer samples and non-cancer samples. Besides development related biological processes and pathways were dramatically disordered. For the DMGs, we identified 11 transcriptional factors regulating them. Moreover, we screened out 21 relationships between DMGs and their transcriptional targets. Five microRNAs are reported to be regulated by DNA methylation genes. Finally a regulation network of DNA methylation was constructed. CONCLUSIONS: DNA methylation participates in carcinogenesis at the transcriptional and post-transcriptional level. Aberrant DNA methylation will prevent its binding with the upstream regulatory proteins, inhibit the function of downstream target genes and regulate the expression of downstream miRNA, and consequently affect cell development, immuneresponse and apoptosis.

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TÍTULO / TITLE: - Aerosol administration of phospho-sulindac inhibits lung tumorigenesis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1158/1535-7163.MCT-13-0006-T
AUTORES / AUTHORS: - Cheng KW; Wong CC; Alston N; Mackenzie GG; Huang L; Ouyang N; Xie G; Wiedmann T; Rigas B
INSTITUCIÓN / INSTITUTION: - IDivision of Cancer Prevention, THE STATE UNIVERSITY OF NEW YORK.
RESUMEN / SUMMARY: - Phospho-sulindac (PS) is a sulindac derivative with promising anticancer activity in lung cancer, but its limited metabolic stability presents a major challenge for systemic therapy. We reasoned that inhalation delivery of PS might overcome first-pass metabolism and produce high levels of intact drug in lung tumors. Here, we developed a system for aerosolization of PS and evaluated the antitumor efficacy of inhaled PS in an orthotopic model of human non-small cell lung cancer (A549 cells). We found that administration by inhalation delivered high levels of PS to the lungs and minimized its hydrolysis to less active metabolites. Consequently, inhaled PS (6.5mg/kg) was highly effective in inhibiting lung tumorigenesis (75%, p<0.01) and significantly improved the survival of mice bearing orthotopic A549 xenografts. Mechanistically, PS suppressed lung tumorigenesis by 1) inhibiting EGFR activation, leading to profound inhibition of Raf/MEK/ERK and PI3K/AKT/mTOR survival cascades; 2) inducing oxidative stress, which provokes the collapse of mitochondrial membrane potential and mitochondria-dependent cell death; and 3) inducing autophagic cell death. Our data establish that inhalation delivery of PS is an efficacious approach to the prevention of lung cancer, which merits further evaluation.

[554]

TÍTULO / TITLE: - Pharmacological activation of PKM2 slows lung tumor xenograft growth.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1158/1535-7163.MCT-13-0026
AUTORES / AUTHORS: - Parnell KM; Foulks JM; Nix RN; Clifford A; Bullough J; Luo B; Senina A; Vollmer D; Liu J; McCarthy V; Xu Y; Saunders M; Liu XH; Pearce S; Wright K; O'Reily M; McCullar MV; Ho KK; Kanner SB
INSTITUCIÓN / INSTITUTION: - 1Research and Development, Astex Pharmaceuticals, Inc.
RESUMEN / SUMMARY: Inactivation of the M2 form of pyruvate kinase (PKM2) in cancer cells is associated with increased tumorigenicity. To test the hypothesis that tumor growth may be inhibited through the PKM2 pathway, we generated a series of small molecule PKM2 activators. The compounds exhibited low nM activity in both biochemical and cell-based PKM2 activity assays. These compounds did not affect the growth of cancer cell lines under normal conditions in vitro, but strongly inhibited the proliferation of multiple lung cancer cell lines when serine was absent from the cell culture media. In addition, PKM2 activators inhibited the growth of an aggressive lung adenocarcinoma xenograft. These findings demonstrate that PKM2 activation by small molecules influences the growth of cancer cells in vitro and in vivo, and suggest that such compounds may augment cancer therapies.

TÍTULO / TITLE: SPECT/CT of lung nodules using In-DOTA-c(RGDfK) in a mouse lung carcinogenesis model.

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


AUTORES / AUTHORS: Hayakawa T; Mutoh M; Imai T; Tsuta K; Yanaka A; Fujii H; Yoshimoto M

INSTITUCIÓN / INSTITUTION: Division of Cancer Prevention Research, National Cancer Center Research Institute, 5-1-1 Chuo-ku, Tokyo, 104-0045, Japan.

RESUMEN / SUMMARY: OBJECTIVE: Lung cancer is one of the leading causes of cancer-related deaths worldwide, including Japan. Although computed tomography (CT) can detect small lung lesions such as those appearing as ground glass opacity, it cannot differentiate between malignant and non-malignant lesions. Previously, we have shown that single photon emission computed tomography (SPECT) imaging using 111In-DOTA-c(RGDfK), an imaging probe of alphavbeta3 integrin, is useful for the early detection of pancreatic cancer in a hamster pancreatic carcinogenesis model. In this study, we aimed to assess the usefulness of SPECT/CT with 111In-DOTA-c(RGDfK) for the evaluation of the malignancy of lung cancer.

METHODS: Lung tumors were induced by a single intraperitoneal injection (250 mg/kg) of urethane in male A/J mice. Twenty-six weeks after the urethane treatment, SPECT was performed an hour after injection of 111In-DOTA-c(RGDfK). Following this, the radioactivity ratios of tumor to normal lung tissue were measured by autoradiography (ARG) in the excised lung samples. We also examined the expression of alphavbeta3 integrin in mouse and human lung samples. RESULTS: Urethane treatment induced 5 hyperplasias, 41 adenomas
and 12 adenocarcinomas in the lungs of 8 A/J mice. SPECT with 111In-DOTA-c(RGDfK) could clearly visualize lung nodules, though we failed to detect small lung nodules like adenoma and hyperplasias (adenocarcinoma: 66.7 %, adenoma: 33.6 %, hyperplasia: 0.0 %). ARG analysis revealed significant uptake of 111In-DOTA-c(RGDfK) in all the lesions. Moreover, tumor to normal lung tissue ratios increased along with the progression of carcinogenesis. Histopathological examination using human lung tissue samples revealed clear up-regulation of alphavbeta3 integrin in well-differentiated adenocarcinoma (Noguchi type B and C) rather than atypical adenomatous hyperplasia.

CONCLUSION: Although there are some limitations in evaluating the malignancy of small lung tumors using 111In-DOTA-c(RGDfK), SPECT with 111In-DOTA-c(RGDfK) might be a useful non-invasive imaging approach for evaluating the characteristics of lung tumors in mice, thus showing potential for use in humans.

[557]

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Henley SJ; Larson TC; Wu M; Antao VC; Lewis M; Pinheiro GA; Eheman C
INSTITUCIÓN / INSTITUTION: - Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Atlanta, GA 30341, USA. skh3@cdc.gov
RESUMEN / SUMMARY: - BACKGROUND: The decline in asbestos use in the United States may impact mesothelioma incidence. OBJECTIVE: This report provides national and state-specific estimates of mesothelioma incidence in the United States using cancer surveillance data for the entire US population. METHODS: Data from the National Program for Cancer Registries and the Surveillance, Epidemiology, and End Results program were used to calculate incidence rates and annual percent change. RESULTS: During 2003-2008, an average of 1.05 mesothelioma cases per 100 000 persons were diagnosed annually in the United States; the number of cases diagnosed each year remained level, whereas rates decreased among men and were stable among women. CONCLUSION: US population-based cancer registry data can be used to determine the burden of mesothelioma and track its decline. Even 30 years after peak asbestos use in the United States, 3200 mesothelioma cases are diagnosed annually, showing that the US population is still at risk.
The impact of the sequence of pulmonary vessel ligation during anatomic resection for lung cancer on long-term survival - a prospective randomized trial.

Abstract Purpose: The aim of this prospective randomized trial was to assess the influence of the sequence of pulmonary vessel ligation, during anatomic resection, on long term survival in patients with NSCLC. Material/Methods: This prospective randomized study included 385 patients treated surgically with lobectomy or pneumonectomy and standard lymphadenectomy between 1999 and 2003. Patients were randomly assigned to either primary ligation of the pulmonary artery or arteries (group A - 215 patients) or of the pulmonary vein or veins (group V - 170 patients). Patients were excluded if the sequence of vessel ligation was affected by technical difficulties or anatomic limitations. Univariate and multivariate analyses included: the sequence of vessel ligation, age, gender, tumor histology, stage (TNM), and cause of death (cancer related or non-cancer related). Results: Median follow-up was 63 months. The groups were comparable regarding gender, histology, type of resection, and T, N, and overall stage. Overall, 5-year survival reached 50% in group A and 54% in group V (p = 0.82) and did not differ significantly in cancer related and non-cancer related deaths (p = 0.67 and p = 0.26, respectively). Univariate analysis identified higher T and N factors, advanced stage, pneumonectomy, male sex, and older age as negative prognostic factors. Multivariate analysis demonstrated that age, T3-4 disease, and nodal involvement were associated with inferior survival. Conclusions: The sequence of pulmonary vessel ligation during anatomic resection for non-small cell lung cancer does not significantly affect long-term survival.

PET-based delineation of tumour volumes in lung cancer: comparison with pathological findings.

Abstract Purpose: The aim of this prospective study was to compare PET-based delineation of tumour volumes with pathological findings in patients with lung cancer. Material/Methods: This prospective study included 10 patients with lung cancer who underwent PET-CT and surgical resection. PET volumes were delineated by two independent readers, while pathological volumes were manually drawn. Results: The mean difference between PET and pathological volumes was 10.3% (range -46% to 85%). Conclusions: PET-based delineation of tumour volumes in lung cancer is comparable with pathological findings.
PURPOSE: The objective of the study was to validate an adaptive, contrast-oriented thresholding algorithm (COA) for tumour delineation in 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for non-small cell lung cancer (NSCLC) in comparison with pathological findings. The impact of tumour localization, tumour size and uptake heterogeneity on PET delineation results was also investigated.

METHODS: PET tumour delineation by COA was compared with both CT delineation and pathological findings in 15 patients to investigate its validity. Correlations between anatomical volume, metabolic volume and the pathology reference as well as between the corresponding maximal diameters were determined. Differences between PET delineations and pathological results were investigated with respect to tumour localization and uptake heterogeneity.

RESULTS: The delineated volumes and maximal diameters measured on PET and CT images significantly correlated with the pathology reference (both $r > 0.95$, $p < 0.0001$). Both PET and CT contours resulted in overestimation of the pathological volume (PET $32.5 +/- 26.5\%$, CT $46.6 +/- 27.4\%$). CT volumes were larger than those delineated on PET images (CT $60.6 +/- 86.3$ ml, PET $48.3 +/- 61.7$ ml). Maximal tumour diameters were similar for PET and CT ($51.4 +/- 19.8$ mm for CT versus $53.4 +/- 19.1$ mm for PET), slightly overestimating the pathological reference (mean difference CT $4.3 +/- 3.2$ mm, PET $6.2 +/- 5.1$ mm). PET volumes of lung tumours located in the lower lobe were significantly different from those determined from pathology ($p = 0.037$), whereas no significant differences were observed for tumours located in the upper lobe ($p = 0.066$). Only minor correlation was found between pathological tumour size and PET heterogeneity ($r = -0.24$). CONCLUSION: PET tumour delineation by COA showed a good correlation with pathological findings. Tumour localization had an influence on PET delineation results. The impact of tracer uptake heterogeneity on PET delineation should be considered carefully and individually in each patient. Altogether, PET tumour delineation by COA for NSCLC patients is feasible and reliable with the potential for routine clinical application.
ENLACE AL TEXTO COMPLETO (GRATUITO O DE PAGO) 1177/1098612X13489675

AUTORES / AUTHORS: - Keenihan EK; Lynch S; Priestnall SL; Harrington NT; Benigni L; Lamb CR

INSTITUCIÓN / INSTITUTION: - 1Department of Clinical Sciences and Services, The Royal Veterinary College, North Mymms, UK.

RESUMEN / SUMMARY: - Two cats had chronic respiratory signs associated with pulmonary carcinoma. In each case, computed tomography demonstrated similar pulmonary masses, pleural fluid and osteolytic expansile rib lesions as a result of local costal spread. This is the first report of feline primary pulmonary adenocarcinoma with local spread to the ribs, causing osteolysis. Although pleural involvement is common with this neoplasm, local spread to ribs is rarely reported.

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TÍTULO / TITLE: - miR-135ª/b Modulate Cisplatin Resistance of Human Lung Cancer Cell Line by Targeting MCL1.

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


AUTORES / AUTHORS: - Zhou L; Qiu T; Xu J; Wang T; Wang J; Zhou X; Huang Z; Zhu W; Shu Y; Liu P

INSTITUCIÓN / INSTITUTION: - Department of Oncology, First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing, 210029, China.

RESUMEN / SUMMARY: - microRNAs (miRNAs) are short non-coding RNA molecules, which post-transcriptionally regulate genes expression and play crucial roles in diverse biological processes, such as development, differentiation, apoptosis, and proliferation. Here, we investigated the possible role of miRNAs in the development of drug resistance in human lung cancer cell line. We found that miR-135ª/b were downregulated while MCL1 was upregulated in A549/CDDP (cisplatin) cells, compared with the parental A549 cells. In vitro drug sensitivity assay demonstrated that overexpression of miR-135ª/b sensitized A549/CDDP cells to cisplatin. The luciferase activity of MCL1 3'-untranslated region-based reporter constructed in A549/CDDP cells suggested that MCL1 was the direct target gene of miR-135ª/b. Enforced miR-135ª/b expression reduced MCL1 protein level and sensitized A549/CDDP cells to CDDP-induced apoptosis. Taken together, our findings first suggested that hsa-miR-135ª/b could play a role in the development of CDDP resistance in lung cancer cell line at least in part by modulation of apoptosis via targeting MCL1.
[562]
**TITULO / TITLE:** - Strengthening Context-Dependent Anti-Cancer Effects on Non-Small Cell Lung Carcinoma by Inhibition of Both MET and EGFR.

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

**REVISTA / JOURNAL:** - Mol Cancer Ther. 2013 May 29. 1158/1535-7163.MCT-13-0016

**AUTORES / AUTHORS:** - Zhang YW; Staal B; Essenburg C; Lewis S; Kaufman D; Vande Woude GF

**INSTITUCION / INSTITUTION:** - Laboratory of Molecular Oncology, Van Andel Research Institute.

**RESUMEN / SUMMARY:** - The MET and EGFR receptor tyrosine kinases (RTKs) are often coexpressed and may cross-talk in driving the development and progression of non-small cell lung carcinoma (NSCLC). In addition, MET amplification is an alternative resistance mechanism for escaping EGFR-targeted therapy. To assess the benefits of combined targeting of MET and EGFR for treating NSCLC, we investigated the activities of these two RTK pathways in NSCLC cell lines and evaluated their responses to SGX523 and erlotinib, the small-molecule kinase inhibitors of MET and EGFR, respectively. We showed that MET interacts with and cross-activates EGFR in MET-amplified or -overexpressed cells. The inhibition of both MET and EGFR results in maximal suppression of downstream signaling and of cell proliferation when their ligands are present. Furthermore, we demonstrated that SGX523 plus erlotinib strengthens anti-cancer activity in vivo in a cellular context-dependent manner. The combination led to the regression of H1993 tumors by enhancing the suppression of proliferation and inducing apoptosis, whereas H1373 tumor growth was significantly reduced by the combination via suppression of proliferation without inducing apoptosis. SGX523 alone was sufficient to achieve near-complete regression of EBC-1 tumors; its combination with erlotinib strongly inhibited the viability of a population of insensitive cells emerging from an SGX523-treated EBC-1 tumor recurrence. Our data suggest that inhibition of both MET and EGFR can enhance anti-cancer effects against NSCLC in a context-dependent manner and thus provide a strong rationale for combining MET and EGFR inhibitors in treating NSCLC.

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[563]
**TITULO / TITLE:** - The pivotal role of IKKalpha in the development of spontaneous lung squamous cell carcinomas.

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


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Here, we report that kinase-dead IKKalpha knockin mice develop spontaneous lung squamous cell carcinomas (SCCs) associated with IKKalpha downregulation and marked pulmonary inflammation. IKKalpha reduction upregulated the expression of p63, Trim29, and keratin 5 (K5), which serve as diagnostic markers for human lung SCCs. IKKalpha(low)K5(+)p63(hi) cell expansion and SCC formation were accompanied by inflammation-associated deregulation of oncogenes, tumor suppressors, and stem cell regulators. Reintroducing transgenic K5.IKKalpha, depleting macrophages, and reconstituting irradiated mutant animals with wild-type bone marrow (BM) prevented SCC development, suggesting that BM-derived IKKalpha mutant macrophages promote the transition of IKKalpha(low)K5(+)p63(hi) cells to tumor cells. This mouse model resembles human lung SCCs, sheds light on the mechanisms underlying lung malignancy development, and identifies targets for therapy of lung SCCs.

[564]

**TÍTULO / TITLE:** - Interplay between heme oxygenase-1 and miR-378 affects non-small cell lung carcinoma growth, vascularization and metastasis.

**RESUMEN / SUMMARY:** - Aims: Heme oxygenase-1 (HO-1, HMOX1) can prevent tumor initiation while in various tumors it has been demonstrated to promote growth, angiogenesis and metastasis. Here we investigated whether HMOX1 can modulate microRNAs and regulate human non-small cell lung cancer (NSCLC) development. Results: Stable HMOX1 overexpression in NSCLC NCI-H292 cells upregulated tumor suppressive microRNAs, whereas significantly diminished expression of oncomirs and angiomirs. The most potently downregulated was miR-378. HMOX1 also upregulated p53, downregulated Ang-1 and MUC5AC, reduced proliferation, migration and diminished
angiogenic potential. Carbon monoxide was a mediator of HMOX1 effects on proliferation, migration and miR-378 expression. In contrast, stable miR-378 overexpression decreased HMOX1 and p53, while enhanced expression of MUC5AC, VEGF, IL-8 and Ang-1 and consequently increased proliferation, migration and stimulation of endothelial cells. Adenoviral delivery of HMOX1 reversed miR-378 effect on proliferation and migration of cancer cells. In vivo, HMOX1 overexpressing tumors were smaller, less vascularized and oxygenated and less metastatic. Overexpression of miR-378 exerted opposite effects. Accordingly, in patients with NSCLC, HMOX1 expression was lower in metastases to lymph nodes than in primary tumors.

Innovation and Conclusion: In vitro and in vivo data indicate that the interplay between HMOX1 and miR-378 significantly modulates NSCLC progression and angiogenesis, suggesting miR-378 as a new therapeutic target. Rebound Track: This work was rejected during standard peer review and rescued by Rebound Peer Review (Antioxid Redox Signal 16: 293-296, 2012) with the following serving as open reviewers: James F. George, Mahin D. Maines, Justin C. Mason and Yasufumi Sato.

[565]

**TÍTULO** / **TITLE:** - mTOR, p70S6K, AKT and ERK1/2 levels predict sensitivity to mTOR and PI3K/mTOR inhibitors in human bronchial carcinoids.

**RESUMEN** / **SUMMARY:** - Bronchial carcinoids (BC) are rare neuroendocrine tumors that are still orphan of medical treatment. Human BC primary cultures may display resistance to Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), in terms of cell viability reduction. Our aim is to assess whether the novel dual PI3K/mTOR inhibitor, NVP-BEZ235, may be effective in Everolimus-resistant human BC tissues and cell lines. In addition, we search for possible markers of mTOR inhibitors efficacy, that may help in identifying the patients that may benefit from mTOR inhibitors treatment, sparing them from ineffective therapy. We found that NVP-BEZ235 is twice as potent as Everolimus in reducing cell viability and activating apoptosis in human BC tissues that display sensitivity to mTOR inhibitors, but is not effective in Everolimus-resistant BC tissues and cell lines, that by-pass cyclin D1 down-regulation and escape G0/G1 blockade. Rebound AKT activation was not observed in response to treatment with either mTOR inhibitor in ‘resistant’ BC cells. In addition to total mTOR levels, putative markers of BC sensitivity to
mTOR inhibitors are represented by AKT, p70S6K and ERK1/2 protein levels. Finally, we validated these markers in an independent BC group. These data indicate that the dual PI3K/mTOR inhibitor NVP-BEZ235 is more potent than Everolimus in reducing human BC cell proliferation. ‘Resistant’ cells display lower levels of mTOR, p70S6K, AKT and ERK1/2, indicating that these proteins may be useful as predictive markers of resistance to mTOR and PI3K/mTOR inhibitors in human BC.

[566]
TÍTULO / TITLE: - Primary pleural epithelioid hemangioendothelioma compressing the myocardium.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yu L; Gu T; Xiu Z; Shi E; Zhao X
INSTITUCIÓN / INSTITUTION: - Department of Cardiac Surgery, The First Affiliated Hospital of China Medical University, Shenyang, P.R. China.
RESUMEN / SUMMARY: - Epithelioid haemangioendothelioma (EH) is a rare malignant tumor of vascular origin that usually arises in bone, liver, soft tissue, or lung. EH originating in the pleura has been less frequently described. We describe an uncommon case of pleural EH compressing the myocardium in a 39-year-old woman. The patient was diagnosed with pleural EH confirmed by surgery and immunohistochemistry. She sustained stable disease 14 months after the diagnosis and her symptoms improved after systemic chemotherapy with carboplatin and etoposide. Complete surgical excision of pleural EH followed chemotherapy may prolong survival. doi: 10.1111/jocs.12094 (J Card Surg 2013;28:266-268).

[567]
TÍTULO / TITLE: - A 76-year-old Man with a Right Lung Adenocarcinoma and Invasive Aspergillosis.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Santos VM; Trindade MC; Souza DW; Menezes AI; Oguma PM; Nascimento AL
INSTITUCIÓN / INSTITUTION: - Medical Course of Catholic University, Brasilia, DF, Brazil, vitorinomodesto@gmail.com.
A 76-year-old male with adenocarcinoma on the right lung underwent five cycles of chemotherapy with pemetrexed disodium, cisplatin, and dexamethasone. Imaging studies of control showed a node in a cavitary lesion on the left lung, and the main hypothesis was Aspergillus infection. PCR was utilized and contributed to establish the early diagnosis in this patient with invasive aspergillosis. Furthermore, the species Aspergillus fumigatus was characterized by its growing at 50 degrees C but not at 10 degrees C, typical culture features, and presence of subclavate vesicles. Diagnosis criteria for Aspergillus pulmonary infection include characteristic clinical and imaging findings, elevated C-reactive protein and erythrocyte sedimentation rate, positive specific serological test, and isolation of Aspergillus from bronchoalveolar cultures. Molecular methods, as PCR, have been useful to complement the conventional microbiological investigations in immunocompromised people with invasive fungal infections. The patient was successfully treated with a schedule of voriconazole 4 mg/kg intravenous infusion every 12 h for 21 days and then switched to oral administration of 200 mg twice a day. He has been comfortable, maintaining normal vital signs, and the results of the periodical microbiologic tests of control are negative. Pathogenesis of invasive aspergillosis in patients with lung cancer is not completely understood. Case studies may contribute to a better knowledge about Aspergillus infection in this setting.

[568]

TÍTULO / TITLE: - Management of Small Cell Carcinoma of Esophagus in China.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s11605-013-2204-7
AUTORES / AUTHORS: - Lu XJ; Luo JD; Ling Y; Kong YZ; Feng LL; Zhou J; Wang F
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Changzhou Tumor Hospital Soochow University, Changzhou, 213002,, Jiangsu Province, China, luxujing68@yahoo.com.cn.
RESUMEN / SUMMARY: - PURPOSE: Small cell carcinoma of esophagus (SCEC) is characterized by high malignancy and early metastasis. Although the morbidity of SCEC is very low, few studies of patients with SCEC have been conducted in China, there are no sufficient studies of SCEC conducted and reported in the existing published works, and the choices of treatment remain controversial. In this work, we aim to study the clinical characteristics of SCEC, and explore the corresponding treatment and prognosis through retrospective analysis. MATERIAL AND METHODS: The original articles were identified through the leading digital libraries in China in which the terms "esophagus or
esophageal" and “small cell esophageal carcinoma” appeared from 2005 to 2009, 1,176 eligible cases were reviewed for clinical data. Analysis of survival was conducted using the Kaplan-Meier method, and differences were compared using the log-rank test. RESULTS: One thousand one hundred seventy-six eligible cases were analyzed; the median age of patients was 57 years, with a male-to-female ratio of 2.4:1. The number of SCEC accounted for 1.26% of esophageal cancer treated in the same period. Of the tumors, 89.7% were located in mid- and lower thoracic esophagus. The average tumor length was 5.4 cm (0.5-17 cm). The median overall survival was 11.1 months for all patients. The 1-, 2-, 3-, and 5-year average overall survival rates of 469 patients was 51.1, 25.5, 13.2, 7.9%, respectively. The median survival time for LD patients who received systemic treatment was 16.8 m, whereas for those who received local treatment (surgery), the median survival time was 10.1 m; the median survival time for ED patients who received systemic treatment was 7.4 m, compared with 5.8 m for those who received sole treatment (chemotherapy or radiotherapy). CONCLUSIONS: SCEC is a tumor characterized by high malignancy and early metastasis. Although our retrospective analysis cannot provide definitive conclusions on the optimal treatment modality for SCEC, however, our results suggest that systemic treatment combined with surgical resection plays a major role in the therapy of SCEC, systemic therapy may be an effective approach for the treatment of SCEC, and randomized, prospective, multicenter studies are needed to identify optimal treatment modalities for SCEC.

[569]
TÍTULO / TITLE: - Lung carcinoid with pulmonary vein and left atrial neoplastic thrombus.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Anile M; Mazzesi G; Diso D; Patella M; Russo E; Torromeo C; Vitolo D; Venuta F
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, University of Rome Sapienza, Policlinico Umberto I, Rome, Italy.

[570]
TÍTULO / TITLE: - Primary pulmonary carcinosarcoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Single bone metastasis of the humeral head revealing a lung carcinoma.

Nuclear beta-catenin accumulation is associated with increased expression of Nanog protein and predicts poor prognosis of non-small cell lung cancer.
expression in the A549 and H23 cells can be enhanced by adding EGF, Nanog expression in the A549 and H23 cells with knockdown of beta-catenin can not be obviously enhanced by adding EGF. CONCLUSION: We propose that evaluation of subcellular localization of beta-catenin and Nanog expression is of clinical significance for patients with NSCLC.

[573]
**TÍTULO / TITLE:** - EGFR Mutations in Indian Lung Cancer Patients: Clinical Correlation and Outcome to EGFR Targeted Therapy.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

-●●Enlace al texto completo (gratuito o de pago)

**AUTORES / AUTHORS:** - Noronha V; Prabhash K; Thavamani A; Chougule A; Purandare N; Joshi A; Sharma R; Desai S; Jambekar N; Dutt A; Mulherkar R
**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, Tata Memorial Hospital, Tata Memorial Center, Mumbai, India.

**RESUMEN / SUMMARY:** - Screening for EGFR mutation is a key molecular test for management of lung cancer patients. Outcome of patients with mutation receiving EGFR tyrosine kinase inhibitor is known to be better across different ethnic populations. However, frequency of EGFR mutations and the clinical response in most other ethnic populations, including India, remains to be explored. We conducted a retrospective analysis of Indian lung cancer patients who were managed with oral tyrosine kinase inhibitors. Majority of the patients in the study had adenocarcinoma and were non-smokers. 39/111 patients tested positive for EGFR kinase domain mutations determined by Taqman based real time PCR. The overall response to oral TKI therapy was 30%. Patients with an activating mutation of EGFR had a response rate of 74%, while the response rate in patients with wild type EGFR was 5%, which was a statistically significant difference. Progression free survival of patients with EGFR mutations was 10 months compared to 2 months for EGFR mutation negative patients. Overall survival was 19 months for EGFR mutation patients and 13 months for mutation negative patients. This study emphasizes EGFR mutation as an important predictive marker for response to oral tyrosine kinase inhibitors in the Indian population.

[574]
**TÍTULO / TITLE:** - The Importance of Molecular Profiling in Predicting Response to Epidermal Growth Factor Receptor Family Inhibitors in Non-Small-Cell Lung Cancer: Focus on Clinical Trial Results.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
In recent years, the epidermal growth factor receptor (EGFR) family has become a key focus of non-small-cell lung cancer biology and targeted therapies, such as the reversible EGFR tyrosine kinase inhibitors erlotinib and gefitinib. Initially, response to these agents was associated with certain demographic and clinical characteristics; subsequently, it was discovered that these subgroups were more likely to harbor specific mutations in the EGFR gene that enhanced tumor response. However, the presence of these mutations does not equate to therapeutic success. Other aspects of EGFR family signaling, including other types of EGFR mutations, EGFR protein expression, EGFR gene amplification, mediators of downstream signaling, and other receptors with similar downstream pathways may all play a role in response or resistance to treatment. The identification of these and other molecular determinants is driving the development of novel therapies designed to achieve improved clinical outcomes in patients.
With the therapeutic options for patients with advanced NSCLC increasing, concerns are being raised that the efficacy of drugs measured by OS may be diluted in clinical trials, thereby underestimating their true clinical benefit. That possibility, together with the need to have efficacious drugs available to patients earlier, has resulted in the search for a surrogate to the OS endpoint in advanced NSCLC. The present article follows up the recent article on PFS as a surrogate. Although advances in identifying PFS as a valid surrogate endpoint for OS have been made in other tumour types, in advanced NSCLC, such surrogacy has not been formally validated. Until it has, OS should remain the primary endpoint of clinical trials in advanced NSCLC.

[576]

TÍTULO / TITLE: Expression of gamma-aminobutyric acid receptors on neoplastic growth and prediction of prognosis in non-small cell lung cancer.

RESUMEN / SUMMARY: BACKGROUND: Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the adult mammalian brain, but exerts physiologic effects other than that on neurotransmitter in non-neuronal peripheral tissues and organs. GABA may affect cancer growth through activation GABA receptors. We investigated the gene expression of GABA receptors in tissue of non-small cell lung cancers (NSCLC) and non-cancerous tissues, and found that the gene expression of GABA receptor phenotypes was correlated with tumorigenesis and clinical prognosis. METHODS: Sixty-one snap-frozen human samples of NSCLC tissues and paired non-cancerous tissues (5cm away from tumor) were analyzed. Gene expression of GABA receptors was detected by Real-time quantitative PCR (RT-qPCR). Survival times in relation to the expression of GABA receptor phenotypes were analyzed. Human NSCLC cell lines H1299, A549, H520, H460 and human bronchial epithelial cell line BEAS-2B were used to determine the phenotypes of GABA inhibitory effects on cancer cell growth. The effects of exogenous administration of GABA on H1299 cell growth were examined. RESULTS: The gene expressions were significantly higher in NSCLC tissues than in the paired non-cancerous tissues for GABAA receptor subunit alpha3 (GABRA3, P = 0.030); for GABAA receptor subunit epsilon (GABRE, P = 0.036); and GABAB
receptor subunit 2 (GABBR2, $P = 0.005$). Kaplan-Meier curves showed that patients with high expression of GABBR2 gene and low expression of GABRA3 gene had a better prognosis ($P < 0.05$). The administration of GABA resulted in suppressed proliferation of NSCLC cell lines in a dose- and time-dependent manner. The use of the GABA receptor antagonist CGP35348 could reverse the inhibitory effect. CONCLUSIONS: The pattern of GABA receptor gene phenotype expression may be involved in the regulation of tumorigenesis. A high expression of GABBR2 with a low expression of GABRA3 may predict a better outcome. The treatment with GABA attenuates cancer cell growth in vitro. The expression of GABA receptor may be not only promising genetic therapeutic targets but may also serve as valuable prognostic markers for NSCLC.

[577]

**TÍTULO / TITLE:** Treatment of malignant effusion by oncolytic virotherapy in an experimental subcutaneous xenograft model of lung cancer.

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


Enlace al texto completo (gratuito o de pago) 1186/1479-5876-11-106

**AUTORES / AUTHORS:** Weibel S; Hofmann E; Basse-Luesebrink TC; Donat U; Seubert C; Adelfinger M; Gnamlin P; Kober C; Frentzen A; Gentschev I; Jakob PM; Szalay AA

**INSTITUCIÓN / INSTITUTION:** Department of Biochemistry, Biocenter, University of Wuerzburg, Wuerzburg D-97074, Germany. aasalay@genelux.com.

**RESUMEN / SUMMARY:** BACKGROUND: Malignant pleural effusion (MPE) is associated with advanced stages of lung cancer and is mainly dependent on invasion of the pleura and expression of vascular endothelial growth factor (VEGF) by cancer cells. As MPE indicates an incurable disease with limited palliative treatment options and poor outcome, there is an urgent need for new and efficient treatment options. METHODS: In this study, we used subcutaneously generated PC14PE6 lung adenocarcinoma xenografts in athymic mice that developed subcutaneous malignant effusions (ME) which mimic pleural effusions of the orthotopic model. Using this approach monitoring of therapeutic intervention was facilitated by direct observation of subcutaneous ME formation without the need of sacrificing mice or special imaging equipment as in case of MPE. Further, we tested oncolytic virotherapy using Vaccinia virus as a novel treatment modality against ME in this subcutaneous PC14PE6 xenograft model of advanced lung adenocarcinoma. RESULTS: We demonstrated significant therapeutic efficacy of Vaccinia virus treatment of both advanced lung adenocarcinoma and tumor-associated ME. We attribute the efficacy to the virus-mediated reduction of tumor cell-derived VEGF levels in
tumors, decreased invasion of tumor cells into the peritumoral tissue, and to viral infection of the blood vessel-invading tumor cells. Moreover, we showed that the use of oncolytic Vaccinia virus encoding for a single-chain antibody (scAb) against VEGF (GLAF-1) significantly enhanced mono-therapy of oncolytic treatment. CONCLUSIONS: Here, we demonstrate for the first time that oncolytic virotherapy using tumor-specific Vaccinia virus represents a novel and promising treatment modality for therapy of ME associated with advanced lung cancer.

[578]
TÍTULO / TITLE: - Expression of Connexin 43 and E-cadherin Protein and mRNA in Non-small Cell Lung Cancers in Chinese Patients.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhao JQ; Sun FJ; Liu SS; Yang J; Wu YQ; Li GS; Chen QY; Wang JX
INSTITUCIÓN / INSTITUTION: - First Affiliated Hospital, Zhengzhou University, Zhengzhou, China E-mail : bcd2009@126.com.
RESUMEN / SUMMARY: - Aim: Connexin 43 (Cx43) and E-cadherin are important biomarkers related with cancer. Their expression at protein and mRNA levels was here investigated in 50 primary lung carcinoma tissues and 20 samples of adjacent normal tissue of Chinese patients with non-small cell lung cancer (NSCLC). Methods: Protein and mRNA expression were evaluated by ABC immunohistochemistry and RT-PCR. Results: (1) The positive expression rates of Cx43 and E-cadherin protein were higher in the adjacent normal tissues than those in the primary lung carcinoma tissues; (2) the positive expression rates of Cx43 and E-cadherin protein decreased with NSCLC progression; (3) the expression of E-cadherin protein was not related with the pathological type of NSCLC; and (4) the relative quantity of the Cx43 or E-cadherin mRNA expression was correlated with the the histological type, clinical stage, cancer cell differentiation and the lymph node metastasis. Conclusion: The data suggested that the Cx43 and E-cadherin are reduced with NSCLC progression, and might be important biomarkers for judging the metastasis and prognosis.

[579]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fu SL; Tang HX; Liao YD; Jiang WY; Xu QZ; Deng Y; Fu XN
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China, t0102005@126.com.
RESUMEN / SUMMARY: - Insulin-like growth factor-I (IGF-I) is a mitogenic and anti-apoptotic factor. Serum IGF-I concentration is related to some cancer risk and tumor progression. The aim of this research was to study the association of preoperative serum IGF-I concentration with clinicopathological parameters and prognosis of non-small cell lung cancer (NSCLC). Preoperative serum IGF-I concentration was measured in 80 consecutive patients with NSCLC who underwent radical lung cancer resection, and 45 patients with benign pulmonary lesion (BPL) by using enzyme linked immunosorbent assay (ELISA). The results showed that the serum IGF-I concentration was elevated and correlated with clinicopathological parameters and overall survival (OS) in NSCLC patients. Serum IGF-I concentration was significantly higher in patients with NSCLC than in those with BPL. The IGF-I concentrations were significantly higher in NSCLC patients with >/=T2, N1-3, and in IIIA-IV but not in those with <T2, N0, or IA-IIB. The increased serum IGF-I concentration was significantly correlated with poor prognosis. Our data show the positive correlation between IGF-I serum concentration and the tumor size for the first time. It seems that IGF-I related to the progression of lung cancer may depend on autocrine/paracrine function. In addition, our study reveals that higher serum IGF-I concentration is correlated with larger tumor size, advanced stages, local lymph node metastasis and worse prognosis, indicating that endocrine IGF-I is also important for the progression for NSCLC.

[580]
TÍTULO / TITLE: - Combination of four gene markers to detect circulating tumor cells in the peripheral blood of patients with advanced lung adenocarcinoma using real-time PCR.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yu Y; Xu G; Cao J; Jin S; Man Y; Shang L
INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The Third Affiliated Hospital of Harbin Medical University, Harbin 150080, P.R. China.
RESUMEN / SUMMARY: - The aim of this study was to establish a robust and reliable assay for the detection of circulating tumor cells (CTCs) in the peripheral blood (PB) of patients with advanced lung adenocarcinoma. We used
real-time reverse transcription PCR (RT-PCR) to detect survivin, human telomerase reverse transcriptase (hTERT), cytokeratin-7 (CK-7) and thyroid transcription factor 1 (TTF-1) mRNA expression levels in 68 advanced lung adenocarcinoma patients and 30 healthy patients. Statistical analyses were additionally performed to examine the correlation between the mRNA expression levels of these markers with the clinicopathological features of advanced lung adenocarcinoma patients. The sensitivity of these four mRNA markers in the PB of advanced lung adenocarcinoma patients was 41.18, 61.76, 41.18 and 35.29%, respectively. The sensitivity of these four markers combined was 82.35%, which was significantly higher compared with single marker detection. Statistical analysis demonstrated that high expression levels of survivin, hTERT and TTF-1 mRNA are positively correlated with lymph node classification, and high expression levels of survivin, hTERT, CK7 and TTF-1 mRNA are positively correlated with distant metastasis (P<0.05). In addition, overexpression of these four mRNA markers is positively correlated with disease progression (P<0.05). Our data suggest that the combination of survivin, hTERT, CK-7 and TTF-1 mRNA markers may provide a valuable tool for CTC detection and is associated with disease progression in advanced lung adenocarcinoma patients.

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TÍTULO / TITLE: - Stereotactic Body Radiotherapy in Patients With Stage I Non-Small-Cell Lung Cancer Aged 75 Years and Older: Retrospective Results from a Multicenter Consortium.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Samuels MA; Kandula S; Koru-Sengul T; Bogart JA; Salama JK; Aridgides PD; Gajra A; Lilenbaum RC
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Miami, Miller School of Medicine, Miami, FL. Electronic address: msamuels2@med.miami.edu.
RESUMEN / SUMMARY: - BACKGROUND: This study was a retrospective analysis of elderly patients treated with stereotactic body radiotherapy (SBRT) in the setting of a multi-institutional consortium. PATIENTS AND METHODS: Three institutions pooled data on patients aged >/= 75 years who received SBRT for stage I non-small-cell lung cancer (NSCLC). Forty-seven tumors in 46 patients were analyzed in patients aged 75 to 92 years (median, 82 years). Treatment was delivered during 2007 to 2009, with a median follow-up of 12.4 months. All patients underwent staging positron emission tomography-computed tomography (PET-CT), and 87% of tumors were confirmed by biopsy results. Total doses were 35 to 60 Gy, mainly in 3 to 5 fractions. All tumors were
treated using a linear accelerator, with 96% of patients receiving 3-dimensional (3D) conformal RT and 4% undergoing intensity modulated RT (IMRT).

RESULTS: At the time of analysis, the local failure rate was 2% (1 of 47). The regional failure rate was 9% (4 of 47). The distant failure rate was 6% (3 of 47). The combined failure rate was 15% (7 of 47) because 1 patient experienced both regional and distant failure. Among 20 tumors with any acute toxicity, there were no >= grade 3 toxicities. Pneumonitis (n = 10) grades 1 (n = 3) and 2 (n = 2) was seen in 15% and 10% of patients, respectively; these data were missing for 25% of patients. CONCLUSION: SBRT in patients aged >= 75 years with stage I NSCLC proved tolerable, with toxicity rates comparable to those in younger patients. Excellent rates of local, regional, and distant control were achieved at a median follow-up of 12.4 months. This patient population represents a rapidly growing segment of the early lung cancer population, and SBRT appears to be a safe and effective treatment option for patients who are not optimal candidates for surgery.

[582]

**TÍTULO / TITLE:** - Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer patients.

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


**AUTORES / AUTHORS:** - Grigorescu AC; Bala C

**INSTITUCIÓN / INSTITUTION:** - Department of Medical Oncology, “Prof. Dr. Alexandru Trestioreanu” Oncology Institute, Bucharest, Romania.

**RESUMEN / SUMMARY:** - Purpose: The purpose of the present trial was to investigate whether clinical benefit can be obtained by concurrent administration of erlotinib with gemcitabine as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2.

**Methods:** Included were chemotherapy-naive patients with histologically/cytologically documented unresectable advanced and/or metastatic (stage IIIB/IV) NSCLC and ECOG PS 2. In this phase II, single-arm study, all patients received first-line gemcitabine plus erlotinib for 6 cycles or until disease progression, unacceptable toxicity or patient withdrawal due to any reason. The primary study objectives were the evaluation of disease response and the time to progression. Secondary objectives included evaluation of overall survival and the safety profile of gemcitabine plus erlotinib. Results: Nineteen eligible patients were studied. The overall response rate (complete response/CR and partial response/PR) was 15.8% and the clinical benefit rate (CR+PR+stable disease/SD) 36.84%. The median overall survival for the whole study group was 39 weeks (95% CI 27-51) and the median time to disease progression for 19 evaluable patients was 15 weeks (95% CI 7-36). The safety profile of the combination was acceptable with only 2 serious adverse events. Conclusion: Taking into account similar published clinical
studies we conclude that gemcitabine plus erlotinib achieve superior response rate and comparable overall survival with acceptable toxicity compared to monochemotherapy with gemcitabine. This combination represents a treatment option for patients with advanced NSCLC and ECOG PS 2.

[583]

**TITULO / TITLE:** - DNA repair genotype and lung cancer risk in the beta-carotene and retinol efficacy trial.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Doherty JA; Sakoda LC; Loomis MM; Barnett MJ; Julianto L; Thornquist MD; Neuhouser ML; Weiss NS; Goodman GE; Chen C

**INSTITUCIÓN / INSTITUTION:** - The Geisel School of Medicine at Dartmouth Lebanon, NH, USA; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center Seattle, WA, USA.

**RESUMEN / SUMMARY:** - Many carcinogens in tobacco smoke cause DNA damage, and some of that damage can be mitigated by the actions of DNA repair enzymes. In a case-control study nested within the Beta-Carotene and Retinol Efficacy Trial, a randomized chemoprevention trial in current and former heavy smokers, we examined whether lung cancer risk was associated with variation in 26 base excision repair, mismatch repair, and homologous recombination repair genes. Analyses were limited to Caucasians (744 cases, 1477 controls), and logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for individual SNPs and common haplotypes, with adjustment for matching factors. Lung cancer associations were observed (p<0.05) with SNPs in MSH5 (rs3131379, rs707938), MSH2 (rs2303428), UNG (rs246079), and PCNA (rs25406). MSH5 rs3131379 is a documented lung cancer susceptibility locus in complete linkage disequilibrium with rs3117582 in BAT3, and we observed associations similar in magnitude to those in prior studies (per A allele OR 1.37, 95% CI 1.13-1.65). UNG was associated with lung cancer risk at the gene level (p=0.02), and the A allele of rs246079 was associated with an increased risk (per A allele OR 1.15, 95% CI 1.01-1.31). We observed stronger associations with UNG rs246079 among individuals who carried the risk genotypes (AG/AA) for MSH5 rs3131379 (pinteraction= 0.038). Our results provide additional evidence to suggest that the MSH5/BAT3 locus is associated with increased lung cancer risk among smokers, and that associations with other SNPs may vary depending upon MSH5/BAT3 genotype. Future studies to examine this possibility are warranted.

[584]

**TÍTULO / TITLE:** - XPG is Predictive Gene of Clinical Outcome in Advanced Non-small-cell Lung Cancer with Platinum Drug Therapy.
RESUMEN / SUMMARY: Polymorphisms in XPG are considered to contribute to the clinical outcome of patients receiving platinum drug chemotherapy. We aimed to investigate the role of five potential SNPs of XPG gene on the response to platinum-based chemotherapy in advanced Chinese NSCLC patients. A total of 451 patients with newly diagnosed and histopathologically confirmed primary NSCLC were consecutively collected. XPG rs2296147, rs4150261, rs17655, rs1047768 and rs2094258 were genotyped by the Taqman real-time polymerase chain reaction (PCR). In our study, we found patients carrying rs1057768 TT genotype had a significantly lower treatment response when compared with the CC genotype (OR=0.38, 95% CI=0.18-0.78). Patients carrying rs1047768 TT genotype showed a significantly short median PFS (11.2 months) and OS (13.6 months) than CC genotype, and the hazard ratios (HR) for PFS and OS were 2.06 (1.01-4.50) and 2.29 (1.21-2.49), respectively. Moreover, we found a significant decreased risk of death from NSCLC among patients carrying the rs2296147 TT genotype when compared with the CC genotype, the HR (95% CI) for OS being 0.50 (0.27-0.95). In conclusion, our study found that polymorphisms in rs1047768 C/T and rs2296147 C/T are associated with response to platinum-based chemotherapy in advanced NSCLC, and XPG polymorphisms could be predictive of prognosis.

[585] TÍTULO / TITLE: The Association between COX-2 Polymorphisms and Hematologic Toxicity in Patients with Advanced Non-Small-Cell Lung Cancer Treated with Platinum-Based Chemotherapy.

RESUMEN / SUMMARY: BACKGROUND AND OBJECTIVE: Overexpression of COX-2 is proved to contribute to tumor promotion and carcinogenesis through
stimulating cell proliferation, inhibiting apoptosis and enhancing the invasiveness of cancer cells. Apoptosis-related molecules are potential predictive markers for survival and toxicity in platinum treatment. This study aimed at investigating the association between COX-2 polymorphisms and the occurrence of grade 3 or 4 toxicity in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. MATERIALS AND METHODS: Two hundred and twelve patients with inoperable stage IIIB-IV NSCLC received first-line chemotherapy between 2007 and 2009 were recruited in this study. Four functional COX-2 polymorphisms were genotyped by PCR-based restriction fragment length polymorphism (RFLP) methods. RESULTS: The incidence of grade 3 or 4 hematologic toxicity was significantly higher in G allele carriers of the COX-2 rs689466 (-1195G/A) polymorphism compared with wild-type homozygotes AA (P value = 0.008; odds ratio, 2.47; 95% confidence internal, 1.26-4.84) and the significance still existed after the Bonferroni correction. Statistically significant difference was also found in grade 3 or 4 leukopenia (P value = 0.010; OR = 2.82; 95%CI = 1.28-6.20). No other significant association was observed between genotype and toxicity in the study. The haplotype analysis showed that the haplotype AGG was associated with a reduced risk of grade 3 or 4 hematologic and leukopenia toxicity (P value = 0.009; OR = 0.59; 95%CI = 0.39-0.88 and P value = 0.025; OR = 0.61; 95%CI = 0.39-0.94, respectively) while the haplotype GGG was associated with an increased risk of grade 3 or 4 hematologic and leukopenia toxicity (P value = 0.009; OR = 1.71; 95%CI = 1.14-2.56 and P value = 0.025; OR = 1.65; 95%CI = 1.06-2.57, respectively). CONCLUSION: This investigation for the first time suggested that polymorphism in COX-2 rs689466 may be a potent bio-marker in predicting severe hematologic toxicity in NSCLC patients after platinum-based chemotherapy.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Naim Younes R; Gross JL; Abrao FG; Rodrigues Pereira J
INSTITUCIÓN / INSTITUTION: - Department of Surgery, Oncology Center of Hospital Sao Jose, University of Sao Paulo, Sao Paulo, Brazil - fernandocabrao@uol.com.br.
RESUMEN / SUMMARY: - Aim: Outcome of patients with locally advanced non-small-cell lung cancer (NCSLC) is generally poor, with five-year survival rate of only 23%, when patients are treated with surgery only. The presentation of positive adjuvant therapy trials in NSCLC has changed clinical practice, doubling the number of patients with completely resected NSCLC referred for
adjuvant chemotherapy since 2004. Furthermore, few large studies described a large number of stage III patients in non-Asiatic patients and they showed controversial results about survival in completely resected stage IIIA NSCLC. The objective of this study was to evaluate the impact of adjuvant chemotherapy in completely resected stage IIIA NSCLC, administered on a routine basis, outside clinical trials. Methods: This is a retrospective study of patients with stage IIIA NSCLC treated between 1990 and 2008, and included in a continuous, consecutive database. Inclusion criteria were: age >18 years, complete surgical resection, and pathologically confirmed as stage IIIA. The following clinical data were obtained: age, gender, performance status, histological type, chemotherapy regimens, status at last follow-up and hospital where the treatment occurred. Kaplan-Meier’s method was used to determine actuarial survival. Differences in survival were determined by Breslow and log rank analyses. Results: According to these inclusion criteria, 415 patients were considered for the present study. The median follow-up time of all patients was 38.2 months. The adjuvant chemotherapeutic treatment affected survival significantly (P <0.001). Also the type of chemotherapeutic treatment affected survival (P \leq 0.001). Conclusion: Cisplatin-based adjuvant chemotherapy was beneficial in patients who had a completed resected stage IIIA carcinoma.

[587]
TÍTULO / TITLE: - Bilateral orbital metastases from small cell lung cancer: a case report.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Tezcan Y
INSTITUCIÓN / INSTITUTION: - Selcuk University Medical School, Konya, Turkey. yilmaztezcan@yahoo.com
RESUMEN / SUMMARY: - A 46-year-old man with a history of heavy smoking for last 20 years presented with coughing. Computed tomography (CT) scan of the thorax showed a mass in right lung tissue. A fine needle aspiration biopsy (FNAB) confirmed the diagnosis of small cell lung cancer (SCLC), with limited stage at presentation. CT scan and MRI of the orbits demonstrated that the solid masses separately invaded the posterior orbita bilaterally. Then, we made a diagnosis of bilateral posterior orbital metastases from SCLC. Simulation CT imaging was obtained, using head mask. Both of the orbital masses were contoured as the planning target volume. A palliative radiotherapy of 30 Gy was planned, with 3D conformal technique using 12-15 MeV electrons. I presented the case of rare bilateral posterior orbital metastasis due to SCLC.

[588]
TÍTULO / TITLE: - The Impact of Cigarette Smoking on the Frequency of and Qualitative Differences in KRAS Mutations in Korean Patients with Lung Adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratis o de pago) 3349/ymj.2013.54.4.865
AUTORES / AUTHORS: - Kim HR; Ahn JR; Lee JG; Bang DH; Ha SJ; Hong YK; Kim SM; Nam KC; Rha SY; Soo RA; Riely GJ; Kim JH; Cho BC
INSTITUCIÓN / INSTITUTION: - Yonsei Cancer Center, Division of Medical Oncology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemungu, Seoul 120-752, Korea. cbc1971@yuhs.ac.
RESUMEN / SUMMARY: - Purpose: This study was designed to determine the relationship of cigarette smoking to the frequency and qualitative differences among KRAS mutations in lung adenocarcinomas from Korean patients. Materials and Methods: Detailed smoking histories were obtained from 200 consecutively enrolled patients with lung adenocarcinoma according to a standard protocol. EGFR (exons 18 to 21) and KRAS (codons 12/13) mutations were determined via direct-sequencing. Results: The incidence of KRAS mutations was 8% (16 of 200) in patients with lung adenocarcinoma. KRAS mutations were found in 5.8% (7 of 120) of tumors from never-smokers, 15% (6 of 40) from former-smokers, and 7.5% (3 of 40) from current-smokers. The frequency of KRAS mutations did not differ significantly according to smoking history (p=0.435). Never-smokers were significantly more likely than former or current smokers to have a transition mutation (G-->A or C-->T) rather than a transversion mutation (G-->T or G-->C) that is known to be smoking-related (p=0.011). In a Cox regression model, the adjusted hazard ratios for the risk of progression with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) were 0.24 (95% CI, 0.14-0.42; p<0.001) for the EGFR mutation and 1.27 (95% CI, 0.58-2.79; p=0.537) for the KRAS mutation. Conclusion: Cigarette smoking did not influence the frequency of KRAS mutations in lung adenocarcinomas in Korean patients, but influenced qualitative differences in the KRAS mutations.

TÍTULO / TITLE: - Correlation Between EGFR Mutations and Serum Tumor Markers in Lung Adenocarcinoma Patients.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pan JB; Hou YH; Zhang GJ
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Henan Provincial People's Hospital, Zhengzhou, China E-mail: jinbingpan@126.com.
RESUMEN / SUMMARY: - Background: Mutations affecting the epidermal growth factor receptor (EGFR) are good predictors of clinical efficacy of EGFR tyrosine kinase inhibitors (TKI) in patients with non-small cell lung cancer. Serum carcinoembryonic antigen (CEA) levels are also regarded as predictive for the efficacy of EGFR-TKI and EGFR gene mutations. This study analyzed the association between EGFR gene mutations and clinical features, including serum tumor marker levels in lung adenocarcinomas patients. Patients and Methods: A total of 70 lung adenocarcinoma patients with complete clinical data and pathological specimens were investigated. EGFR gene mutations at exons 19 and 21 were assessed. Serum tumor markers were detected by protein chip- chemiluminescence at the corresponding time, and correlations were analyzed. Results: Mutations of the EGFR gene were detected in 27 of the 70 patients and the serum CEA and CA242 concentrations were found to be significantly associated with the incidence of EGFR gene mutations (P<0.05). The AUCs for CEA and CA242 were 0.724 (95% CI: 0.598-0.850, P<0.05) and 0.769 (95% CI: 0.523-0.800, P<0.05) respectively. Conclusions: Serum CEA and CA242 levels are associated with mutations of the EGFR gene in patients with lung adenocarcinomas.

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TÍTULO / TITLE: - Primary neuroendocrine lung tumor presenting with acute ileal obstruction. Case report.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Li Destri G; Ferraro MJ; Vecchio G; Musumeci A; Calabrini M; Giarrizzo A
RESUMEN / SUMMARY: - The authors describe a clinical case of a patient with neuroendocrine carcinoma of the lung diagnosed after the onset of an intestinal obstruction from an ileal metastasis. A review of literature reveals that the incidence of symptomatic gastro-intestinal metastases from lung cancer has been estimated to be about 2-3% and is exceedingly rare that the intestinal symptoms may be the initial presentation of cancer of the lung. The authors emphasize the difficulty of preoperative diagnosis of gastro-intestinal metastases which is made, almost always, too late because of the lack of specific symptoms. In our case, on account of the computed tomography, we leaned towards the diagnosis of lymphoma because of the double mediastinal and abdominal localization. Furthermore, this diagnosis was supported by the fact that the pulmonary lesion did not have clear radiological features of a lung cancer. The prognosis is poor because once intestinal metastases occur, other metastatic sites, which would make surgery only a palliative measure, are already present. The review of the literature shows that the average survival rate of these patients is 136 days. In our case the patient survived 277 days.
TÍTULO / TITLE: - Potential Predictors of Sensitivity to Pemetrexed as First-line Chemotherapy for Patients with Advanced Non-Squamous NSCLCs.

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


AUTORES / AUTHORS: - Lu YY; Huang XE; Xu L; Liu DG; Cao J; Wu XY; Liu J; Xiang J

INSTITUCIÓN / INSTITUTION: - Department of Chemotherapy, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University and Jiangsu Institute of Cancer Research, Nanjing, China E-mail: huangxinen06@yahoo.com.cn, xulin_83@yahoo.cn.

RESUMEN / SUMMARY: - Background: Pemetrexed (PEM) is effective in first-line treatment for patients with non-squamous non-small cell lung cancer (NSCLC). However there are currently no definitive determinants to certify which patients could benefit from PEM. To improve the efficacy of PEM combined with platinum as first-line therapy for advanced non-squamous NSCLC, we conducted this retrospective study to detect potential determinants of this regimen. Methods: We recruited 109 patients with advanced non-squamous NSCLC who received PEM with a platinum as first-line therapy from June 2006 to February 2013 in Jiangsu Cancer Hospital. Multiple variables (age, sex, smoking, degree of cell differentiation, hemoglobin, platinum drugs combined, positions of metastasis) were selected. Logistic regression analysis was used to analyse relationships between these variables and tumor response. Result: In univariate analysis, we found that age and platinum significantly influenced the results of PEM therapy (P<0.05). In multivariable analysis, no factors were independently significant. Conclusion: Our analysis did not suggest that the age, sex, metastasis of liver or other organs, hemoglobin, smoking history and pathological differentiation are associated with the response of PEM. We should conduct further analyses with larger sample size to reconfirm this issue.

[592]

TÍTULO / TITLE: - Chemotherapy for extensive-stage small-cell lung cancer with idiopathic pulmonary fibrosis.

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


AUTORES / AUTHORS: - Watanabe N; Taniguchi H; Kondoh Y; Kimura T; Kataoka K; NishiYama O; Kondo M; Hasegawa Y
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi, 489-8642, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is associated with an independent increased risk of lung carcinogenesis. The benefit of chemotherapy for extensive-stage small-cell lung cancer (ED-SCLC) in cases of IPF remains unknown. This study was conducted to elucidate the efficacy of chemotherapy for ED-SCLC in patients with IPF. METHODS: This was a retrospective observational study of ED-SCLC patients with IPF (all with distant metastasis) who received systemic chemotherapy. The response rate, toxicity, overall survival, and progression-free survival (PFS) were investigated. RESULTS: Eleven patients treated with chemotherapy between January 2005 and December 2011 were the subjects of this study. The overall response rate with the 1st regimen was 63.6 %. The median overall survival was 7.0 months, and the median PFS was 4.7 months. CONCLUSION: Our results suggest that ED-SCLC patients with IPF may benefit from chemotherapy. A prospective study will be needed to confirm this in the future.

[593]

TÍTULO / TITLE: - Dose-volumetric parameters and prediction of severe acute esophagitis in patients with locally-advanced non small-cell lung cancer treated with neoadjuvant concurrent hyperfractionated-accelerated chemoradiotherapy.

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


AUTORES / AUTHORS: - Manapov F; Sepe S; Niyazi M; Belka C; Friedel G; Budach W

RESUMEN / SUMMARY: - BACKGROUND: To identify dose-volume parameters predictive for severity of acute esophagitis (CTC > grade 2) in locally-advanced non small-cell lung cancer (LA-NSCLC) patients treated with neoadjuvant concurrent hyperfractionated-accelerated chemoradiotherapy (HA-CRT) a retrospective analysis was performed. 88 patients were treated with HA-CRT followed by radical surgery. Predictive power of absolute oesophageal length, absolute and relative oesophageal volume included in the 95%-isodose, patient- and tumor-related factors for severity of acute esophagitis was assessed.

FINDINGS: A total of 82 patients (93%) developed radiation-induced acute esophagitis. Grade 1 was documented in 1 (1%), grade 2 in 55 (67%), grade 3 in 23 (28%) and grade 4 in 3 (4%) patients, respectively. Absolute oesophageal volume included in the 95%-isodose (42.8 Gy) achieved 13.5 cm3 (range: 3 -- 29 cm3). Of the tested variables in univariate analysis, absolute oesophageal volume included in the 95%-Isodose was found to be the only significant variable (p = 0.03) predicting severe acute esophagitis (CTC > grade 2). For this volume a gradation scale of the likelihood of severity was built.
CONCLUSION: Increase of absolute oesophageal volume included in the 95%-isodose correlates with severity of acute esophagitis in LA-NSCLC patients treated with neo-adjuvant concurrent HA-CRT.

[594]
TÍTULO / TITLE: Reasons for delay in diagnosis and treatment of lung cancer among patients in Lublin Voivodeship who were consulted in Thoracic Surgery Department.

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


AUTORES / AUTHORS: Sawicki M; Szczyrek M; Krawczyk P; Rybojad P; Jablonka A; Milanowski J

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Medical University, Lublin, Poland. marek.sawicki@umlub.pl

RESUMEN / SUMMARY: INTRODUCTION: Despite the progress which has been made in the diagnosis and treatment of lung cancer, it is still one of the main causes of death in both men and women. The introduction of new therapeutic modalities did not improve the 5-year survival results of lung cancer patients. The Lublin Voivodeship is a sparsely-inhabited area with little urbanization and a population of about 2.2 million people. Only 46.8% of its citizens live in the towns, while the national average is 61.9%. OBJECTIVES: The aim of the study was to compare the differences in the periods of time and reasons for delay in diagnosis and initiation of treatment of lung cancer among patients who are inhabitants of the rural and urban regions of Lublin Voivodeship, and who were consulted in Thoracic Surgery Department. MATERIALS AND METHODS: 300 lung cancer patients who were consulted in the Thoracic Surgery Outpatient Clinic or who were hospitalized in the Department of Thoracic Surgery in the period between 2 January 2010 - 7 January 2011 were included in the study. Delays were calculated for two periods of time: 1) time from the first signs of the disease to the first medical examination; 2) the time from the first visit to a doctor to the start of treatment, or disqualification from the causative treatment. The time of the first delay for the urban and rural populations was similar and ranged from 2-37 weeks and 2-23 weeks, respectively. Lack of time and disregard of signs of disease were the most commonly reasons given for the first delay among rural residents. The urban population indicated fear and lack of time as the main reasons of delay. Assessment of the second reason for delay was possible thanks to a specially designed research protocol which gathered the main reasons of delay in several subgroups that enabled their statistical evaluation. The length of second period was similar for both populations. RESULTS: There were no significant differences in the length of the time of delay between the two assessed groups. In both groups, delays dependent on poor healthcare access were similar. Among rural inhabitants, the most often reasons of delay were waiting for
hospital admission and re-bronchoscopy. In the urban population, the most common reasons for delay were waiting for hospitalization and CT procedure. CONCLUSIONS: The results of the presented research allowed the following conclusions to be drawn: between the two assessed groups there were no differences in the length of the time of delay; 2) delays in diagnosis and treatment were too long for the patients and could affect the severity of the disease and final prognosis; 3) there is a need for intensification of information campaigns on lung cancer in order to reduce the delays dependent on patients, and to improve the cooperation of family doctors, pulmonologists, thoracic surgeons and oncologists.

[595]

TÍTULO / TITLE: - Improvement of Internal Tumor Volumes of Non-Small Cell Lung Cancer Patients for Radiation Treatment Planning Using Interpolated Average CT in PET/CT.

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


●●Enlace al texto completo (gratuito o de pago)

AUTORES / AUTHORS: - Wang YC; Tseng HL; Lin YH; Kao CH; Huang WC; Huang TC

INSTITUCIÓN / INSTITUTION: - Division of Radiation Oncology, China Medical University Hospital, Taichung City, Taiwan.

RESUMEN / SUMMARY: - Respiratory motion causes uncertainties in tumor edges on either computed tomography (CT) or positron emission tomography (PET) images and causes misalignment when registering PET and CT images. This phenomenon may cause radiation oncologists to delineate tumor volume inaccurately in radiotherapy treatment planning. The purpose of this study was to analyze radiology applications using interpolated average CT (IACT) as attenuation correction (AC) to diminish the occurrence of this scenario. Thirteen non-small cell lung cancer patients were recruited for the present comparison study. Each patient had full-inspiration, full-expiration CT images and free breathing PET images by an integrated PET/CT scan. IACT for AC in PETIACT was used to reduce the PET/CT misalignment. The standardized uptake value (SUV) correction with a low radiation dose was applied, and its tumor volume delineation was compared to those from HCT/PETHCT. The misalignment between the PETIACT and IACT was reduced when compared to the difference between PETHCT and HCT. The range of tumor motion was from 4 to 17 mm in the patient cohort. For HCT and PETHCT, correction was from 72% to 91%, while for IACT and PETIACT, correction was from 73% to 93% (*p<0.0001). The maximum and minimum differences in SUVmax were 0.18% and 27.27%
for PETHCT and PETIACT, respectively. The largest percentage differences in the tumor volumes between HCT/PET and IACT/PET were observed in tumors located in the lowest lobe of the lung. Internal tumor volume defined by functional information using IACT/PETIACT fusion images for lung cancer would reduce the inaccuracy of tumor delineation in radiation therapy planning.

[596]

**TÍTULO / TITLE:** - Idiopathic pulmonary fibrosis as a prognostic factor in non-small cell lung cancer.

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


**AUTORES / AUTHORS:** - Goto T; Maeshima A; Oyamada Y; Kato R

**INSTITUCIÓN / INSTITUTION:** - Department of General Thoracic Surgery, National Hospital Organization Tokyo Medical Center, Meguro-ku, Tokyo, 152-8902, Japan, taichiro@1997.jukuin.keio.ac.jp.

**RESUMEN / SUMMARY:** - BACKGROUND: We investigated the postoperative mortality and long-term survival of lung cancer patients with underlying idiopathic pulmonary fibrosis (IPF). METHODS: The data of 387 primary lung cancer patients treated by surgical resection at our hospital between 1995 and 2008 were retrospectively reviewed. Clinicopathological characteristics such as age, gender, survival, presence/absence of underlying IPF, atypical adenomatous hyperplasia (AAH), and the associations among these factors were examined. RESULTS: Among the 387 patients, 65 (16.8 %) had underlying IPF as detected by histopathology of the resected specimen (IPF group). The percentages of men and squamous cell carcinomas were significantly higher in the IPF group. None of our patients showed concomitant presence of AAH and IPF. Four of the 65 patients showed acute exacerbation of the IPF postoperatively, and all 4 of these patients died in hospital. In patients with non-small cell lung carcinoma, the postoperative survival tended to be lower in the IPF group than in the non-IPF group. Analysis using a Cox proportional hazards model by disease stage revealed that presence of underlying IPF was a risk factor for postoperative mortality in patients with pathological stage I/II but not for stage III/IV. Respiratory failure was the second main cause of death in the stage I/II lung cancer patients of the IPF group. CONCLUSION: Histopathological evidence of IPF was a risk factor for postoperative mortality and poor long-term survival, especially in patients with stage I/II non-small cell lung cancer, with postoperative respiratory failure representing the major cause of death.

[597]
**TÍTULO / TITLE:** Crizotinib administered via nasogastric and percutaneous endoscopic gastrostomy tubes for the successful treatment of ALK-rearranged lung cancer in a patient with poor performance status.

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


**AUTORES / AUTHORS:** Tamai K; Nagata K; Otsuka K; Nakagawa A; Tachikawa R; Otsuka K; Katakami N; Tomii K

**INSTITUCIÓN / INSTITUTION:** Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan. tamaik@kcho.jp

**RESUMEN / SUMMARY:** Crizotinib—an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor—is effective in non-small-cell lung cancers (NSCLCs) that express ALK. Here, we report a patient with ALK-positive lung adenocarcinoma who was administered crizotinib via nasogastric and percutaneous endoscopic gastrostomy (PEG) tubes, with positive results. This case indicates that patients with ALK-positive NSCLC may successfully be treated with crizotinib via nasogastric or PEG tubes. This approach can even be used as a salvage treatment in patients with poor prognoses.

[598]

**TÍTULO / TITLE:** A patient with anaplastic lymphoma kinase-positive non-small cell lung cancer with development of leptomeningeal carcinomatosis while on targeted treatment with crizotinib.

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


**AUTORES / AUTHORS:** Riess JW; Nagpal S; Neal JW; Wakelee HA

**INSTITUCIÓN / INSTITUTION:** Department of Medicine, Division of Oncology, Division of Neuro-Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California 94305, USA. riessjo@stanford.edu

**RESUMEN / SUMMARY:** Leptomeningeal carcinomatosis (LM) is an infrequent yet morbid and often fatal complication of non-small cell lung cancer (NSCLC). Management of LM is multimodal, often involving systemic chemotherapy, radiotherapy, and a variety of symptom management maneuvers to address elevated intracranial pressure, pain, and mood changes that can accompany the disease. It is increasingly recognized that tumors with actionable mutations in NSCLC, including epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations, respond well to systemic therapy with tyrosine kinase inhibitors yet often progress in the central nervous system. More information is needed regarding the natural history and optimal management of LM in specific molecular subtypes of NSCLC. This case report summarizes the management of a patient with ALK-positive NSCLC who...
developed LM while on targeted treatment with crizotinib within the context of current NCCN Clinical Practice Guidelines in Oncology and recently published studies.

[599]

**TÍTULO / TITLE:** - Referral and Treatment Patterns Among Patients With Stages III and IV Non-Small-Cell Lung Cancer.

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


**AUTORES / AUTHORS:** - Goulart BH; Reyes CM; Fedorenko CR; Mummy DG; Satram-Hoang S; Koepl LM; Blough DK; Ramsey SD

**INSTITUCIÓN / INSTITUTION:** - Fred Hutchinson Cancer Research Center; University of Washington, Seattle, WA; Genentech, San Francisco; and Q.D. Research, Granite Bay, CA.

**RESUMEN / SUMMARY:** - PURPOSE: Little is known about how referrals to different cancer specialists influence cancer care for non-small-cell lung cancer (NSCLC). Among Medicare enrollees, we identified factors of patients and their primary care physician that were associated with referrals to cancer specialists, and how the types of cancer specialists seen correlated with delivery of guideline-based therapies (GBTs). METHODS: Data from patients with stages III and IV NSCLC included in the SEER-Medicare database were linked to their physicians in the American Medical Association Masterfile database. Using logistic regression, we (1) identified patient and physician factors that were associated with referrals to cancer specialists (medical oncologists, radiation oncologists, and surgeons); (2) identified the types of referral to cancer specialists that predicted greater likelihood of receiving GBT (per National Comprehensive Cancer Network guidelines). RESULTS: A total of 28,977 patients with NSCLC diagnosed from January 1, 2000 to December 31, 2005 met eligibility criteria. Younger age, white race, higher income, and primary physician specialty other than family practice predicted higher likelihood of referrals to medical oncologists (P < .01 for all predictors). Seeing the three types of cancer specialists predicted higher likelihood of GBT (stage IIIA: odds ratio [OR] = 20.6; P < .001; IIIB: OR = 77.2; P < .001; and IV: OR = 1.2; P = .011), compared with seeing a medical oncologist only. Use of GBTs increased over the study period (42% to 48% from 2000 to 2005; P < .001).

**CONCLUSIÓN:** Referrals to all types of cancer specialists increased the likelihood of treatment with standard therapies, particularly in stage III patients. However, racial and income disparities still prevent optimal referrals to cancer specialists.

[600]

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


AUTORES / AUTHORS: Sathiakumar N; Delzell E; Morrisey MA; Falkson C; Yong M; Chia V; Blackburn J; Arora T; Kilgore ML

INSTITUCIÓN / INSTITUTION: School of Public Health, University of Alabama at Birmingham. 1665 University Blvd, Birmingham, AL. 35294-0022, USA.

RESUMEN / SUMMARY: BACKGROUND: To quantify the impact of bone metastasis and skeletal-related events (SREs) on mortality among older patients with lung cancer. MATERIALS AND METHODS: Using the linked Surveillance, Epidemiology and End Results-Medicare database, we identified patients aged 65 years or older diagnosed with lung cancer between July 1, 1999 and December 31, 2005 and followed them to determine deaths through December 31, 2006. We classified patients as having possible bone metastasis and SREs using discharge diagnoses from inpatient claims and diagnoses paired with procedure codes from outpatient claims. We used Cox regression to estimate mortality hazards ratios (HR) among patients with bone metastasis with or without SRE, compared to patients without bone metastasis. RESULTS: Among 126,123 patients with lung cancer having a median follow-up of 0.6 years, 24,820 (19.8%) had bone metastasis either at lung cancer diagnosis (9,523, 7.6%) or during follow-up (15,297, 12.1%). SREs occurred in 12,665 (51%) patients with bone metastasis. The HR for death was 2.4 (95% CI = 2.4-2.5) both for patients with bone metastasis but no SRE and for patients with bone metastasis plus SRE, compared to patients without bone metastasis. CONCLUSIONS: Having a bone metastasis, as indicated by Medicare claims, was associated with mortality among patients with lung cancer. We found no difference in mortality between patients with bone metastasis complicated by SRE and patients with bone metastasis but without SRE.

[601]

TITULO / TITLE: Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients.

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


AUTORES / AUTHORS: Lin S; Chen Y; Yang L; Zhou J
INSTITUCIÓN / INSTITUTION: - The Nursing College of Chongqing Medical University, Chongqing, China.

RESUMEN / SUMMARY: - AIMS AND OBJECTIVES: To explore the common symptom cluster in lung cancer patients with surgical treatment and to evaluate the relationships between symptom cluster and patients’ disease outcomes, including functional status and quality of life. BACKGROUND: Lung cancer is one of the leading causes of cancer-related death for both men and women, and its incidence is increasing in China. Growing number of researches confirmed that symptoms in lung cancer patients with chemotherapy and radiotherapy occurred as ‘symptom cluster’ across the disease trajectory and influenced disease outcomes. However, few studies focused on the symptom cluster and its effects on quality of life and functional status of lung cancer surgery patients. DESIGN: This is a descriptive, cross-sectional design. METHODS: Symptoms in lung cancer surgery were assessed by M.D. Anderson Symptom Inventory, Karnofsky Performance Scale and Quality of Life Instruments for Cancer Patients - Lung Cancer. One hundred and forty-five individuals were involved in the survey. RESULTS: The top four common and most severe symptoms were pain, fatigue, disturbed sleep and distress for lung cancer surgery patients. 4.8% (n = 7) and 17.2% (n = 25) of patients reported co-occurrence of two or three symptoms of pain, fatigue, disturbed sleep and distress. About 76.6% (n = 111) of patients reported co-occurrence of all the four symptoms. There were strong negative relationships between the top four symptoms and Karnofsky Performance Scale and Quality of Life Instruments for Cancer Patients - Lung Cancer scores. CONCLUSION: Pain, fatigue, disturbed sleep and distress constituted the common symptom cluster during the disease trajectory in patients with lung cancer who got surgical treatment and negatively affected their quality of life and functional status. RELEVANCE TO CLINICAL PRACTICE: Symptoms in lung cancer surgery patients often occurred as cluster during the trajectory of disease. To improve the well-being of patients, attentions need to be focused on developing symptom cluster management strategies.

[602]

TÍTULO / TITLE: - Pulmonary leiomyosarcoma mimicking glomus tumor at first biopsy and surgically treated with isolated left main bronchus resection: rare clinical documentation.

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


AUTORES / AUTHORS: - Falkenstern-Ge RF; Friedel G; Bode-Erdmann S; Ott G; Mentzel T; Kohlhaufl M; Ott MM
RESUMEN / SUMMARY: - Soft tissue tumors originating within the endobronchial tree are extremely rare and most of them correspond to lipomas or leiomyomas. We here report a rare clinical presentation of leiomyosarcoma mimicking glomus tumor at initial biopsy arising from the left main bronchial trunk leading to left lower lobe atelectasis. Primary leiomyosarcoma of the lung is an unusual malignancy. Among this entity, the endobronchial form is very rare and the preoperative diagnosis is extremely difficult. We documented two different presentations and outcomes of primary endobronchial leiomyosarcoma of the lung. In this clinical presentation, histological study and immunohistochemical stain of the surgical resection provided the final diagnosis. Through the following we present the diagnostic and therapeutic difficulties encountered with endobronchial leiomyosarcoma.

[603]

TÍTULO / TITLE: - Changes in quality of life, dyspnea scores, and lung function in lung cancer patients with airway obstruction after a therapeutic bronchoscopy.

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


Enlace al texto completo (gratuito o de pago)

AUTORES / AUTHORS: - Neumann K; Sundset A; Espinoza A; Kongerud J; Fosse E

INSTITUCIÓN / INSTITUTION: - The Intervention Centre Department of Respiratory Medicine, Oslo University Hospital, Oslo, Norway. kirill.neumann@gmail.com

RESUMEN / SUMMARY: - BACKGROUND: Quality of life (QoL) has been closely linked with symptom intensity in lung cancer patients. It is therefore important to relieve respiratory distress in these severely ill patients, especially because their short life expectancy. This prospective study aimed to evaluate the impact of a therapeutic bronchoscopy on QoL, dyspnea, and lung function in patients with malignant airway obstruction. METHODS: Fifteen cancer patients with airway obstruction were enrolled in the study. All patients were followed up during 2 months by 4 assessments that consisted of a clinical examination, QoL assessment using European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire with LC-13 module, Borg Dyspnea Scale, and lung function tests. RESULTS: The study showed that therapeutic bronchoscopy had a rather persistent effect on QoL and dyspnea, which were sustained for at least 2 months after the procedure. The study population had
also a significant improvement in lung function. CONCLUSION: Therapeutic bronchoscopy has a positive impact on QoL, dyspnea scale values, and lung function in patients with advanced lung cancer and airway obstruction.
inflammatory cytokines was affected by EGFR-TKI treatment for NSCLC. In addition, the clinical outcomes of EGFR-TKI treatment were influenced by the status of the plasma pro-inflammatory cytokines at diagnosis.

[605]
TÍTULO / TITLE: - Extra-pleural pneumonectomy in the setting of tri-modality therapy for patients with malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 3978/j.issn.1000-9604.2013.02.05
AUTORES / AUTHORS: - Chi A; Wen S; Nguyen NP; Jacobson G; Remick S; Tse W; Liao Z
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, West Virginia University, Morgantown, WV 26506, USA;

[606]
TÍTULO / TITLE: - Early pneumothorax as a feature of response to crizotinib therapy in a patient with ALK rearranged lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 1186/1471-2407-13-207
AUTORES / AUTHORS: - Gennatas S; Stanway SJ; Thomas R; Min T; Shah R; O'Brien ME; Popat S
RESUMEN / SUMMARY: - BACKGROUND: Single arm phase 1 and 2 studies on Crizotinib in ALK-positive patients so far have shown rapid and durable responses. Spontaneous pneumothoraces as a result of response to anti-cancer therapy are rare in oncology but have been documented in a number of tumour types including lung cancer. This includes cytotoxic chemotherapy as well as molecular targeted agents such as gefitinib and Bevacizumab. These often require chest drain insertion or surgical intervention with associated morbidity and mortality. They have also been associated with response to treatment. This is the first report we are aware of documenting pneumothorax as response to crizotinib therapy. CASE PRESENTATION: A 48-year-old Caucasian male presented with a Stage IV, TTF1 positive, EGFR wild-type adenocarcinoma of the lung. He received first line chemotherapy with three cycles of cisplatin-pemetrexed chemotherapy with a differential response, and then second-line erlotinib for two months before further radiological evidence of disease progression. Further analysis of his diagnostic specimen identified an ALK rearrangement by fluorescence in situ hybridization (FISH). He was commenced on crizotinib therapy 250 mg orally twice daily. At his 4-week assessment he had a chest radiograph that identified a large left-sided
pneumothorax with disease response evident on the right. Chest CT confirmed a 50% left-sided pneumothorax on a background of overall disease response. A chest tube was inserted with complete resolution of the pneumothorax that did not recur following its removal. CONCLUSION: Our case demonstrates this potential complication of crizotinib therapy and we therefore recommend that pneumothorax be considered in patients on crizotinib presenting with high lung metastatic burden and with worsening dyspnoea.
associated with asbestos exposure. We report a case of cystic mesothelioma of the peritoneum encasing the ovary, which presented as a cystic adnexal mass. As highlighted in this case and other recent reports, a cystic mesothelioma should not be referred to as a benign cystic mesothelioma, as it has potential for locoregional invasion, as well as distant nodal and serosal metastases. This tumour should be treated with aggressive cytoreductive surgery and appropriate chemotherapy. We review the differential diagnosis of this rare entity and suggest guidelines for its differentiation.

[609]

TÍTULO / TITLE: - Detection of minimal residual disease in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chudacek J; Bohanes T; Klein J; Benedikova A; Srovnal J; Szkorupa M; Skalicky P; Skarda J; Hajduch M; Neoral C
INSTITUCIÓN / INSTITUTION: - Department of Surgery I, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic.

BACKGROUND: Even after successful radical treatment of lung cancer, patients in stages I and II of the TNM system very frequently suffer recurrence, which end lethally. Detection of subclinical residual disease after surgery is thus one of the most important emerging diagnostic methods. Minimal residual disease (MRD) is defined as the presence of isolated tumor cells or circulating cells in a patient after curative primary tumor removal and at the same time, no clinical signs of cancer. Conventional methods cannot detect minimal residual disease and hence there is a need for detection using new molecular biological methods. METHODS: We searched the PubMed database for original and review articles on minimal residual disease in lung cancer. Search words were “lung cancer”, “minimal residual disease” and “detection of minimal residual disease”. The publications we found were compared with the results of our own studies on the detection of minimal residual disease in lung cancer and the personal experiences are described. Examination of blood samples from 98 healthy volunteers and bone marrow from 12 patients with non inflammatory and non tumour illness, were used to determine cut-off values for specific markers in the compartments. Subsequently, expression of selected markers in tumor tissue was analysed in a pilot sample of 50 patients with lung cancer and the presence of MRD was measured as expression of values of the tested markers correlated with clinico-pathological characteristics. CONCLUSIONS: Recent studies on other malignancies apart from lung cancer have shown the importance of MRD
detection in the determination of disease progression and prognosis. The methods of MRD diagnostics are based on detection of specific tumor markers. Of these, the most specific for lung cancer, appears to be the LunX protein. The best method for determining MRD is probably RT-PCR. Further studies should expand knowledge in this area: to refine understanding of the importance of tumor markers for prognosis, as well as to confirm the significance of these findings in clinical practice.

[610]
**TÍTULO / TITLE:** Weekly intravenous nanoparticle albumin-bound paclitaxel for elderly patients with stage IV non-small-cell lung cancer: a series of 20 cases.

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


**AUTORES / AUTHORS:** Zheng Q; Yao Y; Nan K

**INSTITUCIÓN / INSTITUTION:** Department of Medical Oncology, the First Affiliated Hospital, Xi’an Jiaotong University, Xi’an, Shaanxi 710061, China.

**RESUMEN / SUMMARY:** The purpose of this study was to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel as a rescue regimen in the treatment of patients with advanced non-small-cell lung cancer. We retrospectively reviewed the medical records of 20 patients with stage IV non-small-cell lung cancer. The patients had progressive disease after standard antitumor therapy and subsequently received intravenous albumin-bound paclitaxel at the dose of 100 mg/m(2) in weekly schedule. Cumulative findings showed that the overall response rate was 30.0%, the disease control rate amounted to 40%, and the 1 year survival rate was 30%. In addition, the median time to progression and the median survival time reached 5 and 10 months, respectively. Meanwhile, no severe hypersensitivity reactions and grade 4 adverse effects were reported. In summary, weekly-administered albumin-bound paclitaxel seems to be an effective and safe regimen for elderly patients with stage IV non-small-cell lung cancer who were refractory to conventional therapy.

[611]
**TÍTULO / TITLE:** An investigation of a symptom cluster in Chinese patients with lung cancer receiving radiotherapy.

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

**REVISTA / JOURNAL:** Contemp Nurse. 2013 May 26.

**AUTORES / AUTHORS:** Chan CW; Richardson A; Richardson J
RESUMEN / SUMMARY: - Abstract Background: The investigation of the clustering of symptoms in patients with cancer is still at an early stage. Initial evidence suggests symptoms such as breathlessness, fatigue and anxiety occur concurrently. Purpose: The purpose of this study was to investigate the existence of a symptom cluster involving breathlessness, fatigue and anxiety in Chinese patients with advanced lung cancer undergoing palliative radiation treatment (RT). Methods: The study was conducted in an oncology out-patient unit of a public funded hospital in Hong Kong. A convenience sample of 140 patients were asked to complete a set of questionnaires at 4 time points including the A-state scale of the State-Trait Anxiety Inventory, a breathlessness visual analogue scale and the intensity subscale of the revised Piper Fatigue Scale at 4 points: 1 day prior to RT (baseline) (T0), and at week 3 (T1), week 6 (T2) and week 12 (T3) after the commencement of the RT. Results: Between 64%-73% of patients experienced all 3 symptoms concurrently across T0-T3. The prevalence of anxiety, fatigue and breathlessness ranged from 65% to 97% respectively. Intensities of breathlessness and fatigue were highest at T1. Significant correlations between the 3 symptoms were moderate across time (r <.50). Conclusion and implication: The high prevalence of the symptom cluster demonstrates a need to assess and manage these symptoms simultaneously in patients with advanced lung cancer.

INSTITUCIÓN / INSTITUTION: - Professor, The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong. Email: whchan@cuhk.edu.hk.

TÍTULO / TITLE: - Usefulness of Serum Carcinoembryonic Antigen (CEA) in evaluating response to chemotherapy in patients with advanced non small-cell lung cancer: a prospective cohort study.

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


AUTORES / AUTHORS: - Arrieta Rodriguez OG; Villarreal-Garza C; Martinez-Barrera L; Morales M; Dorantes-Gallareta Y; Pena-Curiel O; Contreras-Reyes S; Macedo-Perez EO; Alatorre-Alexander J

RESUMEN / SUMMARY: - BACKGROUND: High serum carcinoembryonic antigen (CEA) levels are an independent prognostic factor for recurrence and survival in patients with non-small cell lung cancer (NSCLC). Its role as a predictive marker of treatment response has not been widely characterized. METHODS: 180 patients with advanced NSCLC (stage IIIB or Stage IV), who had an elevated CEA serum level (>10 ng/ml) at baseline and who had no more than one previous chemotherapy regimen, were included. CEA levels were measured
after two treatment cycles of platinum based chemotherapy (93%) or a tyrosine kinase inhibitor (7%). We evaluate the change in serum CEA levels and the association with response measured by RECIST criteria. RESULTS: After two chemotherapy cycles, the patients who achieved an objective response (OR, 28.3%) had a reduction of CEA levels of 55.6% (95%CI [64.3 to 46.8]) compared to its basal level, with an area under the ROC curve (AURC) of 0.945 (95%CI 0.91-0.99), and a sensitivity and specificity of 90.2 and 89.9%, respectively, for a CEA reduction of >=14%. Patients that achieved a decrease in CEA levels >=14% presented an overall response in 78% of cases, stable disease in 20.3% and progression in 1.7%, while patients that did not attain a reduction >=14% had an overall response of 4.1%, stable disease of 63.6% and progression of 32.2% (p < 0.001). Patients with stable (49.4%) and progressive disease (22.2%) had an increase of CEA levels of 9.4% (95%CI 1.5-17.3) and 87.5% (95%CI 60.9-114) from baseline, respectively (p < 0.001). The AURC for progressive disease was 0.911 (95%CI 0.86-0.961), with sensitivity and specificity of 85 and 15%, respectively, for a CEA increase of >=18%. PFS was longer in patients with a >=14% reduction in CEA (8.7 vs. 5.1 months, p < 0.001). Neither reduction of CEA nor OR were predictive of OS. CONCLUSIONS: A CEA level reduction is a sensitive and specific marker of OR, as well as a sensitive indicator for progression to chemotherapy in patients with advanced NSCLC who had an elevated CEA at baseline and had received no more than one chemotherapy regimen. A 14% decrease in CEA levels is associated with a better PFS.
time from onset of coma (Glasgow Coma Scale less than 8). Time between coma and death was significantly shorter in the liver disease patients (cirrhosis and/or HCC: 7.0 h) than in lung cancer (44.0 h, p = 0.045). Total bilirubin was higher in HCC compared with cirrhosis (p<0.01). Rate of usage of narcotic analgesics was higher in lung cancer (20/33: 60.6%) than in liver disease (17/83: 20.5%, p<0.01); analgesics were used more frequently in HCC than in liver cirrhosis (p<0.01). These results suggest that liver cirrhosis and HCC patients do not always require palliative care and that survival time from onset of coma due to liver disease was not prolonged compared with lung cancer.

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**TÍTULO / TITLE:** - The value of MMP-9 for breast and non-small cell lung cancer patients' survival.

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


**AUTORES / AUTHORS:** - Schveigert D; Cicenas S; Bruzas S; Samalavicius NE; Gudleviciene Z; Didziapetriene J

**RESUMEN / SUMMARY:** - ABSTRACT Purpose: Matrix metalloproteinases (MMPs) are implicated in cancer cells invasion and metastasis processes and have been investigated as potential cancer biomarkers. In this study MMP-9 gene expression and MMP-9-1562 C/T polymorphism in breast and non-small cell lung cancer patients' blood and tumor samples and its correlation with clinicopathological parameters were investigated. Material/Methods: MMP-9 gene expression was assessed by reverse transcription - polymerase chain reaction method in 108 cancer patients' blood and tumor samples. MMP-9-1562 C/T polymorphism was determined by the polymerase chain reaction - based restriction fragment length polymorphism method. Results: Significant relationship of MMP-9 gene expression and tumor differentiation grade was found only between groups with G1 and G3 breast tumors. Low survival rates were identified among positive MMP-9 expression in blood and ductal carcinoma of the breast (p=0.01) and negative progesterone receptor reaction (p=0.04). Significant differences in the distribution among genotypes were found between groups with stage I and stages III/IV (p=0.005) as well as between groups with lymph node status N0 and N1 (p<0.001). Breast cancer patients with tumor differentiation grade G3 and identified CC variant had a longer survival time (p=0.014). Shorter survival time was found among positive MMP-9 expression in tumor and stage I non-small cell lung cancer patients with negative lymph node (p=0.012) and squamous cell carcinoma (p=0.019). Conclusions: Expression of MMP-9 in blood and tumor together indicates worse prognosis for breast cancer patients.
Longer telomere length in peripheral white blood cells is associated with risk of lung cancer and the rs2736100 (CLPTM1L-TERT) polymorphism in a prospective cohort study among women in China.

A recent genome-wide association study of lung cancer among never-smoking females in Asia demonstrated that the rs2736100 polymorphism in the TERT-CLPTM1L locus on chromosome 5p15.33 was strongly and significantly associated with risk of adenocarcinoma of the lung. The telomerase gene TERT is a reverse transcriptase that is critical for telomere replication and stabilization by controlling telomere length. We previously found that longer telomere length measured in peripheral white blood cell DNA was associated with increased risk of lung cancer in a prospective cohort study of smoking males in Finland. To follow up on this finding, we carried out a nested case-control study of 215 female lung cancer cases and 215 female controls, 94% of whom were never-smokers, in the prospective Shanghai Women’s Health Study cohort. There was a dose-response relationship between tertiles of telomere length and risk of lung cancer (odds ratio (OR), 95% confidence interval [CI]: 1.0, 1.4 [0.8-2.5], and 2.2 [1.2-4.0], respectively; P trend = 0.003). Further, the association was unchanged by the length of time from blood collection to case diagnosis. In addition, the rs2736100 G allele, which we previously have shown to be associated with risk of lung cancer in this cohort, was significantly associated with longer telomere length in these same study subjects (P trend = 0.030). Our findings suggest that individuals with longer telomere length in peripheral white blood cells may have an increased risk of lung cancer, but require replication in additional prospective cohorts and populations.

Pre- and postoperative self-reported cognitive effectiveness and worry in patients with suspected lung malignancy.

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[616]
目的/objetivos: Examinar la percepción de la efectividad cognitiva y el temor en individuos con sospecha de cáncer de pulmón antes y después de la resección quirúrgica y determinar cualquier diferencia entre individuos con y sin diagnóstico postoperatorio de cáncer de pulmón. Diseño: Diseño longitudinal longitudinal repetido. Ambiente: Un centro de cáncer comprehensivo y un hospital de la Administración de Veteranos en los Estados Unidos del centro occidental. muestra: 15 hombres y 8 mujeres entre 37-82 años (X = 61.4, SD = 10.7) con sospecha de cáncer de pulmón. Métodos: Se utilizaron estadísticas descriptivas para caracterizar los datos. Se utilizaron pruebas t pareadas y análisis de correlación no paramétrica para determinar las relaciones entre las variables principales de estudio. Variables principales de investigación: Percepción de la efectividad en la función cognitiva así como la preocupación general y específica del cáncer. hallazgos: Los pacientes diagnosticados con cáncer de pulmón eran significativamente mayores. Los pacientes se auto-reportaron una percepción reducida de la efectividad en actividades diarias que requieren atención dirigida tanto antes como después de la cirugía. Los pacientes con patología no maligna postoperatoria reportaron mayor preocupación general a cada punto de tiempo, lo que fue significativo después de la cirugía. Conclusiones: Un diagnóstico sospechoso de cáncer de pulmón puede contribuir a la percepción reducida de la efectividad cognitiva. La patología no maligna después de un diagnóstico sospechado de cáncer de pulmón puede estar asociada con el temor continuado. Implicaciones para la Enfermería: La evaluación y las intervenciones de enfermería con el objetivo de apoyar la función cognitiva efectiva y modificar el temor en pacientes con sospecha de cáncer de pulmón son esenciales para optimizar la adaptación. Traducción del conocimiento: El cáncer de pulmón sospechado impone altas demandas en la función cognitiva y emocional. Las enfermeras de oncología se encuentran en posiciones clave para apoyar a los pacientes durante y después del trabajo diagnóstico para el cáncer de pulmón. Los pacientes más jóvenes con reportes postoperatorios no malignos pueden necesitar seguimiento continuado.
RESUMEN / SUMMARY: - Purpose: This retrospective study evaluated whether the maximum standardized uptake value (SUVmax) on 18F-deoxyglucose (FDG)-positron emission tomography (PET) could be used to predict the prognosis of patients with pathological stage I adenocarcinoma. Methods: We analyzed 138 consecutive patients with pathological stage IA or IB lung adenocarcinoma except pure bronchioloalveolar carcinoma (BAC) who underwent preoperative FDG-PET imaging and curative resection from January 2005 to October 2010. We analyzed associations between disease-free survival (DFS) and clinicopathological factors. Results: The 5-year DFS rate was 77.7%. Twenty two patients (15.9%) developed recurrence after surgery. Multivariate analysis identified SUVmax and lymphovascular (ly) involvement as the independent prognostic factors for recurrence (p = 0.0255 and p = 0.0333, respectively). We divided the patients into groups according to SUVmax and ly involvement. The 5-year DFS rate was 97.0% in patients with SUVmax ≤2.5 and without ly involvement, 100% with both SUVmax ≤2.5 and ly involvement, 70.2% with SUVmax >2.5 and without ly involvement, and 53.1% with both SUVmax >2.5 and ly involvement. Conclusions: The results of this study suggest that SUVmax and ly involvement could be used to predict the prognosis of patients with pathological stage I adenocarcinoma. The combination of these prognostic factors could also identify high risk groups of recurrence.

TÍTULO / TITLE: - Cell-type specificity of lung cancer associated with low-dose soil heavy metal contamination in Taiwan: An ecological study.

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


AUTORES / AUTHORS: - Huang HH; Huang JY; Lung CC; Wu CL; Ho CC; Sun YH; Ko PC; Su SY; Chen SC; Liaw YP

INSTITUCIÓN / INSTITUTION: - Department of Public Health and Institute of Public Health, Chung Shan Medical University, No, 110, Sec, 1, Chien-Kuo N, Road, Taichung City, 40201, Taiwan. Liawyp@csmu.edu.tw.

RESUMEN / SUMMARY: - BACKGROUND: Numerous studies have examined the association between heavy metal contamination (including arsenic [As], cadmium [Cd], chromium [Cr], copper [Cu], mercury [Hg], nickel [Ni], lead [Pb], and zinc [Zn]) and lung cancer. However, data from previous studies on pathological cell types are limited, particularly regarding exposure to low-dose soil heavy metal contamination. The purpose of this study was to explore the association between soil heavy metal contamination and lung cancer incidence by specific cell type in Taiwan. METHODS: We conducted an ecological study and calculated the annual averages of eight soil heavy metals (i.e., As, Cd, Cr,
Cu, Hg, Ni, Pb, and Zn) by using data from the Taiwan Environmental Protection Administration from 1982 to 1986. The age-standardized incidence rates of lung cancer according to two major pathological types (adenocarcinoma [AC] and squamous cell carcinoma [SCC]) were obtained from the National Cancer Registry Program conducted in Taiwan from 2001 to 2005. A geographical information system was used to plot the maps of soil heavy metal concentration and lung cancer incidence rates. Poisson regression models were used to obtain the adjusted relative ratios (RR) and 95% confidence intervals (CI) for the lung cancer incidence associated with soil heavy metals. RESULTS: For males, the trend test for lung SCC incidence caused by exposure to Cr, Cu, Hg, Ni, and Zn showed a statistically significant dose-response relationship. However, for lung AC, only Cu and Ni had a significant dose-response relationship. As for females, those achieving a statistically significant dose-response relationship for the trend test were Cr (P = 0.02), Ni (P = 0.02), and Zn (P = 0.02) for lung SCC, and Cu (P < 0.01) and Zn (P = 0.02) for lung AC. CONCLUSION: The current study suggests that a dose-response relationship exists between low-dose soil heavy metal concentration and lung cancer occurrence by specific cell-type; however, the relevant mechanism should be explored further.


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


AUTORES / AUTHORS: - Giacalone NJ; Den RB; Eisenberg R; Chen H; Olson SJ; Massion PP; Carbone DP; Lu B

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA.

RESUMEN / SUMMARY: - Aim: The purpose of this study was to describe the prognostic significance of ALDH7A1 in surgically treated non-small-cell lung carcinoma. (NSCLC). Materials & methods: We immunohistochemically analyzed ALDH7A1 expression in surgically resected NSCLC from 89 patients using a tissue microarray. Results: ALDH7A1 staining was positive in 43 patients and negative in 44 patients, with two tumor sections missing. For stage I NSCLC patients, ALDH7A1 positivity was associated with decreased recurrence-free and overall survival. Multivariate analysis demonstrated that ALDH7A1-expressing NSCLC tumors had a significantly higher incidence of lung cancer recurrence compared with patients with ALDH7A1-negative tumors, although there was no association with overall survival. Conclusion: For
patients with NSCLC, low ALDH7A1 expression was associated with a decreased incidence of cancer recurrence. Specifically in stage I patients, negative staining for ALDH7A1 was associated with improved recurrence-free and overall survival, suggesting a predictive role in surgically treated patients.

[620]

TÍTULO / TITLE: - P38 MAP Kinase Mediates Apoptosis After Genipin Treatment in Non-Small-Cell Lung Cancer H1299 Cells via a Mitochondrial Apoptotic Cascade.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yang X; Yao J; Luo Y; Han Y; Wang Z; Du L
INSTITUCIÓN / INSTITUTION: - Key Laboratory of Bio-resources and Eco-environment of the Ministry of Education, College of Life Sciences, Sichuan University, China.
RESUMEN / SUMMARY: - Genipin, an active constituent of Gardenia fruit, has been reported to show an anti-tumor effect in several cancer cell systems. Here, we demonstrate how genipin exhibits a strong apoptotic cell death effect in human non-small-cell lung cancer H1299 cells. Genipin-mediated decrease in cell viability was observed through apoptosis as demonstrated by induction of a sub-G1 peak through flow cytometry, DNA fragmentation measured by TUNEL assay, and cleavage of poly ADP-ribose-polymerase. During genipin-induced apoptosis, the mitochondrial execution pathway was activated by caspase-9 and -3 activation as examined by a kinetic study, cytochrome c release, and a dose-dependent increase in Bax/Bcl-2 ratio. A search for the downstream pathway reveals that genipin-induced apoptosis was mediated by an increase in phosphorylated p38MAPK expression, which further activated downstream signaling by phosphorylating ATF-2. SB203580, a p38MAPK inhibitor, markedly blocked the formation of TUNEL-positive apoptotic cells in genipin-treated cells. Besides, the interference of p38MAPK inhibited Bax expression and cytochrome c release. Altogether, our observations imply that genipin causes increased levels of Bax in response to p38MAPK signaling, which results in the initiation of mitochondrial death cascade, and therefore it holds promise as a potential chemotherapeutic agent for the treatment of H1299 cells.

[621]

TÍTULO / TITLE: - Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
 Enlace al texto completo (gratuito o de pago) 1186/1749-8090-8-106
BACKGROUND: Until date, there are no clear recommendations for regular perioperative measurements of serum CEA levels for lung cancer in any guidelines. The purpose in the present study is to evaluate the prognostic significance of perioperative serum carcinoembryonic antigen (CEA) levels in patients with pathological-stage I non-small cell lung cancer (NSCLC). METHODS: We retrospectively reviewed 263 completely resected pathological-stage I NSCLC patients whose preoperative and postoperative serum CEA levels were measured. Patients were subdivided according to the perioperative change of CEA levels: continuously normal CEA levels (NN group), continuously high CEA levels (HH group), and high preoperative CEA levels that returned to normal levels post-operation (HN group). The clinicopathological factors and overall survival (OS) among these 3 groups were compared. Univariate and multivariate analyses of the correlation between clinicopathological factors and OS were performed. RESULTS: High preoperative CEA levels significantly correlated with men aged >70 years with smoking history, high serum CYFRA 21–1 levels, greater tumor diameter, presence of visceral pleural invasion (VPI), and moderate-to-poor differentiation. Five-year OS rates in the NN and HH groups were 95.5% and 59.3%, respectively. Four-year OS rate in the HN group was 85.5%. Multivariate analyses indicated tumor diameter of more than 30 mm, presence of VPI, and the HH group were independent unfavorable prognostic factors. CONCLUSIONS: A high postoperative CEA level was an independent unfavorable prognostic factor in pathological-stage I NSCLC patients. Patients with high postoperative CEA levels may benefit from adjuvant chemotherapy.
new molecular markers for tumor cells in regional lymph nodes (LNs) and peripheral blood (PB) from patients with non-small cell lung cancer (NSCLC).

METHODS: Candidate markers were selected based on digital transcript profiling and previous literature. KRT19, CEACAM5, EPCAM, DSG3, SFTPA, SFTPC and SFTPB mRNA levels were initially validated by real-time reverse transcription PCR-based quantification in 16 NSCLC tumors and 22 LNs and 12 PB samples from individuals without known cancer. Five of the candidate markers were selected for secondary validation by quantification in parallel tumor biopsies, regional LNs and PB samples from 55 patients undergoing surgery for NSCLC. LN and PB marker status were compared to clinicopathological patient data.

RESULTS: All selected markers except DSG3 were present at high levels in the primary tumors and at very low or non-detectable levels in normal LNs and PB in the first round of validation, indicating a potential for detecting tumor cells in NSCLC patients. The expression profiles of KRT19, CEACAM5, DSG3, SFTPA and SFTP mRNA were confirmed in the larger group during the secondary validation. Using the highest normal LN level of each marker as threshold, 39 (71%) of the 55 patients had elevated levels of at least one marker in regional LNs. Similarly, 26 (47%) patients had elevated levels of at least one marker in PB. A significantly higher number of patients with adenocarcinomas had positive LN status for these markers, compared with other histological types (P = 0.004).

CONCLUSIONS: Several promising molecular tumor cell markers in regional LNs and PB were identified, including the new SFTPA and SFTP mRNA. Clinical follow-up in a larger cohort is needed to elucidate their prognostic value.
overall survival (OS) were 16.0 and 21.0 months, respectively. The three-year DFS rate was 56.7%, and the OS rate was 75.3%. For serum NSE, the three-year cumulative DFS rate for the normal and elevated group was 67.7% and 51.8% (p = 0.007). The OS in patients with high and normal levels of NSE was 34.0 months and 48.0 months, respectively. The median DFS was 46.0 months versus 32.0 months (p = 0.001), and the OS was 48.0 months versus 44.0 months (p = 0.001) in patients with normal and high levels of CA125. For patients with squamous cell carcinoma, the overall survival was significantly shorter in patients with elevated levels of SCC (p = 0.041). In the multivariate analysis high levels of NSE, CA125 and clinical stage were significantly correlated with worse prognosis (p < 0.05). Patients with all three tumor markers elevated presented the worst prognosis (p < 0.05). In our analysis, high levels of preoperative serum NSE and CA125 are correlated with worse survival in operable NSCLC patients.

[624]

**TÍTULO / TITLE:** Segmentectomy as a safe and equally effective surgical option under complete video-assisted thoracic surgery for patients of stage I non-small cell lung cancer.

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


**AUTORES / AUTHORS:** Zhao X; Qian L; Luo Q; Huang J

**INSTITUCIÓN / INSTITUTION:** Shanghai Lung Cancer Center/Shanghai Chest Hospital, 241 West HuaiHai Road, Shanghai, China. qingquan.luo.shch@gmail.com.

**RESUMEN / SUMMARY:** BACKGROUND: While video-assisted thoracic surgery lobectomy has been widely accepted for the treatment of non-small cell lung cancer, the debate over video-assisted thoracic surgery segmentectomy still remains. This study compared the clinical outcomes using the two procedures for stage I non-small cell lung cancer patients. METHODS: Retrospective review was conducted on patients who underwent video-assisted thoracic surgery segmentectomy or lobectomy for clinical stage I non-small cell lung cancer at Shanghai Chest Hospital between November 2009 and May 2012. Video-assisted thoracic surgery segmentectomy was performed on 36 patients and video-assisted thoracic surgery lobectomy on 138 patients. Comparisons between the 2 groups were performed in patient demographic and clinical characteristics, intraoperative parameters and oncology outcomes. RESULTS: Mean volume of chest tube drainage after operation was smaller for segmentectomy than for lobectomy (1021 ml vs. 1328 ml, P=0.036). Other parameters analysis including blood loss, operation time, chest tube duration and length of hospital stay favors the segmentectomy group numerically.
without significance. There was no significant difference in distributions in both intra and post operative complications. There was one peri-operative mortality from segmentectomy group and all other patients are alive with a median follow up of 327 days. There were 1 (2.8%) locoregional recurrence after segmentectomy and 6 recurrences (4.4%) after lobectomy (P=1.00). Multivariate survival analysis revealed no significant difference in recurrence-free survivals between the two groups. Two patients successfully underwent bilateral segmentectomies and are free of disease. CONCLUSIONS: For patients with stage I non-small cell lung cancer, video-assisted thoracic surgery segmentectomy offers a safe and equally effective option and can be applied to complicated operation such as bilateral segmentectomy.

[625]
TÍTULO / TITLE: - Survival of mesothelioma in a palliative medical care unit in Egypt.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ibrahim N; Abou-Elela E; Darwish D
INSTITUCIÓN / INSTITUTION: - Palliative Medicine Unit, Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK), Kasr El-Aini School of Medicine, Cairo University E-mail: daliaomard@yahoo.com.
RESUMEN / SUMMARY: - Background: This study was to evaluate the survival of patients with pleural and intraperitoneal malignant mesothelioma and to investigate the efficacy of chemotherapy (CT) as well as radiotherapy (RTH) and surgery compared to best supportive care (BSC). Materials and Methods: Forty patients with malignant mesothelioma (38 with pleural and 2 with intraperitoneal) were enrolled. Twenty seven patients underwent (CT) chemotherapy of which 2 also received (RTH) and surgery was only for biopsy in 15/40. Combination chemotherapy included cisplatin-gemcitabine, cisplatin-navelbine and cisplatin (or carboplatin) with premetrexed. Thirteen patients received only best supportive care. Results: A total of 12 (30%) patients were male, and 28 (70%) female. Median age was 54.0 years and the male/female ratio was $\frac{1}{3} . 33$ (P=0.210). Residential exposure played a major role in two regions, Helwan and Shoubra, in 20% and 15%, respectively. Overall mean survival time was 13.9+/−2.29 months. That for patients who had received best supportive care was 7.57+/−1.85 months, for chemotherapy was 16.5+/−3.20 months, and multimodality treatment regimen 27+/−21.0 months (P=0.028). Kaplan-Meier survival did not significantly vary for sex, residence and the pathological types epithelial, mixed and sarcomatous. The median survival for performance status and treatment modalities was significant (P=0.001 and 0.028). Best supportive care using opioids with a mean dose of 147.1 mg (range 0-1680) of morphine sulphate produced good subjective response and reasonable quality of life but did not affect survival. Conclusions: We conclude
that CT prolongs survival compared to BSC in patients with malignant mesothelioma. Moreover, using escalating doses of opioids provides good pain relief and subjective responses.
toxicity can also be biased by bevacizumab eligibility. Selection bias can be large in clinical trials of bevacizumab, so findings from such trials should be interpreted with extreme caution.

[627]

TÍTULO / TITLE: - Cardiotoxicity of cisplatin-based chemotherapy in advanced non-small cell lung cancer patients.

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


AUTORES / AUTHORS: - Demkow U; Stelmaszczyk-Emmel A

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RESUMEN / SUMMARY: - Cardiotoxicity is a well known consequence of cancer chemotherapy. Cisplatin-based combinations are standard regimens in the therapy of advanced non-small cell lung cancer. Administration of cisplatin-containing chemotherapy causes significant oxidative and nitrosative stress in some patients. Cardiac blood biomarkers can be used to evaluate cardiac status, may help to identify patients at risk myocardial damage evaluation and are able to detect subclinical, early-stage cisplatin-induced cardiotoxicity. The relevance of cardiovascular complications in cancer patients and identification of individual risk factors for developing cardiovascular toxicity merit further evaluation and a longer follow-up is needed.

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[628]

TÍTULO / TITLE: - The correlation of SUVmax with pathological characteristics of primary tumor and the value of Tumor/ Lymph node SUVmax ratio for predicting metastasis to lymph nodes in resected NSCLC patients.

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


AUTORES / AUTHORS: - Koksal D; Demirag F; Bayiz H; Ozmen O; Tatci E; Berktas B; Aydogdu K; Yekeler E

INSTITUCIÓN / INSTITUTION: - Chest Diseases Clinic, Ataturk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey. dcckoksal@gmail.com

RESUMEN / SUMMARY: - BACKGROUND: We aimed to investigate the correlation of maximum standardized uptake value (SUVmax) with pathological characteristics of primary tumor and to determine a Tumor/ Lymph node (T/LN)
METHODS: Eighty-one NSCLC patients who had PET/CT examination at initial staging and subsequently underwent surgical resection were retrospectively evaluated. There were 100 PET/CT positive mediastinal or hilar lymph node stations. Pathological characteristics of the tumor such as largest tumor diameter, tumor histology, differentiation, number of mitosis, degree of stromal inflammation, necrosis; etiology of PET/CT positive lymph node stations; SUVmax of primary tumor and positive lymph node stations were recorded. A T/LN SUVmax ratio was calculated for each lymph node station. RESULTS: SUVmax of the primary tumor was positively correlated with the largest tumor diameter (p=0.001, r=0.374), number of mitosis (p<0.001, r=0.405), and postoperative pathological stage (p=0.007, r=0.298). Patients with squamous cell carcinoma had a statistically significant higher mean SUVmax, number of mitosis and advanced N stages compared to adenocarcinoma. The etiology of 100 PET/CT positive lymph node stations were metastasis in 14, anthracosis in 40, reactive in 39, granulomatous in 4, and silicosis in 3 patients. A T/LN SUVmax ratio of 5 or lower was suggestive for a malignant lymph node with a sensitivity of 92.8% and specificity of 47%. CONCLUSIONS: SUVmax of a primary tumor is related to certain pathological characteristics, such as largest diameter, histology, and number of mitosis. A T/LN SUVmax ratio lower than 5 predicts the metastasis to lymph nodes with a high sensitivity.
factors, such as TNM stage. The role of clinical decision making for treating lung adenocarcinoma is predominantly based on subtyping similar to that of breast and prostate cancer.

[630]

**TÍTULO / TITLE:** - A case of pulmonary carcinoid tumour in a pregnant woman successfully treated with bronchoscopic (electrocautery) therapy.

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

**REVISTA / JOURNAL:** - British Medical J (BMJ). Acceso gratuito al texto completo.

- Enlace a la Editora de la Revista [http://bmj.com/search.dtl](http://bmj.com/search.dtl)
- Enlace al texto completo (gratuito o de pago) [1136/bcr-2013-009250](1136/bcr-2013-009250)

**AUTORES / AUTHORS:** - Binesh F; Samet M; Bovanlu TR

**INSTITUCIÓN / INSTITUTION:** - Shahid Sadoughi University of Medical Sciences, Yazd, Iran. binesh44@yahoo.com

**RESUMEN / SUMMARY:** - We present an uncommon case of a carcinoid tumour of the bronchus that was diagnosed during pregnancy in a 28-year-old woman. The patient was admitted at the emergency department with massive haemoptysis. Owing to the patient’s critical condition, she underwent urgent flexible bronchoscopy. Bleeding was controlled by local injection of 500 mg tranexamic acid and electrocautery. After the bleeding has stopped, multiple specimens were taken. Histological examination confirmed typical carcinoid tumour. Owing to repeated haemoptysis, she was treated with bronchoscopic (electrocautery) therapy, and, after delivery, she underwent pulmonary lobectomy. Only a few similar cases were found in the literature reporting bronchopulmonary carcinoid tumour during pregnancy and we could not find any similar case which was treated by electrocautery.

[631]

**TÍTULO / TITLE:** - Analytic performance studies and clinical reproducibility of a real-time PCR assay for the detection of epidermal growth factor receptor gene mutations in formalin-fixed paraffin-embedded tissue specimens of non-small cell lung cancer.

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


- Enlace al texto completo (gratuito o de pago) [1186/1471-2407-13-210](1186/1471-2407-13-210)

**AUTORES / AUTHORS:** - O’Donnell P; Ferguson J; Shyu J; Current R; Rehage T; Tsai J; Christensen M; Tran HB; Chien SS; Shieh F; Wei W; Lawrence HJ; Wu L; Schilling R; Bloom K; Maltzman W; Anderson S; Soviero S
BACKGROUND: Epidermal growth factor receptor (EGFR) gene mutations identify patients with non-small cell lung cancer (NSCLC) who have a high likelihood of benefiting from treatment with anti-EGFR tyrosine kinase inhibitors. Sanger sequencing is widely used for mutation detection but can be technically challenging, resulting in longer turn-around-time, with limited sensitivity for low levels of mutations. This manuscript details the technical performance verification studies and external clinical reproducibility studies of the cobas EGFR Mutation Test, a rapid multiplex real-time PCR assay designed to detect 41 mutations in exons 18, 19, 20 and 21.

METHODS: The assay’s limit of detection was determined using 25 formalin-fixed paraffin-embedded tissue (FFPET)-derived and plasmid DNA blends. Assay performance for a panel of 201 specimens was compared against Sanger sequencing with resolution of discordant specimens by quantitative massively parallel pyrosequencing (MPP). Internal and external reproducibility was assessed using specimens tested in duplicate by different operators, using different reagent lots, instruments and at different sites. The effects on the performance of the cobas EGFR test of endogenous substances and nine therapeutic drugs were evaluated in ten FFPET specimens. Other tests included an evaluation of the effects of necrosis, micro-organisms and homologous DNA sequences on assay performance, and the inclusivity of the assay for less frequent mutations.

RESULTS: A >95% hit rate was obtained in blends with >5% mutant alleles, as determined by MPP analysis, at a total DNA input of 150 ng. The overall percent agreement between Sanger sequencing and the cobas test was 96.7% (negative percent agreement 97.5%; positive percent agreement 95.8%). Assay repeatability was 98% when tested with two operators, instruments, and reagent lots. In the external reproducibility study, the agreement was > 99% across all sites, all operators and all reagent lots for 11/12 tumors tested. Test performance was not compromised by endogenous substances, therapeutic drugs, necrosis up to 85%, and common micro-organisms. All of the assessed less common mutations except one (exon 19 deletion mutation 2236_2248 > AGAC) were detected at a similar DNA input level as that for the corresponding predominant mutation. CONCLUSION: The cobas EGFR Mutation Test is a sensitive, accurate, rapid, and reproducible assay.
OBJECTIVES: Pemetrexed is a thymidylate synthase (TS) inhibitor and is effective in non-small cell lung cancer (NSCLC). 3'-deoxy-3'-[18F]fluorothymidine ((18)F-FLT), a proliferation marker, could potentially identify tumor specific TS-inhibition. The aim of this study was to investigate the effect of pemetrexed-induced TS-inhibition on (18)F-FLT uptake 4 hours after pemetrexed administration in metastatic NSCLC patients. METHODS: Fourteen NSCLC patients underwent dynamic (18)F-FLT positron emission tomography (PET) scans at baseline and 4 hours after the first dose of pemetrexed.Volumes of interest were defined with a 41%, 50% and 70% threshold of the maximum pixel. Kinetic analysis and simplified measures were performed. At one, two, four and six hours after pemetrexed, plasma deoxyuridine was measured as systemic indicator of TS-inhibition. Tumor response measured with response evaluation criteria in solid tumors (RECIST), time to progression (TTP) and overall survival (OS) were determined. RESULTS: Eleven patients had evaluable (18)F-FLT PET scans at baseline and 4 hours after pemetrexed. Two patients had increased (18)F-FLT uptake of 35% and 31% after pemetrexed, whereas two other patients had decreased uptake of 31%. In the remaining seven patients (18)F-FLT uptake did not change beyond test-retest borders. In all patients deoxyuridine levels raised after administration of pemetrexed, implicating pemetrexed-induced TS-inhibition. (18)F-FLT uptake in bone marrow was significantly increased 4 hours after pemetrexed administration. Six weeks after the start of treatment 5 patients had partial response, 4 stable disease and 2 progressive disease. Median TTP was 4.2 months (range 3.0-7.4 months); median OS was 13.0 months (range 5.1-30.8 months). Changes in (18)F-FLT uptake were not predictive for tumor response, TTP or OS. CONCLUSIONS: Measuring TS-inhibition in a clinical setting 4 hours after pemetrexed revealed a non-systematic change in (18)F-FLT uptake within the tumor. No significant association with tumor response, TTP or OS was observed.
RESUMEN / SUMMARY:

BACKGROUND: Most of the metastatic lung lesions are relatively high contrast in comparison to the lung background and easily detected in non-contrast enhancement chest computed tomography alone (NECCT). Pediatric patients may get benefit from its minimal radiation dose and lack of adverse reaction from iodinated contrast agent. OBJECTIVE: To compare effectiveness of non-contrast enhancement chest computed tomography (NECCT) in detecting thoracic metastasis with full protocol chest computed tomography (FPCCT) (chest computed tomography with and without contrast) in non-hematologic extrathoracic malignancy in children. MATERIAL AND METHOD: Both NECCT and FPCCT were evaluated in 50 pediatric patients with non-hematologic extrathoracic malignancy retrospectively. Lung nodules, ground glass opacities, interlobular septal thickening, pleural effusion, pleural thickening, pericardial effusion, endobronchial lesion, and intravascular metastasis were evaluated separately on each CT protocol by two radiologists. RESULTS: Thirty boys and 20 girls were included in the present study (mean age = 10 years and 3 months). The lesions include nodule (333 detected by NECCT (median = 3), 336 detected by CECCT (median = 3)), ground glass opacity (12 detected by NECCT (median = 0), 15 detected by CECCT (median = 0)), interlobular septal thickening (12 detected by NECCT (median = 0), 11 detected by CECCT (median = 0)). There was 100 percent match of calcified nodules (n = 36), pleural effusion (n = 1), pleural thickening (n = 3), intravascular thrombus (n = 2), and mediastinal lymph node (n = 1) between NECCT and FPCCT studies. There was no statistically significant different in capability of demonstrating all lesions between NECCT and FPCCT. Most of the discrepancies between NECCT and FPCCT were from motion artifact, inadequate inspiration, and radiologist’s opinion rather than effect of contrast agent administration itself. CONCLUSION: NECCT is as effective as FPCCT in evaluation of pulmonary metastasis in non-hematologic extrathoracic malignancies. For evaluation of lung metastases in this population, NECCT alone is sufficient.

TÍTULO / TITLE: Can exercise capacity assessed by the shuttle walk test predict the development of post-operative complications in patients with lung cancer?

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

INTRODUCTION: The objective of this study was to assess the role of shuttle walk test in predicting post-operative complications in lung cancer resection surgery. PATIENTS AND METHODS: A consecutive series of patients who were candidate for lung resection surgery with the diagnosis of early stage lung cancer were included to this study. All patients in this study evaluated for exercise capacity testing with shuttle walk test. RESULTS: Twenty for patients were included in this study. Mean age was 61.5 +/- 8.6 years. Pneumonectomy, lobectomy, bilobectomy and wedge resection were performed in 11 (46%), 10 (42%), 2 (8%), and 1 (4%) patients, respectively. Complications occurred only in six patients. There was no statistically significant relationship between risk for development of post-operative complication and age, incremental shuttle walk test, endurance shuttle walk test and exercise capacity evaluated with peak VO(2) (mL/kg/minute) (p> 0.05). CONCLUSION: Shuttle walk tests (incremental and endurance) had a limited role in predicting post-operative complications in lung cancer resections.
**TÍTULO / TITLE:** Multidisciplinary team-based approach for comprehensive preoperative pulmonary rehabilitation including intensive nutritional support for lung cancer patients.

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


**AUTORES / AUTHORS:** Harada H; Yamashita Y; Misumi K; Tsubokawa N; Nakao J; Matsutani J; Yamasaki M; Ohkawachi T; Taniyama K

**INSTITUCIÓN / INSTITUTION:** Department of Respiratory Surgery, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan. haradah@kure-nh.go.jp

**RESUMEN / SUMMARY:** BACKGROUND: To decrease the risk of postoperative complication, improving general and pulmonary conditioning preoperatively should be considered essential for patients scheduled to undergo lung surgery. OBJECTIVE: The aim of this study is to develop a short-term beneficial program of preoperative pulmonary rehabilitation for lung cancer patients. METHODS: From June 2009, comprehensive preoperative pulmonary rehabilitation (CHPR) including intensive nutritional support was performed prospectively using a multidisciplinary team-based approach. Postoperative complication rate and the transitions of pulmonary function in CHPR were compared with historical data of conventional preoperative pulmonary rehabilitation (CVPR) conducted since June 2006. The study population was limited to patients who underwent standard lobectomy. RESULTS: Postoperative complication rate in the CVPR (n = 29) and CHPR (n = 21) were 48.3% and 28.6% (p = 0.2428), respectively. Those in patients with Charlson Comorbidity Index scores >/=2 were 68.8% (n = 16) and 27.3% (n = 11), respectively (p = 0.0341) and those in patients with preoperative risk score in Estimation of Physiologic Ability and Surgical Stress scores >0.3 were 57.9% (n = 19) and 21.4% (n = 14), respectively (p = 0.0362). Vital capacities of pre- and post intervention before surgery in the CHPR group were 2.63+/−0.65 L and 2.75+/−0.63 L (p = 0.0043), respectively; however, their transition in the CVPR group was not statistically significant (p = 0.6815). Forced expiratory volumes in one second of pre- and post intervention before surgery in the CHPR group were 1.73+/−0.46 L and 1.87+/−0.46 L (p = 0.0012), respectively; however, their transition in the CVPR group was not statistically significant (p = 0.6424). CONCLUSIONS: CHPR appeared to be a beneficial and effective short-term preoperative rehabilitation protocol, especially in patients with poor preoperative conditions.

[637]
TÍTULO / TITLE: - Continued erlotinib maintenance and salvage radiation for solitary areas of disease progression: a useful strategy in selected non-small cell lung cancers?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s12094-013-1035-Z
AUTORES / AUTHORS: - Marquez-Medina D; Chachoua A; Martin-Marco A; Desai AM; Garcia-Reglero V; Salud-Salvia A; Muggia F
INSTITUCIÓN / INSTITUTION: - Medical Oncology Department, University Hospital Arnau de Vilanova, Avda. Rovira Roure, Lleida, España, dmarmed@hotmail.com.
RESUMEN / SUMMARY: - PURPOSE: Advanced non-small cell lung cancer (NSCLC) is a common and lethal malignancy that has rarely benefited from chemotherapy. Erlotinib is highly effective in NSCLC patients selected by clinical characteristics and/or the presence of epidermal growth factor receptor-sensitizing mutations. However, the way to delay or bypass erlotinib resistance is not systematically addressed. Different erlotinib-failure modes have been reported in NSCLC, and strategies to prolong erlotinib efficacy are perhaps adaptable to them. We report the feasibility and efficacy of continued erlotinib maintenance and local salvage radiation to overcome erlotinib resistances in selected NSCLC patients. PATIENTS AND METHODS: Thirty of 52 consecutive erlotinib-treated advanced NSCLC from the NYU Langone Medical Center and the Arnau de Vilanova Hospital of Lleida responded initially to erlotinib. Twenty-six patients eventually showed a generalized-progression to erlotinib, and four progressed in solitary tumor sites. These four patients were treated with continued erlotinib maintenance and local salvage radiation. RESULTS: The progression-free survival (PFS) was statistically similar in patients with oligo or generalized-progression to erlotinib. However, all four cases with solitary-progression did benefit from continued erlotinib maintenance and salvage radiation with 41-140 % prolongation of PFS. It was reflected in an improved overall survival when they were compared with patients with generalized-progression (76.4 vs. 19.9 months; p = 0.018). CONCLUSION: Continued erlotinib maintenance and local salvage radiation is feasible and could contribute to a better outcome in selected NSCLC patients with solitary-progression to erlotinib. Prospective randomized trials of this strategy are warranted.

[638]
TÍTULO / TITLE: - In lung cancer patients where a malignant pleural effusion is found at operation could resection ever still be justified?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

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A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was whether surgery could ever be justified in non-small cell lung cancer patients with an unexpected malignant pleural effusion at surgery. Eight papers were chosen to answer the question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. Study limitations included a lack of retrospective studies, the heterogeneous patient population and various treatments applied. Three papers found that surgery-compared to exploratory thoracotomy-was associated with a survival advantage in cases of minimal pleural disease. One paper showed that the median survival time of 58.8 months in patients with pleural effusion was better than that of patients with more extensive pleural dissemination as pleural nodule (10 months; P = 0.0001) or pleural nodule with effusion (19.3 months; P = 0.019). Another study showed that pleural effusion patients with N0-1 status had a median survival time more than 5 years longer than patients with similar or more extensive pleural dissemination but with N2-N3 status. A further study showed a better 5-year survival time in patients with pleural effusion, than in patients with pleural nodule (22.9% vs. 8.9%, respectively; P = 0.45). In two papers, surgery vs. exploratory thoracotomy had better survival in cases of N0 status and of complete tumour resection independently of pleural dissemination. Different strategies were employed to obtain freedom from macroscopic residual tumour, including pneumonectomy, lobar resection or, to a lesser extent, pleurectomy in patients having pleural dissemination. Only one paper reported a worse median survival time after pneumonectomy than for more limited resections (12.8 vs. 24.1 months, respectively; P = 0.0018). In the remaining papers, no comparison between the different resections was made. In all studies except one, surgery was a component of multimodal treatment. Intrapleural chemotherapy was largely applied with systemic adjuvant chemotherapy and/or radiotherapy. The study period and/or year of publication of most papers was 10 years or more, this may explain the different chemotherapy regimens used in the various studies. No current guidelines support surgery over conservative therapy and the identified studies in this review are not strong enough to change this recommendation.

[639]

**TÍTULO / TITLE:** Fast-tracking investigation and staging of patients with lung cancer.

**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
RESUMEN / SUMMARY: Standardized clinical care pathways for the investigation of patients with lung cancer allow for a reduction in the time interval between suspicion of lung cancer and treatment, lower costs, increased patient satisfaction, and quality of care. It may also be associated with a modest increase in survival.

[640]

TÍTULO / TITLE: Pleurodesis with povidone-iodine, as an effective procedure in management of patients with malignant pleural effusion.

RESUMEN / SUMMARY: OBJECTIVE: Overtime, malignant pleural effusion (MPE) arises in advanced-stages of malignancies and frequently heralds a poor prognosis. If the underlying malignancy is chemo sensitive, systemic chemotherapy may control pleural effusion. A common method for the management of the patients with refractory MPE is pleurodesis through the introduction of sclerosing agents such as talc, bleomycin administered/instilled into the pleural cavity. However, the present prospective study aimed to investigate the efficacy and safety of pleurodesis with povidone-iodine (Betadine) in patients with MPE admitted in Sari General Hospital during 2008-2011. METHODS: Thirty-six patients who underwent pleurodesis by instilling povidone-iodine through a thoracostomy tube, as a bedside procedure were enrolled in the study. For evaluating the effect of povidone-iodine on thyroid gland, the authors measured the thyroid function tests before and after the pleurodesis at 1 week. RESULTS: The response to this procedure was complete in 26 patients (72.2%) and partial in 7 patients (19.4%). Treatment failure was displayed in 3 patients (8.3%). The overall success rate was 91.6%. In post-procedure, the most common complaints of the patients were pain...
(35.9%) followed by dyspnea, burning and fever. Povidone-iodine does not affect on thyroid function tests. CONCLUSIONS: Povidone-iodine is an effective, inexpensive, safe and feasible agent for chemical pleurodesis in management of MPE.

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[641]
TITULO / TITLE: - Complete response of 7 years’ duration after chemoradiotherapy followed by gefitinib in a patient with intramedullary spinal cord metastasis from lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2012.12.09
AUTORES / AUTHORS: - Hata Y; Takai Y; Takahashi H; Takagi K; Isobe K; Hasegawa C; Shibuya K; Goto H; Tamaki K; Sato F; Otsuka H
INSTITUCIÓN / INSTITUTION: - Department of Chest Surgery, Toho University Omori Medical Center, Tokyo, Japan;
RESUMEN / SUMMARY: - Intramedullary spinal cord metastasis is a rare but serious complication which causes rapid progression of neurological deficits. Here we report a 35-year-old man presenting with increasing leg pain and gait disturbance, 8 months after surgery for lung adenocarcinoma. Spinal magnetic resonance imaging revealed an intramedullary tumor at the Th7/8 level. Radiotherapy at 35 Gy resulted in transient symptomatic improvement, but during chemotherapy with vinorelbine and cisplatin, symptoms worsened again. Gefitinib was then administered; the patient improved after 2 weeks and has now maintained a complete response for 7 years.

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[642]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
  ●●Enlace a la Editora de la Revista http://bmj.com/search.dtl
  ●●Enlace al texto completo (gratuito o de pago) 1136/bcr-2013-009318
AUTORES / AUTHORS: - D’Antonio A; Addesso M; Caleo O; Caleo A
INSTITUCIÓN / INSTITUTION: - Department of Pathologic Anatomy, AUO San Giovanni di Dio e Ruggi d’Aragona, Salerno, Italy.
RESUMEN / SUMMARY: - Although primary neoplasms of adrenal gland are uncommon, adrenal metastases are frequently encountered in patients with
malignancy, and lung is the most common primary tumour site. Among primary tumours of the adrenal gland non-Hodgkin’s lymphoma (NHL) is a very rare entity. We describe a case of a 79-year-old man with a previous diagnosis of adenocarcinoma of the lung who presented after 2 years with a unilateral adrenal gland mass. A solitary metastasis from pulmonary carcinoma was suspected and a laparoscopic adrenalectomy was performed. Histological examination revealed a diffuse large B-cell NHL. The patient was treated with CHOP regimen plus rituximab and a total remission was achieved. After an 8-month follow-up the patient was free of disease. This is the first reported case of a rare non-synchronous tumoral combination involving lung and adrenal gland, emphasising at the incidental discovery of the NHL during a procedure performed for a pulmonary adenocarcinoma.

[643]

**TÍTULO / TITLE:** - Assessment of recurrence of non-small cell lung cancer after therapy using CT and Integrated PET/CT.

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


**AUTORES / AUTHORS:** - Opoka L; Szolkowska M; Podgajny Z; Kunikowska J; Baranska I; Blasinska-Przerwa K; Jakubowska L; Rudzinski P; Bestry I; Roszkowski-Sliz K

**INSTITUCIÓN / INSTITUTION:** - Department of Radiology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland. lucyna.opoka@wp.pl

**RESUMEN / SUMMARY:** - INTRODUCTION: Non-small cell lung cancer (NSCLC) has become the leading cause of cancer-related deaths in Poland. Follow-up of patients with NSCLC is aimed at early detection of local recurrence, metastatic process, treatment-related complications or second primary lung cancer. We investigated the diagnostic accuracy of FDG-PET-CT in the detection of recurrence of NSCLC after treatment. MATERIAL AND METHODS: Seventy-two NSCLC patients (19 females, 56 males), stage I to IV, who had undergone surgery and/or radiation therapy, occasionally associated with chemotherapy, were retrospectively included in our study. Chest radiographs and thoracic computed tomography (CT) were performed to localize the abnormality prior to PET-CT. All the patients underwent CT and PET-CT in the period from January 2008 until January 2012. All PET images were interpreted in conjunction with thoracic CT. PET-CT and CT diagnoses were correlated with pathological diagnoses. RESULTS: Forty-five patients had recurrent tumour. Tumour recurrence was observed more often in men than in women and also in case of neoplastic cell emboli in lymphatic or blood vessels. In three patients second primary lung cancer was diagnosed. False positive diagnosis of relapse based on PET-CT was obtained in 4 patients, mainly due to inflammatory lesions. The accuracy of PET-CT for diagnosis of recurrence was 94.4% (95% CI 91; 100). CONCLUSIONS: FDG PET-CT was the best method to differentiate recurrent
bronchogenic carcinoma from inflammatory lesions, especially at post-therapeutic sites. It has been shown that PET-CT is more accurate method than CT in recurrent NSCLC. PET-CT results had a further impact on the clinical management and treatment planning.

[644]
TÍTULO/TITLE: - In vitro and in vivo Evaluation of the Antitumor Efficiency of Resveratrol Against Lung Cancer.
RESUMEN/SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES/AUTHORS: - Yin HT; Tian QZ; Guan L; Zhou Y; Huang XE; Zhang H
INSTITUCIÓN/INSTITUTION: - Department of Radiotherapy, the Central Hospital of Xuzhou, Affiliated Hospital of Southeast University, Xuzhou, China E-mail: huangxin06@yahoo.com.cn, zhpu@163.com.
RESUMEN/SUMMARY: - Lung cancer remains a deadly disease with unsatisfactory overall survival. Resveratrol (Res) has the potential to inhibit growth of several types of cancer such as prostate and colorectal examples. In the current study, we evaluated in vitro and in vivo anticancer efficiency of Res in a xenograft model with A549 cells. Cell inhibition effects of Res were measured by MTT assay. Apoptosis of A549 cells was assessed with reference to caspase-3 activity and growth curves of tumor volume and bodyweight of the mice were measured every two days. In vitro cytotoxicity evaluation indicated Res to exert dose-dependent cell inhibition effects against A549 cells with activation of caspase-3. In vivo evaluation showed Res to effectively inhibit the growth of lung cancer in a dose-dependent manner in nude mice. Therefore, we believe that Res might be a promising phytomedicine for cancer therapy and further efforts are needed to explore this potential therapeutic strategy.

[645]
TÍTULO/TITLE: - Reversal of multidrug resistance by cisplatin-loaded magnetic Fe3O4 nanoparticles in A549/DDP lung cancer cells in vitro and in vivo.
RESUMEN/SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 2147/IJN.S43752
AUTORES/AUTHORS: - Li K; Chen B; Xu L; Feng J; Xia G; Cheng J; Wang J; Gao F; Wang X
INSTITUCIÓN/INSTITUTION: - Department of Hematology, Key Medical Disciplines of Jiangsu Province, Zhongda Hospital, Medical School, Southeast University, Nanjing.
The purpose of this study was to explore whether magnetic Fe3O4 nanoparticles (Fe3O4-MNP) loaded with cisplatin (Fe3O4-MNP-DDP) can reverse DDP resistance in lung cancer cells and to investigate mechanisms of multidrug resistance in vitro and in vivo. MTT assay showed that DDP inhibited both A549 cells and DDP-resistant A549 cells in a time-dependent and dose-dependent manner, and that this inhibition was enhanced by Fe3O4-MNP. An increased rate of apoptosis was detected in the Fe3O4-MNP-DDP group compared with a control group and the Fe3O4-MNP group by flow cytometry, and typical morphologic features of apoptosis were confirmed by confocal microscopy. Accumulation of intracellular DDP in the Fe3O4-MNP-DDP group was greater than that in the DDP group by inductively coupled plasma mass spectrometry. Further, lower levels of multidrug resistance-associated protein-1, lung resistance-related protein, Akt, and Bad, and higher levels of caspase-3 genes and proteins, were demonstrated by reverse transcriptase polymerase chain reaction and Western blotting in the presence of Fe3O4-MNP-DDP. We also demonstrated that Fe3O4-MNP enhanced the effect of DDP on tumor growth in BALB/c nude mice bearing DDP-resistant human A549 xenografts by decreasing localization of lung resistance-related protein and Ki-67 immunoreactivity in cells. There were no apparent signs of toxicity in the animals. Overall, these findings suggest potential clinical application of Fe3O4-MNP-DDP to increase cytotoxicity in lung tumor xenografts.

[646]

TÍTULO / TITLE: - In vitro and in vivo effects of geranylgeranyltransferase I inhibitor P61A6 on non-small cell lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zimonjic DB; Chan LN; Tripathi V; Lu J; Kwon O; Popescu NC; Lowy DR; Tamanoi F
INSTITUCIÓN / INSTITUTION: - Department of Microbio., Immunol, & Molec, Genet., Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA. fuyut@microbio.ucla.edu.
RESUMEN / SUMMARY: - BACKGROUND: Lung cancer is the leading cause of cancer-related mortality. Therapies against non-small cell lung cancer (NSCLC) are particularly needed, as this type of cancer is relatively insensitive to chemotherapy and radiation therapy. We recently identified GGTI compounds that are designed to block geranylgeranylation and membrane association of signaling proteins including the Rho family G-proteins. One of the GGTIs is P61A6 which inhibits proliferation of human cancer cells, causes cell cycle effects with G1 accumulation and exhibits tumor-suppressing effects with
human pancreatic cancer xenografts. In this paper, we investigated effects of P61A6 on non-small cell lung cancer (NSCLC) cells in vitro and in vivo.

METHODS: Three non-small cell lung cancer cell lines were used to test the ability of P61A6 to inhibit cell proliferation. Further characterization involved analyses of geranylgeranylation, membrane association and activation of RhoA, and anchorage-dependent and -independent growth, as well as cell cycle effects and examination of cell cycle regulators. We also generated stable cells expressing RhoA-F, which bypasses the geranylgeranylation requirement of wild type RhoA, and examined whether the proliferation inhibition by P61A6 is suppressed in these cells. Tumor xenografts of NSCLC cells growing in nude mice were also used to test P61A6’s tumor-suppressing ability. RESULTS: P61A6 was shown to inhibit proliferation of NSCLC lines H358, H23 and H1507. Detailed analysis of P61A6 effects on H358 cells showed that P61A6 inhibited geranylgeranylation, membrane association of RhoA and caused G1 accumulation associated with decreased cyclin D1/2. The effects of P61A6 to inhibit proliferation could mainly be ascribed to RhoA, as expression of the RhoA-F geranylgeranylation bypass mutant rendered the cells resistant to inhibition by P61A6. We also found that P61A6 treatment of H358 tumor xenografts growing in nude mice reduced their growth as well as the membrane association of RhoA in the tumors. CONCLUSION: Thus, P61A6 inhibits proliferation of NSCLC cells and causes G1 accumulation associated with decreased cyclin D1/2. The result with the RhoA-F mutant suggests that the effect of P61A6 to inhibit proliferation is mainly through the inhibition of RhoA. P61A6 also shows efficacy to inhibit growth of xenograft tumor.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Demirci E; Daloglu F; Gundogdu C; Calik M; Sipal S; Akgun M
INSTITUCION / INSTITUTION: - Department of Pathology, 2Department of Chest Disease, Medical Faculty, Ataturk University, Erzurum, Turkey E-mail cemgun98@hotmail.com.
RESUMEN / SUMMARY: - Background: Lung cancer is the most frequent cancer among men and second highest among women overall, including in Turkey. Cigarette smoking is the most important etiologic factor for the development of cancer in both men and women. Objective: To determine the lung cancer incidence in Northeastern Anatolia Region of Turkey with a focus on clinical properties, cancer subtypes, the relationships of tumors with cigarette smoking and radiological properties of the lesions. Materials and Methods: In a retrospective study design, 566 lung cancer cases diagnosed at the Pathology
Department of Ataturk University in Erzurum over the last seven years extending from January 2006 to June 2012 were investigated. The results were compared with statistical analyses. Results: The most common histopathological subtype of primary bronchogenic carcinoma in our study was found to be the squamous cell carcinoma, 46.1% (261 out of 566), and the second was small cell lung carcinoma 15.7% (89 out of 566). Based on our data, an overall male predominance was noted with a male/female ratio of 6.1/1. While 296 (52.2%) of the patients were found to be smokers at the time of diagnosis, 125 (22.0%) were nonsmokers and 145 (25.6%) were ex-smokers. Smoking status was found to have a strong correlation with primary lung cancer (p <0.05), and there were significant differences between males and females (p<0.001). Conclusion: Although relative prominence of subtypes of lung cancers differ between Turkish and other populations, lung cancer overall remains as an important health problem in Turkey. Our findings stress the critical need for effective cancer prevention programs such as anti-smoking campaigns.

[648]

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

AUTORES / AUTHORS: - Caffo O; Dipasquale M; Murgia V; Veccia A; Galligioni E

INSTITUCIÓN / INSTITUTION: - Santa Chiara Hospital, Department of Medical Oncology, Largo Medaglie d'Oro, 38100 Trento, Italy +390461902121; +390461903364; orazio.caffo@apss.tn.it.

RESUMEN / SUMMARY: - Introduction: Non-small-cell lung cancer (NSCLC) is one of the most frequently diagnosed cancers, and one of the leading causes of cancer-related mortality. As most newly diagnosed patients present distant metastases, chemotherapy is the treatment of choice. Chemotherapy also plays a central role in postoperative and radical treatment in addition to radiotherapy. Areas covered: This paper reviews the role of vinorelbine, both alone and in combination with platinum-derivates, in the treatment of NSCLC. The authors review its efficacy at different stages of disease and under different conditions. Specifically, the authors evaluate its pharmacokinetic and toxicity profile and provide insight into its future as an NSCLC therapeutic. Expert opinion: In the first-line treatment of advanced NSCLC, the use of vinorelbine-based regimens may be less efficacious in controlling disease than other combinations. However, since their activity is not related to histology, vinorelbine still has potential as a first-line treatment for NSCLC patients in whom histology has
failed to distinguish non-squamous from squamous histotypes. The use of an oral formulation may furthermore improve tolerability and patient compliance. Vinorelbine should be the drug of choice in the adjuvant setting as the vinorelbine/cisplatin doublet is the only regimen so far that has led to a survival gain in two Phase III trials. In patients aged > 70 years, vinorelbine (together with gemcitabine) should furthermore be the reference drug for first- and second-line therapy when single-agent chemotherapy is the treatment of choice. However, new efforts still need to be made to develop oral schedules for NSCLC.

[649]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

[650]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Morrison BJ; Steel JC; Morris JC
INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Medicine, University of Cincinnati, Cincinnati, OH 45267-0562, USA.

AUTORES / AUTHORS: - Perez BA; Ghafoori AP; Lee CL; Johnston SM; Li Y; Moroshek JG; Ma Y; Mukherjee S; Kim Y; Badea CT; Kirsch DG
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Duke University Medical Center Durham, NC, USA.

RESUMEN / SUMMARY: - Purpose: Non-small cell lung cancers (NSCLC) are a heterogeneous group of carcinomas harboring a variety of different gene mutations. We have utilized two distinct genetically engineered mouse models of human NSCLC (adenocarcinoma) to investigate how genetic factors within tumor parenchymal cells influence the in vivo tumor growth delay after one or two fractions of radiation therapy (RT). Materials and Methods: Primary lung adenocarcinomas were generated in vivo in mice by intranasal delivery of an adenovirus expressing Cre-recombinase. Lung cancers expressed oncogenic Kras(G12D) and were also deficient in one of two tumor suppressor genes: p53 or Ink4a/ARF. Mice received no radiation treatment or whole lung irradiation in a single fraction (11.6 Gy) or in two 7.3 Gy fractions (14.6 Gy total) separated by
24 h. In each case, the biologically effective dose (BED) equaled 25 Gy10.
Response to RT was assessed by micro-CT 2 weeks after treatment.
Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and
immunohistochemical staining were performed to assess the integrity of the p53
pathway, the G1 cell-cycle checkpoint, and apoptosis. Results: Tumor growth
rates prior to RT were similar for the two genetic variants of lung
adenocarcinoma. Lung cancers with wild-type (WT) p53 (LSL-Kras;
Ink4a/ARF(FL/FL) mice) responded better to two daily fractions of 7.3 Gy
compared to a single fraction of 11.6 Gy (P = 0.002). There was no statistically
significant difference in the response of lung cancers deficient in p53 (LSL-Kras;
p53(FL/FL) mice) to a single fraction (11.6 Gy) compared to 7.3 Gy x 2 (P =
0.23). Expression of the p53 target genes p21 and PUMA were higher and
bromodeoxyuridine uptake was lower after RT in tumors with WT p53.
Conclusion: Using an in vivo model of malignant lung cancer in mice, we
demonstrate that the response of primary lung cancers to one or two fractions
of RT can be influenced by specific gene mutations.

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[651]

TÍTULO / TITLE: - Clinical implication of microscopic anthracotic pigment in
mediastinal staging of non-small cell lung cancer by endobronchial ultrasound-
guided transbronchial needle aspiration.

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


AUTORES / AUTHORS: - Park YS; Lee J; Pang JC; Chung DH; Lee SM; Yim JJ;
Yang SC; Yoo CG; Kim YW; Han SK

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary and Critical Care Medicine,
Department of Internal Medicine and Lung Institute, Seoul National University
College of Medicine, Seoul, Korea. mdyspark@gmail.com

RESUMEN / SUMMARY: - Microscopic anthracotic pigment (MAP) is frequently
observed in endobronchial ultrasound-guided transbronchial needle aspiration
(EBUS-TBNA) specimen in non-small cell lung cancer, but its clinical
interpretation is not well-known. The aim of this study was to evaluate the
clinical implication of MAP in mediastinal staging of non-small cell lung cancer.
From May 2010 to July 2011, consecutive potentially operable non-small cell
lung cancer patients who underwent EBUS-TBNA for mediastinal staging were
recruited. Of the total 133 patients, 102 (76.7%) were male patients. Median
age was 68 yr. Total 279 mediastinal lymph nodes were sampled by EBUS-
TBNA; station 4R (100, 35.8%) and station 7 (86, 30.8%) were the most
common sites. Malignant lymph nodes were 100 (35.8%). MAP was observed
in 61 (21.7%) lymph nodes, and among them only 3 were malignant lymph
nodes (P < 0.001). The lymph nodes with MAP were smaller (9.0 vs 10.8 mm, P = 0.001) and showed low standard uptake values on FDG-PET (4.4 vs 4.7, P = 0.256). In multivariate analysis, MAP was negatively associated with malignant lymph node (adjusted OR, 0.12; 95% CI, 0.03-0.42; P < 0.001). In potentially operable non-small cell lung cancer patients, MAP in endobronchial ultrasound-guided transbronchial needle aspiration specimens is strongly associated with benign mediastinal and hilar lymph nodes.

[652]
TÍTULO / TITLE: - Defective Lung Macrophage Function in Lung Cancer+/- Chronic Obstructive Pulmonary Disease (COPD/Emphysema)-Mediated by Cancer Cell Production of PGE2?
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago)
1371/journal.pone.0061573
AUTORES / AUTHORS: - Dehle FC; Mukaro VR; Jurisevic C; Moffat D; Ahern J; Hodge G; Jersmann H; Reynolds PN; Hodge S
INSTITUCIÓN / INSTITUTION: - Lung Research Laboratory, Hanson Institute, Adelaide, South Australia, Australia ; Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia.
RESUMEN / SUMMARY: - In chronic obstructive pulmonary disease (COPD/emphysema) we have shown a reduced ability of lung and alveolar (AM) macrophages to phagocytose apoptotic cells (defective 'efferocytosis'), associated with evidence of secondary cellular necrosis and a resultant inflammatory response in the airway. It is unknown whether this defect is present in cancer (no COPD) and if so, whether this results from soluble mediators produced by cancer cells. We investigated efferocytosis in AM (26 controls, 15 healthy smokers, 37 COPD, 20 COPD+ non small cell lung cancer (NSCLC) and 8 patients with NSCLC without COPD) and tumor and tumor-free lung tissue macrophages (21 NSCLC with/13 without COPD). To investigate the effects of soluble mediators produced by lung cancer cells we then treated AM or U937 macrophages with cancer cell line supernatant and assessed their efferocytosis ability. We qualitatively identified Arachidonic Acid (AA) metabolites in cancer cells by LC-ESI-MSMS, and assessed the effects of COX inhibition (using indomethacin) on efferocytosis. Decreased efferocytosis was noted in all cancer/COPD groups in all compartments. Conditioned media from cancer cell cultures decreased the efferocytosis ability of both AM and U937 macrophages with the most pronounced effects occurring with supernatant from SCLC (an aggressive lung cancer type). AA metabolites identified in cancer cells included PGE2. The inhibitory effect of PGE2 on efferocytosis, and the
involvement of the COX-2 pathway were shown. Efferocytosis is decreased in COPD/emphysema and lung cancer; the latter at least partially a result of inhibition by soluble mediators produced by cancer cells that include PGE2.

[653]
TÍTULO / TITLE: - Expression of the epithelial-mesenchymal transition-related proteins and their clinical significance in lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1186/1746-1596-8-89
AUTORES / AUTHORS: - Shi Y; Wu H; Zhang M; Ding L; Meng F; Fan X
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, Nanjing, China. fqmeng2004@126.com.
RESUMEN / SUMMARY: - BACKGROUND: Epithelial-mesenchymal transition (EMT) is defined as switching of polarized epithelial cells to a migratory fibroblastoid phenotype. EMT is known to be involved in the progression and metastasis of various cancers. The aim was to evaluate that whether EMT-related proteins' alterations are associated with clinicopathological features and prognosis in lung adenocarcinoma. METHODS: The expression of EMT-related proteins including cytokeratin, E-cadherin, TTF-1, beta-catenin, vimentin, Snail, Twist, CD44 was evaluated by immunohistochemistry using a tissue array method in the lung adenocarcinoma tissues of 95 patients. In addition, clinicopathological characteristics and survival were compared with the expression of EMT-related proteins. RESULTS: Loss of epithelial proteins and/or acquisition of the expression of mesenchymal proteins were observed in lung adenocarcinoma. These proteins’ alteration was associated with poor cell differentiation and poor patients' outcome, respectively. Subjects were divided into two groups according to the number of EMT-related proteins' alteration. A higher number of EMT-related proteins’ alteration was found to be significantly associated with unfavorable outcome. Multivariate analysis showed that a higher number of EMT-related proteins’ alteration was independently associated with poor prognosis. CONCLUSIONS: The number of EMT-related proteins' alteration is a significant prognostic marker to predict overall survival in patients with lung adenocarcinoma. The information generated will be valuable for the prognosis of patients with lung adenocarcinoma. VIRTUAL SLIDES: The virtual slides for this article can be found here: http://www.diagnosticpathology.diagnomx.eu/vs/1007838329872974.

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[654]
TÍTULO / TITLE: - Update of epidermal growth factor receptor-tyrosine kinase inhibitors in non-small-cell lung cancer.
RESUMEN / SUMMARY: Lung cancer is the leading cause of cancer-related death in the world. Prior to the era of targeted therapy, platinum-based doublet chemotherapy was the first-line therapy of choice for patients with metastatic non-small-cell lung cancer (NSCLC). The availability of agents that target epidermal growth factor receptor (EGFR)-tyrosine kinase, as well as inhibitors against anaplastic lymphoma kinase (ALK) gene rearrangement or ROS-1 gene rearrangement product, has provided promising clinical benefits in specific subpopulations of NSCLC. At present, only first-generation EGFR-tyrosine kinase inhibitors (TKIs) (erlotinib and gefitinib) are available for clinical use. Second-generation irreversible EGFR-TKIs, such as afatinib, are still in clinical trials. In current clinical practice, EGFR-TKI is the first-line treatment of choice for metastatic NSCLC patients with tumor EGFR mutation or as salvage therapy in NSCLC patients who received systemic chemotherapy previously. Platinum-based doublet chemotherapy continues to be the standard of care for those treatment-naive patients with EGFR wild-type tumor or unknown EGFR status. Even though all investigators agree with the use of EGFR-TKI as the first-line treatment in tumor EGFR-mutated patients, only 10-30% of NSCLC patients have mutated EGFR, and there was no obvious survival difference when EGFR-TKIs were used in a second-line setting versus a first-line treatment in EGFR-mutated patients. Thus, the molecular complexity of lung cancer emphasizes the need for optimizing treatment by seeking a more personalized approach to care, including searching for driver oncogenes, managing the emergence of resistance and overcoming that resistance, and optimizing the sequence of treatment. Numerous other novel targeted agents are now in clinical development, including new agents targeting novel pathways and those that may have the potential to overcome the limitations or resistance associated with currently available EGFR-TKIs. In this report, we review the clinical data of EGFR-TKIs as molecular-targeted therapies in NSCLC.
Discoveries over the last decade have fundamentally transformed the way we define lung cancer. Gone are the days of the simple binary classification system of non-small cell lung cancer (NSCLC) and small cell lung cancer. Today, accurate identification of the histological and molecular subtype of NSCLC is required for selecting standard cytotoxic chemotherapy and targeted therapies. The identification of anaplastic lymphoma kinase (ALK) rearrangements in 5-7% of NSCLC patients and the rapid clinical development of crizotinib for these patients is the most recent clinical example necessitating the proper identification of the molecular characteristics of NSCLC for treatment decisions. The discovery of ALK rearrangements in NSCLC serendipitously coincided with the development of crizotinib for other ALK or MET driven malignancies. The clinical development of crizotinib for ALK-positive NSCLC patients has been an amazing success story of translational medicine that relied on the prior clinical experience of other targeted predecessors (i.e. erlotinib in EGFR mutant NSCLC) and a compound ready for clinical development to gain expedited FDA approval. This review discusses the clinical development and use of crizotinib in NSCLC.
strategies used to treat lung cancer. A better understanding of these drug-resistance mechanisms could potentially benefit from the development of a more robust personalized medicine approach for the treatment of lung cancer.

[657]

**TÍTULO / TITLE:** Lung cancer incidence by smoking status in Korean men: 16-years of observations in the Seoul Male Cancer Cohort study.

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


**AUTORES / AUTHORS:** Bae JM; Li ZM; Shin MH; Kim DH; Lee MS; Ahn YO

**INSTITUCIÓN / INSTITUTION:** Department of Preventive Medicine, Jeju National University School of Medicine, Jeju, Korea. jmbae@jejunu.ac.kr

**RESUMEN / SUMMARY:** The relative risk (RR) of smoking and mortality of lung cancer in British doctors was previously reported to have increased throughout a 40-yr period. Here, we evaluated this RR based on the incidence of lung cancer in Korean men using a longer follow-up period. We compared our data to the RR reported in a study using a 10-yr follow-up period; the subjects and methods were identical to those of the previous paper with the exception of the follow-up period, which ended on December 31, 2008. We found that the RR of smoking habits in patients with lung cancer did not increase, and that the data showed narrowing 95% confidence intervals over a longer observation in Korean men. Estimated lung cancers attributable to smoking were 55.6%. These results highlight the need for an intervention program to help patients quit smoking in Korea.

[658]

**TÍTULO / TITLE:** Abnormal methylation of seven genes and their associations with clinical characteristics in early stage non-small cell lung cancer.

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


**AUTORES / AUTHORS:** Zhao Y; Zhou H; Ma K; Sun J; Feng X; Geng J; Gu J; Wang W; Zhang H; He Y; Guo S; Zhou X; Yu J; Lin Q

**INSTITUCIÓN / INSTITUTION:** State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200032;

**RESUMEN / SUMMARY:** To identify novel abnormally methylated genes in early stage non-small cell lung cancer (NSCLC), we analyzed the methylation status of 13 genes (ALX1, BCL2, FOXL2, HPP1, MYF6, OC2, PDGFRA, PHOX2A,
PITX2, RARB, SIX6, SMPD3 and SOX1) in cancer tissues from 101 cases of stage I NSCLC patients and lung tissues from 30 cases of non-cancerous lung disease controls, using methylation-specific PCR (MSP). The methylation frequencies (29.70-64.36%) of 7 genes (MYF6, SIX6, SOX1, RARB, BCL2, PHOX2A and FOLX2) in stage I NSCLC were significantly higher compared with those in non-cancerous lung disease controls (P<0.05). The co-methylation of SIX6 and SOX1, or the co-methylation of SIX6, RARB and SOX1 was associated with adenocarcinoma (ADC), and the co-methylation of BCL2, RARB and SIX6 was associated with smoking. A panel of 4 genes (MYF6, SIX6, BCL2 and RARB) may offer a sensitivity of 93.07% and a specificity of 83.33% in the diagnosis of stage I NSCLC. Furthermore, we also detected the expression of 8 pathological markers (VEGF, HER-2, P53, P21, EGFR, CHGA, SYN and EMA) in cancer tissues of stage I NSCLC by immunohistochemistry, and found that high expression levels of p53 and CHGA were associated with the methylation of BCL2 (P=0.025) and PHOX2A (P=0.023), respectively. In this study, among the 7 genes which demonstrated hypermethylation in stage I NSCLC compared with non-cancerous lung diseases, 5 genes (MYF6, SIX6, PHOX2A, FOLX2 and SOX1) were found for the first time to be abnormally methylated in NSCLC. Further study of these genes shed light on the carcinogenesis of NSCLC.

[659]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Ahn MJ; Park SY; Kim WK; Cho JH; Chang BJ; Kim DJ; Ahn JS; Park K; Han JS
INSTITUCIÓN / INSTITUTION: Division of Hematology-Oncology, Department of Internal Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul 135-710, Korea;
RESUMEN / SUMMARY: Phospholipase D (PLD) has an important role in various biological functions including vesicular transport, endocytosis, exocytosis, cell migration, and mitosis. These cellular biological processes are deregulated in the development of various human tumors. In order to explore the relationship between the PLD1 gene and risk of non-small cell lung cancer (NSCLC), single nucleotide polymorphisms (SNP) in the PLD1 exon region were surveyed in 211 NSCLC patients and 205 normal controls. In this study, we identified six SNPs at exon 23 in the PLD1 gene. Among the six SNPs, the most notable was a heterozygous A to C transition at nucleotide 2698 (A2698C, p<0.001). In addition, the genotype frequencies of A2744C (AC+CC) and A2756C (AC+CC) were associated with gender (female, A2744C and A2756C: p=0.071) in NSCLC patients. Interestingly, although the SNP A2698C did not cause change
in amino acid, correlation between odd ratio of NSCLC patients and the SNP A2698C was observed to be statistically significant.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kitamura J; Takahashi Y; Neri S; Tomii K; Katakami N
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Kobe City Medical Center General Hospital.
RESUMEN / SUMMARY: - A lung squamous cell carcinoma complicated by lung abscess was found in a 38-year-old female never smoker. After a transbronchial lung biopsy, she complained of chest pain and had a persistent fever. A right middle lobectomy was performed to alleviate her symptoms and complete surgical resection was achieved. She reported no exposure to factors that increase the likelihood of lung cancer. Unknown factors or the patient’s lung cancer susceptibility might cause the disease. Survival time is generally shorter in young patients than old patients, but careful observation and aggressive treatment can improve prognoses. A case such as this is rare in the extant literature.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhou H; Luo Y; Chen JH; Hu J; Luo YZ; Wang W; Zeng Y; Xiao L
INSTITUCIÓN / INSTITUTION: - Tumor Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan 410013, P.R. China.
RESUMEN / SUMMARY: - The upregulation of tribbles homolog 3 (TRB3), a pseudokinase in mammals, has been observed in several types of malignant cancer, including thyroid, ovarian, liver and colorectal cancer. However, the pathological role and the regulatory mechanism of TRB3 in cancer remain unknown. In the current study, we demonstrated that the expression of TRB3 was upregulated in non-small cell lung cancer (NSCLC), correlating with tumor metastasis, disease recurrence and poor survival in patients. Knocking down TRB3 in aggressive lung cancer cell lines was demonstrated to significantly inhibit their malignant behaviors, including in vitro invasion and cell proliferation,
as well as in vivo metastasis and tumor growth. The correlation between TRB3 and Notch 1 expression revealed that Notch 1 was downregulated by the knockdown of TRB3 in the lung adenocarcinoma cell lines. These results have provided insights into the correlation between TRB3 expression and lung cancer progression, and thus may have potential for the prognosis and therapy of lung cancer.

[662]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yu Y; He J
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Cancer Institute and Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, 100021, China.
RESUMEN / SUMMARY: - Non-small-cell lung cancer (NSCLC) is the most common cause of premature death among the malignant diseases worldwide. The current staging criteria do not fully capture the complexity of this disease. Molecular biology techniques, particularly gene expression microarrays, proteomics, and next-generation sequencing, have recently been developed to facilitate effectively its molecular classification. The underlying etiology, pathogenesis, therapeutics, and prognosis of NSCLC based on an improved molecular classification scheme may promote individualized treatment and improve clinical outcomes. This review focuses on the molecular classification of NSCLC based on gene expression microarray technology reported during the past decade, as well as their applications for improving the diagnosis, staging and treatment of NSCLC, including the discovery of prognostic markers or potential therapeutic targets. We highlight some of the recent studies that may refine the identification of NSCLC subtypes using novel techniques such as epigenetics, proteomics, or deep sequencing.

[663]
TÍTULO / TITLE: - Spect-guidance to Reduce Radioactive Dose to Functioning Lung for Stage III Non-small Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wang ZT; Wei LL; Ding XP; Sun MP; Sun HF; Li BS
INSTITUCIÓN / INSTITUTION: - Sixth Department of Radiation Oncology, Shandong Cancer Hospital, Jinan, China E-mail: baoshenglicn@163.com.
Objective: To investigate the treatment effect of additional information obtained by single photon emission computed tomography (SPECT) lung perfusion imaging (LPI) in the radiotherapy planning process for patients with stage III non-small cell lung cancer (NSCLC).

Methods: 39 patients with stage III NSCLC were enrolled. Gross tumor volume (GTV) was outlined by SPECT/CT images, SPECT-LPIs being used to define functional lung (FL) and non-functional lung (NFL) regions. Two sets of IMRT plans were designed to deliver 64Gy to PTV. One was a regular IMRT plan using CT images only (Plan 1), and the other was a corresponding IMRT plan using co-registered images (Plan 2). FLVx (the % volume of functional lung receiving >/=x Gy) and WLVx (% volume of whole lung to receive >/=x Gy) were compared by paired Student’s t test. Kendalls correlation was used to analyze the factor(s) related with the FLV20 decrease. Results: Compared with plan 1, both WLVx and FLVx were decreased in plan 2. WLV10, WLV15, WLV20, WLV25, WLV30 and WLV35 decreased 9.7%, 13.8%, 17.2%, 12.9%, 9.8% and 9.8%, and FLV10, FLV15, FLV20, FLV25, FLV30 and FLV35 decreased 10.8%, 14.6%, 17.3%, 14.5%, 14.5% and 10.5%. FLVx decreased significantly compared with WLVx. There were significant differences in WLV10, WLV15, WLV20, WLV25, WLV3 and FLV10, FLV15, FLV20, FLV25, FLV30 between plan 1 and plan 2 (P=0.002, 0.000, 0.000, 0.005, 0.027 and 0.002, 0.000, 0.000, 0.006, 0.010). According to Kendall correlation analysis, NFL had a negative relation with the percentage FLV20 decrease (r=-0.559, P<0.01), while the distance of PTV and NFL center had a significantly positive relation with the percentage of FLV20 decrease (r=0.768, P<0.01). Conclusion: Routine use of SPECT-LPI for patients undergoing radiotherapy planning for stage III NSCLC appears warranted.

[664]


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


AUTORES / AUTHORS: - Vergnenegre A; Borget I; Chouaid C

INSTITUCIÓN / INSTITUTION: - Service de Pathologie Respiratoire et d’Allergologie, CHU Dupuytren, Limoges, France ; Inserm, U707, Paris, France.

RESUMEN / SUMMARY: - BACKGROUND: The incidence of lung cancer and the cost of drug treatment have increased dramatically in the last decade. This article examines the costs of new target agents, such as tyrosine kinase inhibitors (TKIs) and anti-angiogenic drugs. METHODS: This study uses PubMed research to focus on the topics of lung cancer, economics, and new
targeted therapies. RESULTS: The published papers only addressed TKIs and anti-angiogenic antibodies. For gefitinib, the results favored a clinical-based selection, despite the low number of studies. Erlotinib was studied in second line and as a maintenance treatment (with the studies reaching opposite conclusions in terms of cost-effectiveness). Economic analyses were not in favor of bevacizumab, but the studies on this topic were very heterogeneous. CONCLUSION: The economic impact of a drug depends on the health care system organization. Future clinical trials must include economic analyses, particularly with TKIs in the first line.

[665]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Liu F; Liu D; Yang Y; Zhao S
INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, P.R. China.
RESUMEN / SUMMARY: Chemotherapy is one of the main methods of cancer treatment and is known to induce autophagy in cancer cells. The main mechanism of chemotherapeutic agents is to promote apoptosis. In the process of chemotherapy, there is a unique association between autophagy and apoptosis. In this study, MDC staining, Hoechst 33342 staining and flow cytometry were used to explore the effects of autophagy on chemotherapy-induced apoptosis in A549 lung cancer cells and the association between autophagy and apoptosis was investigated via the addition of an autophagic inhibitor (3-methyladenine, 3-MA). This study demonstrated that cisplatin and paclitaxel were able to induce autophagy and apoptosis in A549 lung cancer cells and the inhibition of autophagy promoted cisplatin and paclitaxel-induced apoptosis. Furthermore, autophagy may play a protective role in the processes of cisplatin and paclitaxel-induced apoptosis.

[666]
TÍTULO / TITLE: Sinonasal papilloma in Chiang Mai University Hospital.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Fooanant S; Pattarasakulchai T; Tananuvat R; Sittitrai P; Chaiyasate S; Roongrutowattanasiri K; Srivanitchapoom C
INSTITUCIÓN / INSTITUTION: Department of Otolaryngology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.
RESUMEN / SUMMARY: OBJECTIVE: To study sinonasal papilloma patients in terms of clinical characteristics, treatment, outcome, and complications.
MATERIAL AND METHOD: A retrospective descriptive study was done. Sinonasal papilloma data were gathered between 1999 and 2009. There were 63 available patients from the 82 cases. RESULTS: There were nine cases of nasal papilloma (14.3%) and 54 of inverted papilloma (85.7%). The mean age of the inverted papilloma group was higher than the nasal papilloma group (54 +/- 12.97 years vs. 42.4 +/- 24.8 years). The most common symptom was unilateral nasal obstruction. There were three cases of synchronous malignancy in the inverted papilloma and two metachronous (9.3%). Thirty-nine patients (72%) could be followed-up for more than three months. Recurrence was more common in the inverted papilloma group than nasal papilloma (37% vs. 11.1%). The 50% recurrent time of the endoscopic group was 51 weeks and the external group was 14 weeks. The recurrence of the external approach group was 1.59 times the endoscopic group. Ten surgical complications were found in eight inverted papilloma patients (16%) and included three in the endoscopic and five in the external group. Most of them were minor. They were hypoesthesia and epiphora. CONCLUSION: Sinonasal inverted papilloma was common, able to recur and associated with malignancy. Though this was a limited retrospective study, it showed lower recurrence on the endoscopic approach. The life-long follow-up is needed in all cases.

[667]

TÍTULO / TITLE: Genetic variation in ESR2 and estrogen receptor-beta expression in lung tumors.

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


AUTORES / AUTHORS: Song JY; Siegfried JM; Diergaard B; Land SR; Bowser R; Stabile LP; Dacic S; Dhir R; Nukui T; Romkes M; Weissfeld JL

INSTITUCIÓN / INSTITUTION: Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh and University of Pittsburgh Cancer Institute, Pittsburgh, PA, United States.

RESUMEN / SUMMARY: Objective: To investigate the association between inherited variation in the estrogen receptor beta (ERbeta) gene (ESR2) and ERbeta lung tumor expression, a phenotype that possibly affects survival differently in men and women. Methods: We genotyped 135 lung cancer patients for 22 ESR2 single nucleotide polymorphisms (SNPs) and measured nuclear and cytoplasmic ERbeta expression by immunohistochemistry (IHC) in their primary lung tumor. Distributing Allred ERbeta IHC scores according to ESR2 genotype classified under a dominant genetic model, we used rank sum tests to identify ESR2 SNPs significantly associated (p<0.05) with ERbeta
expression. Results: 35%, 35%, and 29% of lung tumors showed no/low (Allred<6), intermediate (Allred 6-7), and maximal (Allred 8) cytoplasmic ERbeta expression, whereas 13%, 27%, and 60% showed no/low, intermediate, and maximal nuclear ERbeta expression. For SNPs rs8021944, rs1256061 and rs10146204, ERbeta expression was higher according to the rank sum test in lung tumors from patients with at least one minor allele. For each of these three SNPs, the odds of maximal (Allred 8) relative to no/low (Allred<6) ERbeta expression was 3-fold higher in tumors from patients with at least one minor allele than in tumors from patients homozygous for the common allele. Conclusion: Inherited variability in ESR2 may determine ERbeta lung tumor expression.

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[668]

TÍTULO / TITLE: - A phase II study of irinotecan as a third- or fourth-line treatment for advanced non-small cell lung cancer: NJLCG0703.

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


AUTORES / AUTHORS: - Matsubara N; Maemondo M; Inoue A; Ishimoto O; Watanabe K; Sakakibara T; Fukuhara T; Morikawa N; Tanaka M; Sugawara S; Nukiwa T

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Miyagi Cancer Center, 47-1 Nodayama, Medeshima-shiote, Natori, 981-1293, Japan.

RESUMEN / SUMMARY: - BACKGROUND: We aimed to evaluate the efficacy and safety of irinotecan monotherapy as a third- or fourth-line treatment for advanced non-small cell lung cancer (NSCLC) patients. METHODS: Patients with advanced NSCLC refractory to 2 or more previous regimens were treated with 80 mg/m2 irinotecan on days 1, 8, and 15, every 4 weeks. The primary endpoint was the overall response rate (ORR), whereas secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity profiles. RESULTS: From December 2007 to April 2009, 32 patients (median age, 60 years) were enrolled. Most of the patients (75.0%) were male, and 18.8% had a performance status of 2. Six partial responses to irinotecan monotherapy were observed (ORR, 18.8%; 95% confidence interval, 5.3%-32.3%). The disease control rate (DCR) was 78.1%, median PFS was 4.0 months, and median survival time (MST) was 10.4 months. Grade 3-4 neutropenia was observed in 22% of patients, but other toxic effects were moderate. No cases of grade 3-4 diarrhea or treatment-related death were noted. Of the 15 patients for whom progressive disease represented the best response to previous treatment regimens, 2 exhibited a partial response and 9 showed stable disease after irinotecan monotherapy, with a DCR of 73.3%,

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median PFS of 4.4 months, and MST of 8.2 months. CONCLUSIONS: Irinotecan monotherapy is effective for advanced NSCLC patients who have previously failed 2 or more treatment regimens.

[669]

TITULO / TITLE: Slug increases sensitivity to tubulin-binding agents via the downregulation of betaIII and betaIVA-tubulin in lung cancer cells.

RESUMEN / SUMMARY: Transcription factor Slug/SNAI2 (snail homolog 2) plays a key role in the induction of the epithelial mesenchymal transition in cancer cells; however, whether the overexpression of Slug mediates the malignant phenotype and alters drug sensitivity in lung cancer cells remains largely unclear. We investigated Slug focusing on its biological function and involvement in drug sensitivity in lung cancer cells. Stable Slug transfectants showed typical morphological changes compared with control cells. Slug overexpression did not change the cellular proliferations; however, migration activity and anchorage-independent growth activity with an antiapoptotic effect were increased. Interestingly, stable Slug overexpression increased drug sensitivity to tubulin-binding agents including vinorelbine, vincristine, and paclitaxel (5.8- to 8.9-fold increase) in several lung cancer cell lines but did not increase sensitivity to agents other than tubulin-binding agents. Real-time RT-PCR (polymerase chain reaction) and western blotting revealed that Slug overexpression downregulated the expression of betaIII and betaIVA-tubulin, which is considered to be a major factor determining sensitivity to tubulin-binding agents. A luciferase reporter assay confirmed that Slug suppressed the promoter activity of betaIVA-tubulin at a transcriptional level. Slug overexpression enhanced tumor growth, whereas Slug overexpression increased drug sensitivity to vinorelbine with the downregulation of betaIII and betaIV-tubulin in vivo. Immunohistochemistry of Slug with clinical lung cancer samples showed that Slug overexpression tended to be involved in response to tubulin-binding agents. In conclusion, our data indicate that Slug mediates an aggressive phenotype including enhanced migration activity, anoikis suppression, and tumor growth, but increases sensitivity to tubulin-binding agents.
agents via the downregulation of betaIII and betaIVa-tubulin in lung cancer cells.

[670]
TÍTULO / TITLE: - A case of adolescent lung cancer resectable by the microthoracoscopic one-port method.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Nakagawa T; Hamanaka R; Nakano T; Oiwa K; Nakazato K; Ogura G; Masuda R; Nakamura N; Iwazaki M
INSTITUCIÓN / INSTITUTION: - Division of General Thoracic Surgery, Department of Surgery Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. k167999@is.icc.u-tokai.ac.jp
RESUMEN / SUMMARY: - An abnormal shadow was detected in a 15-year-old male adolescent by routine chest radiography during a school medical examination. Further detailed examination demonstrated stage IA primary lung adenocarcinoma in the right inferior lobe. The patient then underwent surgery. The right inferior lobe was resected, and the mediastinal lymph node was dissected by the microthoracoscopic one-port method. Thoracoscopic surgery for stage IA primary adult lung cancer has been established. However, no report has been published on thoracoscopic surgery, particularly the one-port method, for rare primary lung cancer in an adolescent, as demonstrated in this case.

[671]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yu J; Wang Q; Chen N; Sun Y; Wang X; Wu L; Chen S; Yuan H; Xu A; Wang J
INSTITUCIÓN / INSTITUTION: - School of Nuclear Science and Technology, University of Science and Technology of China, Hefei 230027, PR China.
RESUMEN / SUMMARY: - Mitochondrial transcription factor A (TFAM), the first well-characterized transcription factor from vertebrate mitochondria, is closely related to mitochondrial DNA (mtDNA) maintenance and repair. Recent evidence has shown that the ratio of mtDNA to nuclearDNA (nDNA) is increased in both human cells and murine tissues after ionizing radiation (IR). However, the underlying mechanism has not as yet been clearly identified. In the present study, we demonstrated that in human lung adenocarcinoma A549 cells, expression of TFAM was upregulated, together with the increase of the relative mtDNA copy number and cytochrome c oxidase (COX) activity after
alpha-particle irradiation. Furthermore, short hairpin RNA (shRNA)-mediated TFAM knockdown inhibited the enhancement of the relative mtDNA copy number and COX activity caused by alpha-particles. Taken together, our data suggested that TFAM plays a crucial role in regulating mtDNA amplification and mitochondrial biogenesis under IR conditions.

[672]
**TITULO / TITLE:** Biomarkers and molecular testing for early detection, diagnosis, and therapeutic prediction of lung cancer.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary

**AUTORES / AUTHORS:** Pass HI; Beer DG; Joseph S; Massion P
**INSTITUCIÓN / INSTITUTION:** Department of Cardiothoracic Surgery, NYU Langone Medical Center, 530 First Avenue, 9V, New York, NY 10016, USA. Harvey.Pass@nyumc.org

**RESUMEN / SUMMARY:** The search for biomarkers in the management of lung cancer involves the use of multiple platforms to examine changes in gene, protein, and microRNA expression. Multiple studies have been published in an attempt to describe early detection, diagnostic, prognostic, and predictive biomarkers using chiefly tissues and blood elements. Studies are characterized by a lack of commonality of specific biomarkers, and a lack of validated, clinically useful markers. The future of biomarker discovery as a means of tailoring therapy for patients with lung cancer will involve next-generation sequencing along with collaborative efforts to integrate and validate candidate markers.

[673]
**TITULO / TITLE:** Dose impact of a carbon fiber couch for stereotactic body radiation therapy of lung tumors.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**REVISTA / JOURNAL:** Nihon Hoshasen Gijutsu Gakkai Zasshi. 2013 Apr;69(4):400-6.

**AUTORES / AUTHORS:** Tominaga H; Araki F; Shimohigashi Y; Kanetake N; Tomiyama Y; Kawasaki K; Iwashita Y; Sakata J; Okuda T
**INSTITUCIÓN / INSTITUTION:** Kumamoto Radiosurgery Clinic.

**RESUMEN / SUMMARY:** The aim of this study was to measure the dose attenuation caused by a carbon fiber radiation therapy table (Imaging Couch Top; ICT, BrainLab) and to evaluate the dosimetric impact of ICT during stereotactic body radiation therapy (SBRT) in lung tumors. The dose attenuation of ICT was measured using an ionization chamber and modeled by means of a
treatment planning system (TPS). SBRT was planned with and without ICT in a lung tumor phantom and ten cases of clinical lung tumors. The results were analyzed from isocenter doses and a dose-volume histogram (DVH): D95, Dmean, V20, V5, homogeneity index (HI), and conformity index (CI). The dose attenuation of the ICT modeled with TPS agreed to within +/-1% of the actually measured values. The isocenter doses, D95 and Dmean with and without ICT showed differences of 4.1-5% for posterior single field and three fields in the phantom study, and differences of 0.6-2.4% for five fields and rotation in the phantom study and six fields in ten clinical cases. The dose impact of ICT was not significant for five or more fields in SBRT. It is thus possible to reduce the dose effect of ICT by modifying the beam angle and beam weight in the treatment plan.

[674]

TITULO / TITLE: Depleting NFAT1 expression inhibits the ability of invasion and migration of human lung cancer cells.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Liu JF; Zhao SH; Wu SS
INSTITUCIÓN / INSTITUTION: Department of thoracic surgery, General Hospital of Beijing Military Region, Nan Men Cang 5, Dongcheng District, Beijing, China. jifu.liu@yahoo.cn.
RESUMEN / SUMMARY: BACKGROUND: Nuclear factor of activated T-cells (NFAT) is a general name applied to a family of transcription factors shown to be important in immune response. One or more members of the NFAT family are expressed in most cells of the immune system. NFAT1 is considered to involve in the development of cardiac, skeletal muscle, nervous systems, and tumorigenesis. METHODS: In the current study, we analyzed MEKK1 expression in 159 surgically resection non-small cell lung cancer patient’s samples by immunohistochemistry and determined its role in SK-EMS-1 cells via RNAi experiment. RESULTS: The abilities of invasion, motility, and adhesion of SK-EMS-1 cells were detected by transwell assay, wound healing assay and adhesion assay, respectively. The result showed NFAT1 was highly expressed in lung tumor tissues instead of adjacent lung tissues (54.1% vs 8.8%, p < 0.05); its overexpression was positively correlated with lymph node metastasis (p < 0.05). Depleting its expression in SK-EMS-1 cells can inhibit its invasion and migration abilities significantly (p < 0.05); and also can reduce proliferation of lung cancer cells (p < 0.05). CONCLUSION: Our study showed NFAT1 plays an important role in origination, invasion and metastasis of non-small lung cancer cells; its underlying action mechanism needs further study.

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[675]

**TÍTULO / TITLE:** Genetic variants associated with increased risk of malignant pleural mesothelioma: a genome-wide association study.

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


Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0061253

**AUTORES / AUTHORS:** Matullo G; Guarrera S; Betti M; Fiorito G; Ferrante D; Voglino F; Cadby G; Di Gaetano C; Rosa F; Russo A; Hirvonen A; Casalone E; Tunesi S; Padoan M; Giordano M; Aspesi A; Casadio C; Ardissone F; Ruffini E; Betta PG; Libener R; Guaschino R; Piccolini E; Neri M; Musk AW; de Klerk NH; Hui J; Beilby J; James AL; Creaney J; Robinson BW; Mukherjee S; Palmer LJ; Mirabelli D; Ugolini D; Bonassi S; Magnani C; Dianzani I

**INSTITUCIÓN / INSTITUTION:** Human Genetics Foundation, HuGeF, Turin, Italy; Department of Medical Sciences, University of Turin, Turin, Italy.

**RESUMEN / SUMMARY:** Asbestos exposure is the main risk factor for malignant pleural mesothelioma (MPM), a rare aggressive tumor. Nevertheless, only 5-17% of those exposed to asbestos develop MPM, suggesting the involvement of other environmental and genetic risk factors. To identify the genetic risk factors that may contribute to the development of MPM, we conducted a genome-wide association study (GWAS; 370,000 genotyped SNPs, 5 million imputed SNPs) in Italy, among 407 MPM cases and 389 controls with a complete history of asbestos exposure. A replication study was also undertaken and included 428 MPM cases and 1269 controls from Australia. Although no single marker reached the genome-wide significance threshold, several associations were supported by haplotype-, chromosomal region-, gene- and gene-ontology process-based analyses. Most of these SNPs were located in regions reported to harbor aberrant alterations in mesothelioma (SLC7A14, THRBI, CEBP350, ADAMTS2, ETV1, PVT1 and MMP14 genes), causing at most a 2-3-fold increase in MPM risk. The Australian replication study showed significant associations in five of these chromosomal regions (3q26.2, 4q32.1, 7p22.2, 14q11.2, 15q14). Multivariate analysis suggested an independent contribution of 10 genetic variants, with an Area Under the ROC Curve (AUC) of 0.76 when only exposure and covariates were included in the model, and of 0.86 when the genetic component was also included, with a substantial increase of asbestos exposure risk estimation (odds ratio, OR: 45.28, 95% confidence interval, CI: 21.52-95.28). These results showed that genetic risk factors may play an additional role in the development of MPM, and that these should be taken into account to better estimate individual MPM risk in individuals who have been exposed to asbestos.

[676]
Cytoreductive surgery combined with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination.

**RESUMEN / SUMMARY:** BACKGROUND: The treatment of thymoma or thymic carcinoma with pleural dissemination remains controversial due to the unpredictable natural history of this tumor. Our study discusses the combination of cytoreductive surgery with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. METHODS: From February 2008 to January 2010, there were four patients with pleural thymoma metastases undergoing cytoreductive surgery and intrathoracic hyperthermic perfusion with chemotherapy at our department. After video-assisted thoracoscopic surgery, the hyperthermic perfusion system was set up for hyperthermic intrapleural chemotherapy. The thoracic cavity was perfused at a speed of approximately 1.8-2.3 L/min with 0.9% normal saline. The intrathoracic temperature remained between 42 degrees C and 43 degrees C. The perfusion process lasted for 2 hours. RESULTS: There were no perioperative deaths. During the hyperthermic perfusion, the patient’s core temperature varied from 36.3 degrees C and 39.3 degrees C and pulse varied from 59 beats/min and 126 beats/min. Intraoperative sinus tachycardia occurred in two elderly patients. No hematologic toxicity and nephrotoxicity was observed within 1 week after surgery. Postoperative pneumonia occurred in one elderly patient. Patients were followed up for 1-4 years. One elderly patient died of heart failure 1 year after surgery. There were no patients with local recurrence or metastases to distant sites. CONCLUSIONS: Cytoreductive surgery and intrathoracic hyperthermic perfusion with chemotherapy may be effective in treating thymoma or thymic carcinoma with pleural dissemination and has an encouraging impact on the patients’ long-term survival.

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Canadian lung cancer relative risk from radon exposure for short periods in childhood compared to a lifetime.

**RESUMEN / SUMMARY:** BACKGROUND: The treatment of thymoma or thymic carcinoma with pleural dissemination remains controversial due to the unpredictable natural history of this tumor. Our study discusses the combination of cytoreductive surgery with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. METHODS: From February 2008 to January 2010, there were four patients with pleural thymoma metastases undergoing cytoreductive surgery and intrathoracic hyperthermic perfusion with chemotherapy at our department. After video-assisted thoracoscopic surgery, the hyperthermic perfusion system was set up for hyperthermic intrapleural chemotherapy. The thoracic cavity was perfused at a speed of approximately 1.8-2.3 L/min with 0.9% normal saline. The intrathoracic temperature remained between 42 degrees C and 43 degrees C. The perfusion process lasted for 2 hours. RESULTS: There were no perioperative deaths. During the hyperthermic perfusion, the patient’s core temperature varied from 36.3 degrees C and 39.3 degrees C and pulse varied from 59 beats/min and 126 beats/min. Intraoperative sinus tachycardia occurred in two elderly patients. No hematologic toxicity and nephrotoxicity was observed within 1 week after surgery. Postoperative pneumonia occurred in one elderly patient. Patients were followed up for 1-4 years. One elderly patient died of heart failure 1 year after surgery. There were no patients with local recurrence or metastases to distant sites. CONCLUSIONS: Cytoreductive surgery and intrathoracic hyperthermic perfusion with chemotherapy may be effective in treating thymoma or thymic carcinoma with pleural dissemination and has an encouraging impact on the patients’ long-term survival.

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**AUTORES / AUTHORS:** Yu L; Jing Y; Ma S; Li F; Zhang YF

**INSTITUCIÓN / INSTITUTION:** Department of Thoracic Surgery, Beijing Tongren Hospital, Capital Medical University, People’s Republic of China.

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**AUTORES / AUTHORS:** Chen J
RESUMEN / SUMMARY: Long-term exposure to elevated indoor radon concentrations has been determined to be the second leading cause of lung cancer in adults after tobacco smoking. With the establishment of a National Radon Program in Canada in 2007 thousands of homes across the country have been tested for radon. Although the vast majority of people are exposed to low or moderate radon concentrations; from time to time; there are homes found with very high concentrations of radon. Among those living in homes with very high radon concentrations, it is typically parents of young children that demonstrate a great deal of concern. They want to know the equivalent risk in terms of the lifetime relative risk of developing lung cancer when a child has lived in a home with high radon for a few years. An answer to this question of risk equivalency is proposed in this paper. The results demonstrate clearly that the higher the radon concentration; the sooner remedial measures should be undertaken; as recommended by Health Canada in the Canadian radon guideline.

TÍTULO / TITLE: A Case of Desmoid-Type Fibromatosis Arising after Thoracotomy for Lung Cancer with a Review of the English and Japanese Literature.

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


AUTORES / AUTHORS: Mori T; Yamada T; Ohba Y; Yoshimoto K; Ikeda K; Shiraishi K; Suzuki M

INSTITUCIÓN / INSTITUTION: Department of Thoracic Surgery, Graduate School of Medical Sciences, Kumamoto University.

RESUMEN / SUMMARY: Chest wall desmoid-type fibromatoses are rare, locally aggressive tumors that occasionally arise from previous thoracotomy sites. Tumors arising from previous sites of thoracotomy to treat malignant disease should be discriminated from the pleural dissemination of the previous malignancy. In this study, we report a case of desmoid-type fibromatosis arising from a site for thoracotomy to treat lung cancer. Additionally we reviewed 15 reported cases of desmoid-type fibromatosis following thoracotomy and summarized their features. A 62-year-old woman was found to have a tumor on computed tomography (CT) at a 1-year routine checkup for lung cancer. The tumor (diameter, 3.4 cm) was located at the previous thoracotomy site. Positron emission tomography (PET) revealed mild 18F-fluorodeoxyglucose (FDG) accumulation in the tumor, with a maximal standardized uptake value (SUVmax) of 1.9. CT-guided biopsy revealed only fibrous tissue. Eighteen months after the biopsy, CT revealed apparent tumor growth, and a biopsy revealed the same histology observed previously. The tumor was removed and
diagnosed as desmoid-type fibromatosis. Currently, the patient is alive without recurrence 4 years after desmoid surgery.

[679]
**TÍTULO / TITLE:** Treatment of cervical vertebral (C1) metastasis of lung cancer with radiotherapy: A case report.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** Ni X; Wu P; Wu C; Wu J; Ji M; Gu X; Tian B
**INSTITUCIÓN / INSTITUTION:** Departments of Oncology, The Third Affiliated Hospital, Soochow University, Changzhou, Jiangsu 213003;
**RESUMEN / SUMMARY:** The present study discusses a patient with C1 vertebral metastasis from adenocarcinoma of the left lung. The patient was a 31-year-old female suffering from neck pain who was referred by her physician. Magnetic resonance imaging revealed osteolytic destruction of the C1 vertebra. Chest and computed tomographic scans revealed lung carcinoma changes involving the left lung. A biopsy confirmed adenocarcinoma of the left lung. Abnormal activity was present in the cervical spine (C1) region in a radionuclide bone scan. The patient was then referred to an oncologist. The spine was stabilized with a rigid collar and a course of radiation therapy and pain medication was initiated immediately. At the 9-month follow-up examination, there was no evidence of progression on the MRI scans and the main neck symptoms had disappeared. At present, the overall survival (OS) time is 11 months. Patients complaining of new onset back or neck pain should be assumed to have vertebral metastasis until proven otherwise. Trivial trauma should be taken seriously in these cases and investigated with appropriate clinical, laboratory and imaging examinations.

[680]
**TÍTULO / TITLE:** Targeted agents in non-small cell lung cancer therapy: What is there on the horizon?
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
**AUTORES / AUTHORS:** Villaflor VM; Salgia R
**INSTITUCIÓN / INSTITUTION:** Department of Medicine, Section of Hematology/Oncology University of Chicago, Chicago, IL, USA.
**RESUMEN / SUMMARY:** Lung cancer is a heterogeneous group of diseases. There has been much research in lung cancer over the past decade which has advanced our ability to treat these patients with a more personalized approach.
The scope of this paper is to review the literature and give a broad understanding of the current molecular targets for which we currently have therapies as well as other targets for which we may soon have therapies. Additionally, we will cover some of the issues of resistance with these targeted therapies. The molecular targets we intend to discuss are epidermal growth factor receptor (EGFR), Vascular endothelial growth factor (VEGF), anaplastic large-cell lymphoma kinase (ALK), KRAS, C-MET/RON, PIK3CA, ROS-1, RET Fibroblast growth factor receptor (FGFR). Ephrins and their receptors, BRAF, and immunotherapies/vaccines. This manuscript only summarizes the work which has been done to date and in no way is meant to be comprehensive.

[681]


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


AUTORES / AUTHORS: - Cao S; Wang C; Huang X; Dai J; Hu L; Liu Y; Chen J; Ma H; Jin G; Hu Z; Xu L; Shen H

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology and Biostatistics, Modern Toxicology Laboratory of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 210009, China;

RESUMEN / SUMMARY: - Apoptosis plays a key role in inhibiting tumor growth, progression and resistance to anti-tumor therapy. We hypothesized that genetic variants in apoptotic genes may affect the prognosis of lung cancer. To test this hypothesis, we selected 38 potentially functional single nucleotide polymorphisms (SNPs) from 12 genes (BAX, BCL2, BID, CASP3, CASP6, CASP7, CASP8, CASP9, CASP10, FAS, FASLG and MCL1) involved in apoptosis to assess their prognostic significance in lung cancer in a Chinese case cohort with 568 non-small cell lung cancer (NSCLC) patients. Thirty-five SNPs passing quality control underwent association analyses, 11 of which were shown to be significantly associated with NSCLC survival (P < 0.05). After Cox stepwise regression analyses, 3 SNPs were independently associated with the outcome of NSCLC (BID rs8190315: P = 0.003; CASP9 rs4645981: P = 0.007 and FAS rs1800682: P = 0.016). A favorable survival of NSCLC was significantly associated with the genotypes of BID rs8190315 AG/GG (adjusted HR = 0.65, 95% CI: 0.49-0.88), CASP9 rs4645981 AA (HR = 0.22, 95% CI: 0.07-0.69) and FAS rs1800682 GG (adjusted HR = 0.67, 95% CI: 0.46-0.97). Time-dependent receptor operation curve (ROC) analysis revealed that the area under curve (AUC) at year 5 was significantly increased from 0.762 to 0.819 after adding the risk score of these 3 SNPs to the clinical risk score. The remaining 32 SNPs were not significantly associated with NSCLC prognosis.
after adjustment for these 3 SNPs. These findings indicate that BID rs8190315, CASP9 rs4645981 and FAS rs1800682 polymorphisms in the apoptotic pathway may be involved in the prognosis of NSCLC in the Chinese population.

[682]
**TÍTULO / TITLE:** Erratum to: Cisplatin plus oral vinorelbine as first-line treatment for advanced non-small-cell lung cancer: a prospective study confirming that the day-8 hemogram is unnecessary.

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

**REVISTA / JOURNAL:** Clin Transl Oncol. 2013 May 14.

**AUTORES / AUTHORS:** Provencio M; Sanchez A; Artal A; Sanchez Torres JM; Garcia Gomez R; Constenla M; de Castro J; Domine M; Vinolas N; Sanchez A; Perez FJ

**INSTITUCIÓN / INSTITUTION:** Department of Medical Oncology, Hospital Universitario Puerta de Hierro, Calle Manuel de Falla 1, 28222, Madrid, España, mprovenciop@gmail.com.

[683]
**TÍTULO / TITLE:** Musashi1 as a potential therapeutic target and diagnostic marker for lung cancer.

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

**REVISTA / JOURNAL:** Oncotarget. 2013 May 21.

**AUTORES / AUTHORS:** Wang XY; Yu H; Linnoila RI; Li L; Li D; Mo B; Okano H; Penalva LO; Glazer RI

**INSTITUCIÓN / INSTITUTION:** Cell and Cancer Biology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

**RESUMEN / SUMMARY:** Lung cancer remains one of the leading causes of cancer-related deaths worldwide with a 5-year survival rate of less than 20%. One approach to improving survival is the identification of biomarkers to detect early stage disease. In this study, we investigated the potential of the stem cell and progenitor cell marker, Musashi1 (Msi1), as a diagnostic marker and potential therapeutic target for lung cancer. Functional studies in A549 bronchioalveolar carcinoma and NCI-H520 squamous cell carcinoma cells revealed that Msi1 was enriched in spheroid cultures of tumor cells and in the CD133+ cell population. Downregulation of Msi1 by lentivirus-mediated expression of an Msi1 shRNA reduced spheroid colony proliferation. Growth inhibition was associated with reduced nuclear localization of beta-catenin and inhibition of the processing of intracellular Notch. In primary lung cancer, Msi1 protein expression was elevated in 86% of 202 tissue microarray specimens, and Msi1 mRNA was increased in 80% of 118 bronchoscopic biopsies,
including metastatic disease, but was rarely detected in adjacent normal lung tissue and in non-malignant diseased tissue. Msi1 was expressed in a diffuse pattern in most tumor subtypes, except in squamous cell carcinomas, where it appeared in a focal pattern in 50% of specimens. Thus, Msi1 is a sensitive and specific diagnostic marker for all lung cancer subtypes.

[684]

TÍTULO / TITLE: - Prognostic implications of treatment delays in the surgical resection of lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Evans WK
INSTITUCIÓN / INSTITUTION: - Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario L8V 5C2, Canada. Bill.Evans@jcc.hhsc.ca
RESUMEN / SUMMARY: - The survival of patients with lung cancer remains low in most developed countries, which is largely attributable to the advanced stage of the disease when it presents. It seems obvious that if lung cancer could be found at an earlier stage, the prognosis of patients would be improved. The evidence from the medical literature on this point is conflicting; most studies suggest that delays in diagnosis are not prognostically important. When strategies are in place to expedite the investigation of individuals suspected of having lung cancer, the stage of disease typically shifts toward earlier-stage disease and resection rates increase.

[685]

TÍTULO / TITLE: - Cytologically diagnosed metastatic small cell lung carcinoma in the mandibular soft tissue.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Pektas ZO; Gunhan O
INSTITUCIÓN / INSTITUTION: - Department of Oral and Maxillofacial Surgery, Baskent University, Adana Medical and Research Center, Kazim Karabekir mah. 37/A, Yuregir 01120, Adana, Turkey. Tel. +90 (322) 3228282 Ext. 1081. Fax. +90 (322) 3227979. E-mail: opektas@baskent-adn.edu.tr.
RESUMEN / SUMMARY: - Metastatic tumors to the oral and maxillofacial region are relatively rare, they constitute 1% of all malignant tumors of the oral cavity. The purpose of this case report is to evaluate the efficiency of fine needle aspiration cytology (FNAC) in the diagnosis of metastatic small cell lung carcinoma. A 50-year-old female patient presenting with a 4x5 cm firm, hemorrhagic, tender swelling on the left mandibular bicuspid gingiva was
evaluated. Her past medical history revealed a mass measuring 8x5 cm in the left pulmonary hilar area with pleural effusion, which was diagnosed as small cell lung carcinoma. A FNAC was performed to the oral mucosal swelling, and cytological examination revealed metastatic small cell lung carcinoma. The duration between diagnosis of the primary lung and development of metastasis was 6 months. The FNAC is a rapid, non-invasive, and safe diagnostic method when carried out with a proper technique, and proved to be a valuable adjunct to a careful physical and radiological examination of the oro-maxillofacial lesions.

[686]

**TITULO / TITLE:** - Malignant pleural mesothelioma: incidence, etiology, diagnosis, treatment, and occupational health.

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


**AUTORES / AUTHORS:** - Neumann V; Loseke S; Nowak D; Herth FJ; Tannapfel A

**INSTITUCIÓN / INSTITUTION:** - German Mesothelioma Register at the Institute of Pathology, Ruhr-University Bochum, Bergmannsheil University Hospital.

**RESUMEN / SUMMARY:** - BACKGROUND: The incidence of malignant mesothelioma in Germany is about 20 cases per million persons per year. Its association with asbestos exposure, usually occupational, has been unequivocally demonstrated. Even though the industrial use of asbestos was forbidden many years ago, new cases of mesothelioma continue to appear because of the long latency of the disease (median, 50 years). Its diagnosis and treatment still present a major challenge for ambulatory and in-hospital care and will do so for years to come. METHODS: This article is based on a selective review of the literature, along with data from the German Mesothelioma Register. RESULTS: 1397 people died of mesothelioma in Germany in 2010. A plateau in the incidence of the disease is predicted between 2015 and 2030. Most mesotheliomas arise from the pleura. The histological subtype and the Karnofsky score are the main prognostic factors. Only limited data are now available to guide treatment with a combination of the available methods (chemotherapy, surgery, radiotherapy). The prognosis is still poor, with a median survival time of only 12 months. Symptom control and the preservation of the patient’s quality of life are the main aspects of care for patients with mesothelioma. CONCLUSION: The incidence of mesothelioma is not expected to drop in the next few years. The available treatments are chemotherapy, surgery, and radiotherapy. Specialized treatment centers now increasingly provide multimodal therapy for treatment of mesothelioma.
Long-Term Treatment with Erlotinib for EGFR Wild-Type Non-Small Cell Lung Cancer: A Case Report.

Enlace al Resumen / Link to its Summary


Enlace al texto completo (gratuito o de pago) 1159/000350680

Polychronidou G; Papakotoulas P

Theagenio Cancer Hospital, Thessaloniki, Greece.

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are known to have greater efficacy in EGFR mutation-positive non-small cell lung cancer (NSCLC), although erlotinib also has activity in wild-type disease. We report the successful long-term maintenance treatment of a patient with EGFR wild-type NSCLC with gefitinib and later erlotinib. The patient (male; 44 years old; smoker) was diagnosed with EGFR wild-type NSCLC after computer tomography had revealed a mediastinal mass, and histology and mutation testing had identified the tumor as an EGFR wild-type grade 3 adenocarcinoma. The patient received multiple rounds of chemotherapy, followed by gefitinib maintenance (3 years). Later on, he received erlotinib maintenance and developed a persistent rash (grade ½) that lasted throughout the treatment. The patient’s condition has remained stable on erlotinib for more than 5 years, with no evidence of progression. We describe the patient’s disease course and treatment in the context of EGFR TKI therapy and the prognostic factors for long-term clinical outcomes of NSCLC, including the development of erlotinib-induced rash.

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Small cell carcinoma of the oral cavity (cheek mucosa): a case report with an immunohistochemical and molecular genetic analysis.


Terada T

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Small cell carcinoma (SCC) of the oral cavity is extremely rare; only one case has been reported in the English Literature. The author herein reports the second case of SCC of the oral cavity. A 59-year-old man presented with oral tumor (5 cm) in the right cheek mucosa. A biopsy was taken. The HE histology was typical SCC consisting of small epithelial cells with hyperchromatic nuclei, molded nuclei, scant nucleocytoplasmic ratio, and negative nucleoli. Immunohistochemically, the tumor cells are positive for pancytokeratin (PCK) WSS, PCK MNF-116, cytokeratin (CK) 34BE12, CK5/6,
CK14, vimentin, KIT (CD117), CD56, synaptophysin, p53 protein, and Ki67 antigen (Ki-67 labeling = 70%). The tumor cells are negative for PCK AE1/3, PSK CAM5.2, CK7, CK8, CK18, CK19, CK20, EMA, NSE, chromogranin, platelet-derived growth factor-alpha (PDGFRA), CD45, CD45RO, CD3, CD20, CD30, CD79a, and bcl-2. A retrospective genetic analysis using PCR-direct sequencing method in paraffin sections identified no mutations of KIT (exons 9, 11, 13 and 17) and PDGFRA (exons 12 and 18) genes. Various imaging modalities including CT and MRI and upper and lower gastrointestinal endoscopy did not identified no tumors other than the oral tumor. Thus, the oral tumor was thought primary. The oral tumor rapidly enlarged, and distant metastases to cervical lymph nodes, ribs and iliac bones emerged. The patient is now treated by cisplatin-based chemotherapy 16 months after the first manifestation.

[689]

**TÍTULO / TITLE:** Diacylglycerol kinase eta modulates oncogenic properties of lung cancer cells.

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

**REVISTA / JOURNAL:** Clin Transl Oncol. 2013 Apr 10.

**AUTORES / AUTHORS:** Nakano T; Iravani A; Kim M; Hozumi Y; Lohse M; Reichert E; Crotty TM; Stafforini DM; Topham MK

**INSTITUCIÓN / INSTITUTION:** Huntsman Cancer Institute, University of Utah, 2000 East Circle of Hope, Salt Lake City, UT, 84112-5550, USA.

**RESUMEN / SUMMARY:** PURPOSE: Lung cancer is a leading cause of cancer deaths and efforts are underway to identify novel therapies to treat these tumors. Diacylglycerol kinase eta (DGKeta), an enzyme that phosphorylates diacylglycerol to form phosphatidic acid, has been shown to modulate MAPK signaling downstream of EGFR, which is an oncogenic driver in some lung cancers. Since mutations in EGFR and K-Ras are common in lung cancer, we hypothesized that limiting the function of DGKeta would attenuate oncogenic properties of lung cancer cells. METHODS: We determined the expression levels of DGKeta in a mouse models of mutant EGFR and K-Ras lung cancer and in human lung cancer cell lines with activating mutations in either EGFR or K-Ras. We also tested the effects of shRNA-mediated depletion of DGKeta in lung cancer cells and tested if DGKeta depletion augmented the effects of afatinib, a new generation EGFR inhibitor. RESULTS: DGKeta was expressed in malignant epithelium from mice with mutant EGFR or K-Ras lung cancer. It was also expressed in human lung cancer cell lines with EGFR or K-Ras mutations. Depleting DGKeta in lung cancer cell lines, harboring mutant EGFR, reduced their growth on plastic and in soft agar and also augmented the effects of afatinib, an EGFR inhibitor. DGKeta depletion also reduced growth of one of
two lung cancer cell lines that harbored mutant K-Ras. CONCLUSIONS: Our data indicate that DGGeta is a potential therapeutic target in lung cancers, especially those harboring EGFR mutations. Our findings warrant further studies to examine the effects of limiting its function in vivo.

[690]

**TÍTULO / TITLE:** - Effect of induction chemotherapy on estimated risk of radiation pneumonitis in bulky non-small cell lung cancer.

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


●●Enlace al texto completo (gratuito o de pago) 1016/j.meddos.2013.03.003

**AUTORES / AUTHORS:** - Amin NP; Miften M; Thornton D; Ryan N; Kavanagh B; Gaspar LE

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Wayne State University and Karmanos Cancer Center, Detroit, MI. Electronic address: npamin@gmail.com.

**RESUMEN / SUMMARY:** - Patients with bulky non-small cell lung cancer (NSCLC) may be at a high risk for radiation pneumonitis (RP) if treated with up-front concurrent chemoradiation. There is limited information about the effect of induction chemotherapy on the volume of normal lung subsequently irradiated. This study aims to estimate the reduction in risk of RP in patients with NSCLC after receiving induction chemotherapy. Between 2004 and 2009, 25 patients with Stage IV NSCLC were treated with chemotherapy alone (no surgery or radiation therapy [RT]) and had computed tomography (CT) scans before and after 2 cycles of chemotherapy. Simulated RT plans were created for the prechemotherapy and postchemotherapy scans so as to deliver 60Gy to the thoracic disease in patients who had either a >20% volumetric increase or decrease in gross tumor volume (GTV) from chemotherapy. The prechemotherapy and postchemotherapy scans were analyzed to compare the percentage of lung volume receiving >/=20Gy (V20), mean lung dose (MLD), and normal tissue complication probability (NTCP). Eight patients (32%) had a GTV reduction >20%, 2 (8%) had GTV increase >20%, and 15 (60%) had stable GTV. In the 8 responders, there was an absolute median GTV decrease of 88.1cc (7.3 to 351.6cc) or a 48% (20% to 62%) relative reduction in tumor burden. One had >20% tumor progression during chemotherapy, yet had an improvement in dosimetric parameters postchemotherapy. Among these 9 patients, the median decrease in V20, MLD, and NTCP was 2.6% (p<0.01), 2.1Gy (p<0.01), and 5.6% (p<0.01), respectively. Less than one-third of patients with NSCLC obtain >20% volumetric tumor reduction from chemotherapy alone. Even with that amount of volumetric reduction, the 5% reduced risk of RP was...
only modest and did not convert previously ineligible patients to safely receive definitive thoracic RT.

Hiwi knockdown inhibits the growth of lung cancer in nude mice.

Hiwi, a human homologue of the Piwi family, plays an important role in stem cell self-renewal and is overexpressed in various human tumors. This study aimed to determine whether an RNA interference-based strategy to suppress Hiwi expression could inhibit tumor growth in a xenograft mouse model. A rare population of SSCloAldebr cells was isolated and identified as lung cancer stem cells in our previous study. Plasmids containing U6 promoter-driven shRNAs against Hiwi or control plasmids were successfully established. The xenograft tumor model was generated by subcutaneously inoculating with lung cancer stem cell SSCloAldebr cells. After the tumor size reached about 8 mm in diameter, shRNA plasmids were injected into the mice via the tail vein three times a week for two weeks, then xenograft tumor growth was assessed. In nude mice, intravenously delivery of Hiwi shRNA plasmids significantly inhibited tumor growth compared to treatment with control scrambled shRNA plasmids or the vehicle PBS. No mice died during the experiment and no adverse events were observed in mice administered the plasmids. Moreover, delivery of Hiwi shRNA plasmids resulted in a significant suppressed expression of Hiwi and ALDH-1 in xenograft tumor samples, based on immunohistochemical analysis. Thus, shRNA-mediated Hiwi gene silencing in lung cancer stem cells by an effective in vivo gene delivery strategy appeared to be an effective therapeutic approach for lung cancer, and may provide some useful clues for RNAi gene therapy in solid cancers.

Inhibition of Metastatic Lung Cancer in C57BL/6 Mice by Marine Mangrove Rhizophora apiculata.

Inhibition of Metastatic Lung Cancer in C57BL/6 Mice by Marine Mangrove Rhizophora apiculata.
INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Karunya University, Karunya Nagar, Tamil Nadu, India E-mail: immunologykarunya@gmail.com, gurukarunya@gmail.com.

RESUMEN / SUMMARY: - Metastasis is one of the hallmarks of malignant neoplasms and is the leading cause of death in many cancer patients. A major challenge in cancer treatment is to find better ways to specifically target tumor metastasis. In this study, the anti-metastatic potential of the methanolic extract of Rhizophora apiculata (R.apiculata) was evaluated using the B16F-10 melanoma induced lung metastasis model in C57BL/6 mice. Metastasis was induced in C57BL/6 mice by injecting highly metastatic B16F-10 melanoma cells through the lateral tail vein. Simultaneous treatment with R.apiculata extract (10 mg/kg b.wt (intraperitoneal) significantly (p<0.01) inhibited pulmonary tumor nodule formation (41.1 %) and also increased the life span (survival rate) 107.3 % of metastatic tumor bearing animals. The administration of R.apiculata extract significantly (p<0.01) reduced biochemical parameters such as lung collagen hydroxyproline, hexosamine, uronic acid content, serum nitric oxide (NO), gamma-glutamyl transpeptidase (GGT) and sialic acid levels when compared to metastasis controls. These results correlated with lung histopathology analysis of R.apiculata extract treated mice showing reduction in lung metastasis and tumor masses. Taken together, our findings support that R.apiculata extract could be used as a potential anti-metastasis agent against lung cancer.

[693]

TÍTULO / TITLE: - Radiotherapy for a second primary lung cancer arising post-pneumonectomy: planning considerations and clinical outcomes.

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


Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.02.07

AUTORES / AUTHORS: - Senthi S; Haasbeek CJ; Lagerwaard FJ; Verbakel WF; de Haan PF; Slotman BJ; Senan S

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands.

RESUMEN / SUMMARY: - Background: Second primary non-small cell lung cancer (SPLC) is a significant cause of death amongst lung cancer survivors. As subsequent surgery is seldom feasible post-pneumonectomy, we studied the long-term clinical outcomes achieved with curative radiotherapy using modern delivery techniques. METHODS: Retrospective review of an institutional database between 2003-2011 identified 27 patients who had received curative radiotherapy for SPLC arising post-pneumonectomy. Treatments included;
stereotactic ablative radiotherapy (SABR, n=20, dose 54-60 Gy in 3-8 fractions), hypofractionated radiotherapy (HFR, n=6, dose 39-60 Gy in 12-23 fractions) and conventional radiotherapy (RT, n=1, 60 Gy in 30 fractions). Clinical follow-up with a CT scan at 3, 6 and 12 months, then yearly was performed. Toxicities were scored using the common toxicity criteria for adverse events (version 4.0).

RESULTS: The median overall survival was 39 months (95% CI, 33-44 months). After a median follow-up of 52 months (95% CI, 37-67 months), any recurrence was observed in four (15%) patients. Actuarial 3-year rates of local, regional and distant recurrences were 8% (95% CI, 0-21 months), 10% (95% CI, 0-23%) and 9% (95% CI, 0-20%), respectively. Patients receiving HFR or RT all had centrally located tumors. Of the patients treated with HFR delivered 12 fractions, 75% (3/4) developed grade 3 or higher radiation pneumonitis (RP), including one probable grade 5 toxicity. Of those receiving RT or HFR in 13 or more fractions no (0/3) grade 3 or worse RP was observed, despite such treatment being used for larger tumors and resulting in worse lung dose-volume histogram metrics. All the patients who developed RP had radiotherapy plans, which prioritized the sparing of central structures over lung sparing. No non-RP grade 3 or higher toxicities were observed. CONCLUSIONS: Curative radiotherapy is an effective treatment for SPLC arising post-pneumonectomy. For larger central tumors, our data suggests that plans should prioritize reducing lung doses above the sparing of central structures.

[694]

**TÍTULO / TITLE:** Radiation enhances the invasion abilities of pulmonary adenocarcinoma cells via STAT3.

**RESUMEN / SUMMARY:** In the present study, the effect of radiation on the invasion of the pulmonary adenocarcinoma cell line, A549, was investigated. Invasion of A549 cells irradiated with 2 and 4 Gy doses of gammaray was detected using the transwell Matrigel invasion assay. Levels of matrix metalloproteinase 2 (MMP2) and phosphorylated signal transducer and activator of transcription 3 (STAT3) were detected by reverse transcription PCR (RT-PCR) and/or immunoblotting. The enzyme activity of MMP2 was examined by gelatin zymography. Results demonstrated that the invasion of A549 cells was significantly enhanced by gammaray radiation at doses of 2 or 4 Gy. In addition, exposure to radiation was found to promote transcriptional expression of MMP2 and increase MMP2 enzyme activity. Irradiation activated the
phosphorylation of STAT3 and promoted the nuclear localization of STAT3. The blockage of STAT3 phosphorylation using a specific inhibitor (AG490) suppressed the irradiation-induced elevation of MMP2 expression, enzyme activity and invasion of A549 cells. Finally, the expression of vascular endothelial growth factor (VEGF) was found to be upregulated by radiation, which was associated with the activation of STAT3. Results of the current study indicate that irradiation leads to activation of STAT3 and translocation to the nucleus, leading to activation of VEGF and MMP2 transcription, resulting in the increased invasion of A549 cells.

[695]
TÍTULO / TITLE: Improving Outcomes in Advanced Lung Cancer: Maintenance therapy in non-small-cell lung carcinoma.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Furrukh M; Burney IA; Kumar S; Zahid KF; Al-Moundhri M
INSTITUCIÓN / INSTITUTION: Department of Medicine, Sultan Qaboos University Hospital & Sultan Qaboos University, Muscat, Oman.
RESUMEN / SUMMARY: Systemic chemotherapy has remained the traditional treatment for metastatic non-small-cell lung carcinoma (NSCLC), enhancing survival rate at 1 year to 29%. The median survival had plateaued at around 10 months until early 2008, and in an attempt to enhance survival in advanced disease, maintenance chemotherapy trials were initiated which had recently demonstrated prolongation of survival by an additional 2-3 months in patients who had performance status (PS) 0-1 and well-preserved organ functions. Suitable patients with any degree of clinical benefit are treated with 4-6 cycles, and then one of the active agents is continued until best response, or toxicity (continued maintenance), or changed to a cross non-resistant single agent (switch maintenance). The article briefly reviews the evolution of systemic therapy and describes key randomised trials of maintenance therapy instituting chemotherapy and targeted agents in an attempt to improve outcomes in advanced metastatic NSCLC, based on certain clinical features, histology, and genetics.

[696]
TÍTULO / TITLE: Apoptosis Effect of Girinimbine Isolated from Murraya koenigii on Lung Cancer Cells In Vitro.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1155/2013/689865

537
Murraya koenigii Spreng has been traditionally claimed as a remedy for cancer. The current study investigated the anticancer effects of girinimbine, a carbazole alkaloid isolated from Murraya koenigii Spreng, on A549 lung cancer cells in relation to apoptotic mechanistic pathway. Girinimbine was isolated from Murraya koenigii Spreng. The antiproliferative activity was assayed using MTT and the apoptosis detection was done by annexin V and lysosomal stability assays. Multiparameter cytotoxicity assays were performed to investigate the change in mitochondrial membrane potential and cytochrome c translocation. ROS, caspase, and human apoptosis proteome profiler assays were done to investigate the apoptotic mechanism of cell death. The MTT assay revealed that the girinimbine induces cell death with an IC50 of 19.01 μM. A significant induction of early phase of apoptosis was shown by annexin V and lysosomal stability assays. After 24 h treatment with 19.01 μM of girinimbine, decrease in the nuclear area and increase in mitochondrial membrane potential and plasma membrane permeability were readily visible. Moreover the translocation of cytochrome c also was observed. Girinimbine mediates its antiproliferative and apoptotic effects through up- and downregulation of apoptotic and antiapoptotic proteins. There was a significant involvement of both intrinsic and extrinsic pathways. Moreover, the upregulation of p53 as well as the cell proliferation repressor proteins, p27 and p21, and the significant role of insulin/IGF-1 signaling were also identified. Moreover the caspases 3 and 8 were found to be significantly activated. Our results taken together indicated that girinimbine may be a potential agent for anticancer drug development.
differentiate healthy individuals and lung cancer cases by analyzing their serum protein profiles and evaluate the efficacy of this method in the early diagnosis of lung cancer. Materials and Methods: 170 patients with lung cancer, 53 under high risk of lung cancer, and 47 healthy people were included in our study. Proteomic analysis of the samples was performed with the SELDI-TOF-MS approach. Results: The most discriminatory peak of the high risk group was 8141. When tree classification analysis was performed between lung cancer and the healthy control group, 11547 was determined as the most discriminatory peak, with a sensitivity of 85.5%, a specificity of 89.4%, a positive predictive value (PPV) of 96.7% and a negative predictive value (NPV) of 62.7%. Conclusions: We determined three different protein peaks 11480, 11547 and 11679 were only present in the lung cancer group. The 8141 peak was found in the high-risk group, but not in the lung cancer and control groups. These peaks may prove to be markers of lung cancer which suggests that they may be used in the early diagnosis of lung cancer.

[698]
Título / Title: - Post-operative immunohistochemical diagnosis of two synchronous primary non-small cell lung cancers in a single lobe.
Resumen / Summary: - Enlace al Resumen / Link to its Summary
Autores / Authors: - Sachithanandan A; N Y
Institución / Institution: - Hospital Serdang, Department of Cardiothoracic Surgery, Selangor, Malaysia. anandsachithanandan@yahoo.com.
Resumen / Summary: - Synchronous primary non-small cell lung cancers (NSCLC) are rare and may be discovered unexpectedly following lung resection. Discrimination from intrapulmonary metastases is important to guide treatment and prognosis but is difficult solely on clinical or radiological findings. Histopathological evaluation with immunohistochemistry (IHC) markers can prove decisive and should feature in the diagnostic algorithm of such patients. We report a rare case of two synchronous primary NSCLCs diagnosed post operatively following pathological examination of the resected lobe, highlighting the value of IHC and discuss the management of such patients.

[699]
Título / Title: - Diagnostic value of superoxide dismutase in tuberculous and malignant pleural effusions.
Resumen / Summary: - Enlace al Resumen / Link to its Summary
Autores / Authors: - Wang XF; Wu YH; Jiao J; Guan CP; Yang XG; Wang MS
The aim of this study was to investigate the diagnostic value of superoxide dismutase (SOD) in tuberculous pleural effusions (TPEs) and malignant pleural effusions (MPEs). Pleural effusion (PE) samples from 100 patients were classified on the basis of diagnosis as TPE (n=57) and MPE (n=43). The activity of SOD was determined by pyrogallol assay. A significant difference was observed in SOD activity (P<0.01) between TPE and MPE, levels of being significantly higher in TPE compared to MPE. With a threshold value of 41 U/L, the area under the ROC curve was 0.653, SOD had a sensitivity of 61.4% and a specificity of 61.0% for differential diagnosis. Thus, SOD activity in PE was not a good biomarker in differentiating TPE and MPE. To the best of our knowledge, five SOD isoforms may be present in PE. Identification of which SOD contributes to the difference of SOD level between TPE and MPE is very important for illustrating mechanisms and improving the differential diagnostic value.

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**TÍTULO / TITLE:** - Good response of malignant pleural effusion from carcinoma of unknown primary site to the anti-tuberculosis therapy: a case report.

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


**AUTORES / AUTHORS:** - Gu Q; Hu C; Qu J

**INSTITUCIÓN / INSTITUTION:** - Department of respiratory medicine, Xiangya Hospital affiliated to Central South University Changsha City, Hunan, 410008, P.R. China.

**RESUMEN / SUMMARY:** - Malignant pleural effusion in patients with cancers or malignant pleural mesothelioma may often appear at the late stage of disease and significantly affect the patients' life quality and survival. However, there is still no very effective treatment to control malignant pleural effusion. Here we report that malignant pleural effusion in one patient was completely relieved for 15 months by the anti-tuberculosis therapy. Case presentation: A 54-year-old female patient complained of cough, dyspnea, chest pain, night sweat and light fever in the afternoon. Computed tomography (CT) of the chest revealed bilateral pleural effusion. But no tumor was found in the lung, pleura and in other sites. Blood test revealed serum carcinoembryonic antigen (CEA) level at 300 ng/mL. One week after we tried anti-tuberculosis combined therapy with isoniazid, pyrazinamide, rifapentine and ethambutol. The pleural effusion in patient was eliminated, along with decreasing CEA. But the CEA increased gradually again when the anti-tuberculosis treatment was forced to discontinuation. Sixteen months after anti-tuberculosis treatment, the symptoms of cough and breathing difficulty relapsed. Chest CT revealed left pleural effusion.
effusion, pleural thickness and pericardium nodules. Thoracoscopy and biopsy were conducted. The pleural nodules specimen was pathologically diagnosed as squamous cell carcinoma. Conclusion We reported a rare case of successfully treating malignant pleural effusion caused by squamous cell carcinoma of unknown primary site with the anti-tuberculosis combined. This report provides useful evidences for that the anti-tubercular agents may have potential anticancer activity in some carcinomas.

[701]


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


AUTORES / AUTHORS: - Sun L; Fan X

INSTITUCIÓN / INSTITUTION: - Department of Histology and Embryology, College of Basic Medicine of Guilin Medical University, Guilin, Guangxi 541004, China.

RESUMEN / SUMMARY: - Lung cancer is one of the most important causes of cancer-related mortality worldwide. Human cytochrome P450 2 &times; 13 enzyme (CYP2A13) is predominantly expressed in the respiratory tract and could catalyze various carcinogens. In this study, we quantified CYP2A13 expression in non-small cell lung cancer (NSCLC) tissues and examined the relation between CYP2A13 and clinicopathologic factors. Thirty-five paired lung cancer and normal tissues were studied for the expression of the CYP2A13 gene by using real-time PCR and Western blotting assays. We also investigated the relationship between CYP2A13 expression and clinicopathologic factors such as age, gender, histology and lymph node status in tumor tissues. SPSS (17.0) statistical software was applied for data analysis. The real-time PCR results showed that there was no significant difference in the CYP2A13 mRNA transcript levels between tumor and paired normal tissues in the 35 samples and in 12 paired squamous cell carcinomas. In adenocarcinoma, the expression of CYP2A13 mRNA in tumor tissues was 12.5% of that in adjacent tissues (P < 0.05) and it was not associated with age, gender, histology and lymph node status of the patients. The amounts of CYP2A13 proteins detected by Western blotting assays correlated well with those of the corresponding mRNAs. In conclusion, the expression of CYP2A13 was downregulated in lung adenocarcinoma. CYP2A13 may be involved in the development and progression of lung adenocarcinoma.

[702]

TÍTULO / TITLE: - Mitochondrial injury induced by nanosized titanium dioxide in A549 cells and rats.
**RESUMEN / SUMMARY:** The nanosized titanium dioxide (nano-TiO2) is an important nanoscale compound applied in many different fields because of its superior performance. Here, an anatase nano-TiO2 showed cytotoxicity in a dosage-dependent manner, which was in accordance with changes of A549 cell ultrastructure, A549 cell viability and intracellular ATP level. The lungs of rats treated with single intratracheal instillation of nano-TiO2 were injured, which was demonstrated by changes of alveolar epithelial cell ultrastructure, lung tissue pathology and lung tissue MDA level. The results of this study indicated that nano-TiO2 should be related to the generation of intracellular reactive oxygen species (ROS), which injured mitochondria and prevented the synthesis of ATP. The cells were approaching to apoptosis eventually. In macroscopic view, the lungs inevitably suffered.

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**TÍTULO / TITLE:** Crude alkaloid extract of Rhazya stricta inhibits cell growth and sensitizes human lung cancer cells to cisplatin through induction of apoptosis.

**RESUMEN / SUMMARY:** There is an urgent need to improve the clinical management of non-small cell lung cancer (NSCLC), one of the most frequent causes of cancer-related deaths in men and women worldwide. Rhazya stricta, an important medicinal plant used in traditional Oriental medicine, possesses anti-oxidant, anti-carcinogenic and free radical scavenging properties. This study was done to explore the potential anticancer activity of a crude alkaloid extract of R. stricta (CAERS) against the NSCLC line A549. CAERS markedly suppressed the growth of A549 cells and considerably enhanced the anti-proliferative potential of cisplatin. CAERS-mediated inhibition of A549 cell growth correlated with the induction of apoptosis that was accompanied by numerous morphological changes, DNA fragmentation, an increase in the...
Bax/Bcl-2 ratio, the release of mitochondrial cytochrome c, activation of caspases 3 and 9 and cleavage of poly(ADP-ribose)-polymerase. CAERS reduced the constitutive expression of anti-apoptotic proteins (Bcl-2, Bcl-XL, Mcl-1 and Survivin) and cell cycle regulating proteins (cyclin D1 and c-Myc), but enhanced expression of the proapoptotic proteins Noxa and BAD. These observations indicate that CAERS induced apoptosis and sensitized NSCLC to cisplatin via a mitochondria-mediated apoptotic pathway. These data provide a rationale for using a combination of CAERS and CDDP to treat NSCLC and other CDDP-resistant tumors.

[704]

**TÍTULO / TITLE:** Casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells.

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


**AUTORES / AUTHORS:** Zhou Y; Peng Y; Mao QQ; Li X; Chen MW; Su J; Tian L; Mao NQ; Long LZ; Quan MF; Liu F; Zhou SF; Zhao YX

**INSTITUCIÓN / INSTITUTION:** Department of Pharmacology of Medical College, Hunan Normal University, Changsha, Hunan 410013, China. zhouyuan1122@126.com

**RESUMEN / SUMMARY:** OBJECTIVE: To assess if casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells. METHODS: Human non-small-cell lung carcinoma cell lines H460, A549 and H157 were cultured in vitro. The cytotoxic activities were determined using MTT assay. The apoptotic cells death was examined by flow cytometry using PI staining and DNA agarose gel electrophoresis. The activities of caspase-3, -8 and -9 were measured via ELISA. Cellular fractionation was determined by flow cytometry to assess release of cytochrome c and the mitochondrial transmembrane potential. Bcl-2/Bcl-XL/XIAP/Bid/DR5 and DR4 proteins were analyzed using western blot. RESULTS: The concentrations required for a 50% decrease in cell growth (IC(50)) ranged from 1.8 to 3.2 μM. Casticin induced rapid apoptosis and triggered a series of effects associated with apoptosis by way of mitochondrial pathway, including the depolarization of the mitochondrial membrane, release of cytochrome c from mitochondria, activation of procaspase-9 and -3, and increase of DNA fragments. Moreover, the pan caspase inhibitor zVAD-FMK and the caspase-3 inhibitor zDEVD-FMK suppressed casticin-induced apoptosis. In addition, casticin induced XIAP and Bcl-XL down-regulation, Bax upregulation and Bid cleavage. In H157 cell line, casticin increased expression of DR5 at protein levels but not affect the expression of DR4. The pretreatment...
with DR5/Fc chimera protein effectively attenuated casticin-induced apoptosis in H157 cells. No correlation was found between cell sensitivity to casticin and that to p53 status, suggesting that casticin induce a p53-independent apoptosis.

CONCLUSIONS: Our results demonstrate that casticin induces caspase-mediated apoptosis via activation of mitochondrial pathway and upregulation of DR5 in human lung cancer cells.

[705]
TÍTULO / TITLE: - miR-146a inhibits cell growth, cell migration and induces apoptosis in non-small cell lung cancer cells.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chen G; Umelo IA; Lv S; Teugels E; Fostier K; Kronenberger P; Dewaele A; Sadones J; Geers C; De Greve J
INSTITUCION / INSTITUTION: - Department of Pathology, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People’s Republic of China.
RESUMEN / SUMMARY: - Aberrant expression of microRNA-146a (miR-146a) has been reported to be involved in the development and progression of various types of cancers. However, its role in non-small cell lung cancer (NSCLC) has not been elucidated. The aim of this study was to investigate the contribution of miR-146a to various aspects of the malignant phenotype of human NSCLCs. In functional experiments, miR-146a suppressed cell growth, induced cellular apoptosis and inhibited EGFR downstream signaling in five NSCLC cell lines (H358, H1650, H1975, HCC827 and H292). miR-146a also inhibited the migratory capacity of these NSCLC cells. On the other hand, miR-146a enhanced the inhibition of cell proliferation by drugs targeting EGFR, including both TKIs (gefitinib, erlotinib, and afatinib) and a monoclonal antibody (cetuximab). These effects were independent of the EGFR mutation status (wild type, sensitizing mutation or resistance mutation), but were less potent compared to the effects of siRNA targeting of EGFR. Our results suggest that these effects of miR-146a are due to its targeting of EGFR and NF-kappaB signaling. We also found, in clinical formalin fixed paraffin embedded (FFPE) lung cancer samples, that low expression of miR-146a was correlated with advanced clinical TNM stages and distant metastasis in NSCLC (P<0.05). The patients with high miR-146a expression in their tumors showed longer progression-free survival (25.6 weeks in miR-146a high patients vs. 4.8 weeks in miR-146a low patients, P<0.05). miR-146a is therefore a strong candidate prognostic biomarker in NSCLC. Thus inducing miR-146a might be a therapeutic strategy for NSCLC.
Two novel nanoscale preparations of micelle and thermosensitive hydrogel for docetaxel to treat malignant tumor.

In this paper, two nanoscale preparations were described for docetaxel encapsulation using poly(epsilon-caprolactone)poly(ethylene glycol)-poly(epsilon-caprolactone) (PCEC) copolymer as carrier for treating malignant tumor. The first formulation was docetaxel-loaded PCEC micelle (D-M), which was characterized by XRD, TEM and Malvern laser particle size and drug release studies. The highest drug-loading of docetaxel in micelle was about 22.1 +/- 1.9%, optimized average diameter and polydispersity index was 25.2 +/- 1.1 nm, 0.13 +/- 0.12, respectively. Another formulation was docetaxel-loaded PCEC thermosensitive hydrogel (D-H), which displayed special gel-sol transition behavior with body temperature. We studied the cytotoxicity and in vitro hemolytic test of blank PCEC copolymer, the result was superiority. The data of relative body weight (RW), relative tumor volume (RV) and micrographs of hematoxylin and eosin (H&E)-stained histological sections showed D-M and D-H had significant antitumor effect and exhibited different characteristics of antitumor activity. Thus, the experiments signified that the combination therapy of intravenous (i.v.) and intratumoral administration using the two formulations maybe an effective way to treat malignant tumor.

Pterostilbene Exerts Antitumor Activity via the Notch1 Signaling Pathway in Human Lung Adenocarcinoma Cells.

Although pterostilbene (PTE) has been shown to have potent antitumor activities against various cancer types, the molecular
mechanisms of these activities remain unclear. In this study, we investigated the antitumor activity of PTE against human lung adenocarcinoma in vitro and in vivo and explored the role of the Notch1 signaling pathway in this process. PTE treatment resulted in a dose- and time-dependent decrease in the viability of A549 cells. Additionally, PTE exhibited strong antitumor activity, as evidenced not only by a reduced mitochondrial membrane potential (MMP) and a decreased intracellular glutathione content but also by increases in the apoptotic index and the level of reactive oxygen species (ROS). Furthermore, PTE treatment induced the activation of the Notch1 Intracellular Domain (NICD) protein and activated Hes1. DAPT (a gamma secretase inhibitor) and Notch1 siRNA prevented the induction of NICD and Hes1 activation by PTE treatment and sensitized the cells to PTE treatment. The down-regulation of Notch signaling also prevented the activation of pro-survival pathways (most notably the PI3K/Akt pathway) after PTE treatment. In summary, lung adenocarcinoma cells may enhance Notch1 activation as a protective mechanism in response to PTE treatment. Combining a gamma secretase inhibitor with PTE treatment may represent a novel approach for treating lung adenocarcinoma by inhibiting the survival pathways of cancer cells.

[708]

**Título / Title:** Assessment of the Anti-invasion Potential and Mechanism of Select Cinnamic Acid Derivatives on Human Lung Adenocarcinoma Cells.

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


**Autores / Authors:** Tsai CM; Yen GC; Sun FM; Yang SF; Weng CJ

**Institución / Institution:** Institute of Medicine, Chung Shan Medical University, No. 110, Sec.1, Jianguo N. Rd., Taichung 40256, Taiwan.

**Resumen / Summary:** Patients with lung adenocarcinoma are often diagnosed with metastasizing symptoms and die of early and distal metastasis. Metastasis is made up of a cascade of interrelated and sequential steps, including cell adhesion, extracellular matrix degradation, cell movement, and invasion. Hence, substances carrying the ability to stop one of the metastasis-associated steps could be a potential candidate for preventing tumor cells from metastasizing and prolonging the life of cancer patients. Cinnamic acid (CA) was demonstrated to be such a candidate for human lung adenocarcinoma cells. Nevertheless, the effectiveness of CA derivatives on invasion of lung cancer cells is still unclear. The aims of this study were to explore the mechanisms underlying several select CA derivatives against invasion of human lung adenocarcinoma A549 cells. The results revealed that caffeic acid (CAA), chlorogenic acid (CHA), and ferulic acid (FA) can inhibit phorbol-12-myristate-13-acetate (PMA)-stimulated invasion of A549 cells at a concentration...
of \( \geq 100 \) muM. The MMP-9 activity was suppressed by these compounds through regulating urokinase-type plasminogen activator (uPA), tissue inhibitor of metalloproteinase (TIMP)-1, plasminogen activator inhibitor (PAI)-1, and PAI-2; the cell-matrix adhesion was decreased by CAA only. The proposed molecular mechanism involved not only decreasing the signaling of MAPK and PI3K/Akt but also inactivating NF-kappaB, AP-1, and STAT3. In the present study, we selected CAA, CHA, and FA as potential inhibitors for invasive behaviors of human lung adenocarcinoma cells and disclosed the possible mechanisms. The association between structural features and anti-invasive activity of these compounds cannot be determined here and needs to be further verified.

[709]

**TÍTULO / TITLE:** - A pilot study: sequential gemcitabine/cisplatin and icotinib as induction therapy for stage IIB to IIIA non-small-cell lung adenocarcinoma.

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


**AUTORES / AUTHORS:** - Lv C; Ma Y; Feng Q; Fang F; Bai H; Zhao B; Yan S; Wu N; Zheng Q; Li S; Chen J; Wang J; Feng Y; Wang Y; Pei Y; Fang J; Yang Y

**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery II, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, 52 Fucheng Road, Beijing, Haidian District, 100142, China. zlyangyue@bjmu.edu.cn.

**RESUMEN / SUMMARY:** - BACKGROUND: A phase II clinical trial previously evaluated the sequential administration of erlotinib after chemotherapy for advanced non-small-cell lung cancer (NSCLC). This current pilot study assessed the feasibility of sequential induction therapy in patients with stage IIB to IIIA NSCLC adenocarcinoma. METHODS: Patients received gemcitabine 1,250 mg/m² on days 1 and 8 and cisplatin 75 mg/m² on day 1, followed by oral icotinib (125 mg, three times a day) on days 15 to 28. A repeat computed tomography (CT) scan evaluated the response to the induction treatment after two 4-week cycles and eligible patients underwent surgical resection. The primary objective was to assess the objective response rate (ORR), while EGFR and KRAS mutations and mRNA and protein expression levels of ERCC1 and RRM1 were analyzed in tumor tissues and blood samples. RESULTS: Eleven patients, most with stage IIIB disease, completed preoperative treatment. Five patients achieved partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (ORR=45%) and six patients underwent resection. Common toxicities included neutropenia, alanine transaminase (ALT) elevation, fatigue, dry skin, rash, nausea, alopecia and anorexia. No serious complications were recorded.
perioperatively. Three patients had exon 19 deletions and those with EGFR mutations were more likely to achieve a clinical response (P= 0.083). Furthermore, most cases who achieved a clinical response had low levels of ERCC1 expression and high levels of RRM1. CONCLUSIONS: Two cycles of sequentially administered gemcitabine/cisplatin with icotinib as an induction treatment is a feasible and efficacious approach for stage IIB to IIIA NSCLC adenocarcinoma, which provides evidence for the further investigation of these chemotherapeutic and molecularly targeted therapies.

[710]

**TÍTULO / TITLE:** - Induction of long intergenic non-coding RNA HOTAIR in lung cancer cells by type I collagen.

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


**AUTORES / AUTHORS:** - Zhuang Y; Wang X; Nguyen HT; Zhuo Y; Cui X; Fewell C; Flemington EK; Shan B

**INSTITUCIÓN / INSTITUTION:** - Department of Medicine and Pathology, Tulane University School of Medicine, 1430 Tulane Ave, SL-9, New Orleans, LA, 70112, USA. bshan@tulane.edu.

**RESUMEN / SUMMARY:** - BACKGROUND: The tumor microenvironment is a crucial determinant in tumor progression. Interstitial extracellular matrix (ECM), such as type I collagen (Col-1), is aberrantly enriched in the tumor microenvironment and promotes tumor progression. Long intergenic non-coding RNAs (lincRNA) are a new family of regulatory RNAs that modulate fundamental cellular processes via diverse mechanisms. FINDINGS: We investigated whether the expression of lincRNAs was regulated by the tumor promoting Col-1. In a three-dimensional organotypic culture model using the reconstituted basement membrane ECM Matrigel (rBM 3-D), supplementation of Col-1 disrupted acini, a differentiation feature of well-differentiated lung adenocarcinoma cells, and concurrently induced the expression of a tumor-promoting lincRNA, HOX transcript antisense RNA (HOTAIR). Induction of HOTAIR by Col-1 was diminished by a neutralizing antibody against the Col-1 receptor alpha2beta1 integrin. Col-1 activates the expression of a reporter gene controlled by the human HOTAIR promoter. Moreover the expression of HOTAIR and Col-1 was concurrently up-regulated in human non-small cell lung cancer. CONCLUSIONS: Our findings indicate that tumor-promoting Col-1 up-regulates the expression of HOTAIR in NSCLC cells. These initial results warrant further investigation of HOTAIR and other lincRNA genes in lung tumorigenesis.

[711]
TÍTULO / TITLE: - RASEF is a novel diagnostic biomarker and a therapeutic target for lung cancer.

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


AUTORES / AUTHORS: - Oshita H; Nishino R; Takano A; Fujitomo T; Aragaki M; Kato T; Akiyama H; Tsuchiya E; Kohno N; Nakamura Y; Daigo Y

INSTITUCIÓN / INSTITUTION: - Human Genome Center, Institute of Medical Science, The University of Tokyo.

RESUMEN / SUMMARY: - Genome-wide gene expression profile analyses revealed that Ras and EF-hand domain containing (RASEF) was significantly transactivated in the majority of lung cancers. Transient expression of RASEF promoted cell growth, whereas transfection of siRNA for RASEF to lung cancer cells reduced its expression and resulted in growth suppression of the cancer cells. Immunohistochemical staining using tumor tissue microarrays consisting of 341 archived non-small cell lung cancers revealed the association of strong RASEF positivity with poor prognosis (P = 0.0034 by multivariate analysis). RASEF could bind to extracellular signal-regulated kinase (ERK) ½ and appeared to enhance the ERK1/2 signaling. In addition, inhibition of interaction between RASEF and ERK1/2 using cell-permeable peptide that corresponded to the ERK1/2-interacting site of RASEF protein, suppressed growth of lung cancer cells. RASEF may play important roles in lung carcinogenesis, and could be useful as a prognostic biomarker and a target for the development of new molecular therapies.

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TÍTULO / TITLE: - Repeated favorable responses to epidermal growth factor receptor-tyrosine kinase inhibitors in a case of advanced lung adenocarcinoma.

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


AUTORES / AUTHORS: - Kim EY; Kim YH; Ban HJ; Oh IJ; Kwon YS; Kim KS; Kim YI; Lim SC; Kim YC

INSTITUCIÓN / INSTITUTION: - Lung and Esophageal Cancer Clinic, Chonnam National University Hwasun Hospital, Hwasun, Korea.; Department of Internal Medicine, Chonnam National University Medical School, Hwasun, Korea.

RESUMEN / SUMMARY: - The presence of epidermal growth factor receptor (EGFR) mutation is a prognostic and predictive marker for EGFR-tyrosine kinase inhibitor (TKI) therapy. However, inevitably, relapse occurs due to the development of acquired resistance, such as T790M mutation. We report a case of repeated responses to EGFR-TKIs in a never-smoked woman with
adenocarcinoma. After six cycles of Gemcitabine and cisplatin, the patient was treated by gefitinib for 4 months until progression. Following the six cycles of third-line pemetrexed, gefitinib retreatment was initiated and continued with a partial response for 6 months. After progression, she was recruited for an irreversible EGFR inhibitor trial, and the time to progression was 11 months. Although EGFR direct sequencing on the initial diagnostic specimen revealed a wild-type, we performed a rebiopsy from the progressed subcarinal node at the end of the trial. The result of peptide nucleic acid clamping showed L858R/L861Q.

[713]

TÍTULO / TITLE: - Bone morphogenetic protein type I receptor antagonists decrease growth and induce cell death of lung cancer cell lines.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Langenfeld E; Hong CC; Lanke G; Langenfeld J
INSTITUCIÓN / INSTITUTION: - Department of Surgery, Division of Thoracic Surgery, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA.
RESUMEN / SUMMARY: - Bone morphogenetic proteins (BMPs) are highly conserved morphogens that are essential for normal development. BMP-2 is highly expressed in the majority of non-small cell lung carcinomas (NSCLC) but not in normal lung tissue or benign lung tumors. The effects of the BMP signaling cascade on the growth and survival of cancer cells is poorly understood. We show that BMP signaling is basally active in lung cancer cell lines, which can be effectively inhibited with selective antagonists of the BMP type I receptors. Lung cancer cell lines express alk2, alk3, and alk6 and inhibition of a single BMP receptor was not sufficient to decrease signaling. Inhibition of more than one type I receptor was required to decrease BMP signaling in lung cancer cell lines. BMP receptor antagonists and silencing of BMP type I receptors with siRNA induced cell death, inhibited cell growth, and caused a significant decrease in the expression of inhibitor of differentiation (Id1, Id2, and Id3) family members, which are known to regulate cell growth and survival in many types of cancers. BMP receptor antagonists also decreased clonogenic cell growth. Knockdown of Id3 significantly decreased cell growth and induced cell death of lung cancer cells. H1299 cells stably overexpressing Id3 were resistant to growth suppression and induction of cell death induced by the BMP antagonist DMH2. These studies suggest that BMP signaling promotes cell growth and survival of lung cancer cells, which is mediated through its regulation of Id family members. Selective antagonists of the BMP
type I receptors represents a potential means to pharmacologically treat NSCLC and other carcinomas with an activated BMP signaling cascade.

[714]

- Stemness and inducing differentiation of small cell lung cancer NCI-H446 cells.

- Enlace al Resumen / Link to its Summary

  - Enlace al texto completo (gratuito o de pago) 1038/cddis.2013.152

- Zhang Z; Zhou Y; Qian H; Shao G; Lu X; Chen Q; Sun X; Chen D; Yin R; Zhu H; Shao Q; Xu W

- School of Medical Science and Laboratory Medicine, Jiangsu University, Zhenjiang, Jiangsu, People’s Republic of China.

- Small cell lung cancer (SCLC) accounts for nearly 15% of human lung cancers and is one of the most aggressive solid tumors. The SCLC cells are thought to derive from self-renewing pulmonary neuroendocrine cells by oncogenic transformation. However, whether the SCLC cells possess stemness and plasticity for differentiation as normal stem cells has not been well understood thus far. In this study, we investigated the expressions of multilineage stem cell markers in the cancer cells of SCLC cell line (NCI-H446) and analyzed their clonogenicity, tumorigenicity, and plasticity for inducing differentiation. It has been found that most cancer cells of the cell line expressed multilineage stem cell markers under the routine culture conditions and generated single-cell clones in anchorage-dependent or -independent conditions. These cancer cells could form subcutaneous xenograft tumors and orthotopic lung xenograft tumors in BALB/C-nude mice. Most cells in xenograft tumors expressed stem cell markers and proliferation cell nuclear antigen Ki67, suggesting that these cancer cells remained stemness and highly proliferative ability in vivo. Intriguingly, the cancer cells could be induced to differentiate into neurons, adipocytes, and osteocytes, respectively, in vitro. During the processes of cellular phenotype-conversions, autophagy and apoptosis were two main metabolic events. There is cross-talking between autophagy and apoptosis in the differentiated cancer cells. In addition, the effects of the inhibitor and agonist for Sirtuin1/2 on the inducing osteogenic differentiation indicated that Sirtuin1/2 had an important role in this process. Taken together, these results indicate that most cancer cells of NCI-H446 cell line possess stemness and plasticity for multilineage differentiation. These findings have potentially some translational applications in treatments of SCLC with inducing differentiation therapy.

[715]
TÍTULO / TITLE: Bronchogenic cyst: Clinical course from antenatal diagnosis to postnatal thoracoscopic resection.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORs: Maurin S; Hery G; Bourliere B; Potier A; Guys JM; Lagausie PD
INSTITUCIÓN / INSTITUTION: Department of Pediatric Surgery, Marseille University, France.
RESUMEN / SUMMARY: PURPOSE: The purpose of this study was to describe an approach to surgical management of bronchogenic cysts based on the natural course observed from the time of antenatal screening to surgical resection in patients treated at our institution and reported in the literature.
MATERIALS AND METHODS: We retrospectively reviewed the clinical features of all children presenting bronchogenic cyst diagnosed antenatally from 2007 to 2010. A total of six children were included. RESULTS: Antenatal diagnosis was accurate in 62.5% of cases. In the first year of life, the size of the cyst remained stable in four patients, doubled in one, and increased 30% within six months in one. The indication for surgery was emphysema of the left bronchus in two patients and rapid growth in two patients. One patient is still awaiting surgery. CONCLUSION: Bronchogenic cysts grow slowly in the first months of life, but growth is exponential even in the absence of complications. We recommend complete resection before the age of two years to prevent infectious complications and facilitate surgery.

[716]
TÍTULO / TITLE: PIK3CA gene mutation associated with poor prognosis of lung adenocarcinoma.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORs: Zhang L; Shi L; Zhao X; Wang Y; Yue W
INSTITUCIÓN / INSTITUTION: Department of Molecular and Cellular Biology, Beijing Chest Hospital, Capital Medical University, Beijing TB and Thoracic Tumor Research Institute, Beijing, People’s Republic of China.
RESUMEN / SUMMARY: PURPOSE: PIK3CA gene mutations have been detected in many malignancies, but the frequency of different mutations and their role in the carcinogenesis of lung adenocarcinoma are still unclear. The purpose of this study was to explore the clinical pathological impact and prognostic implications of PIK3CA mutations in lung adenocarcinoma.
METHODS: Five common PIK3CA mutations (E542K, E545K, and E545D
mutation in exon 9, H1047R and H1047L mutation in exon 20) were detected by amplification refractory mutation system (ARMS) allele-specific polymerase chain reaction (PCR), in 122 patients with lung adenocarcinoma. The relationships were studied between these mutations and various clinicopathologic variables (age, lymph node status, distant metastasis, clinicopathologic stage, smoking status, and progression-free survival).

RESULTS: In total, 25 mutations were identified, of which 24 mutations were clustered in exon 20, and one mutation in exon 9. The most common mutations were H1047R (18 out of the 122 patients, 14.8%) in exon 20. PIK3CA-mutated tumors were more frequently found in patients with lymph node positive metastasis status (P < 0.05). There was no significant association between PIK3CA mutations and age, distant metastasis, smoking status, or clinicopathologic stage. However, mutations were found less frequently in the early clinicopathologic stage patients (six in 50 cases, 12%) than in advanced stage (19 in 72 cases, 26.4%). Higher frequency of H1047R mutations was associated with poor prognosis, and this association reached statistical significance (P < 0.05). CONCLUSION: Our data indicate that the PIK3CA mutations H1047R and H1047L are significant genetic alterations in lung adenocarcinoma. Among lung adenocarcinoma patients who underwent curative resection, PIK3CA mutations were associated with shorter progression-free survival. Our findings demonstrated a significant role of PIK3CA in lung adenocarcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Glotzer OS; Fabian T; Chandra A; Bakhos CT
INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Albany Medical Center, Department of Surgery, Albany Medical College, Albany, New York, USA.
RESUMEN / SUMMARY: - BACKGROUND: Our objective was to evaluate and review the current literature on the treatment of non-small cell lung cancer (NSCLC) in the elderly. METHODS: We selected recent peer-reviewed articles addressing ageing, cancer treatment in the elderly, and lung cancer treatment in the elderly. We defined elderly as over the age of 70. RESULTS: The population is ageing dramatically throughout most of the world. Given that situation, clinicians are seeing and being asked to treat more elderly patients that have NSCLC. Elderly patients are less likely to participate or be allowed to participate in prospective or retrospective studies of treatments for NSCLC.
Elderly patients are also less likely to be staged appropriately for their advanced tumors, and are less likely to be referred for surgery or adjuvant therapy after surgery. When treatment is tailored to patient comorbidities but not to age, the data support survival and outcomes comparable to those of younger patients.

CONCLUSIONS: Data are limited on the treatment of elderly patients with NSCLC. No data exist to support limiting recommendations for treatment based on age alone. Treatments should be determined on an individual basis.

[718]
TÍTULO / TITLE: - Physiology and clinical applications of cardiopulmonary exercise testing in lung cancer surgery.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

[719]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
investigated the correlation between the Glutathione S-transferase T1 (GSTT1) null genotype and lung cancer risk in Asian population but yielded inconclusive results. METHODOLOGY: PRINCIPAL FINDINGS: We performed a meta-analysis of 23 studies including 4065 cases and 5390 controls. We assessed the strength of the association of GSTT1 with lung cancer risk and performed sub-group analyses by source of controls, smoking status, histological types, and sample size. A statistically significant correlation between GSTT1 null genotype and lung cancer in Asian population was observed (OR = 1.28, 95% CI = 1.10, 1.49; P heterogeneity < 0.001 and I(2) = 62.0%). Sub-group analysis revealed there was a statistically increased lung cancer risk in ever-smokers who carried the GSTT1 null genotype (OR = 1.94, 95% CI = 1.27, 2.96; P heterogeneity = 0.02 and I(2) = 58.1%). It was also indicated that GSTT1 null genotype could increase lung cancer risk among population-based studies (OR = 1.25, 95% CI = 1.04, 1.50; P heterogeneity = 0.003 and I(2) = 56.8%). The positive association was also found in studies of sample size (< 500 participants) (OR = 1.34, 95% CI = 1.10, 1.62; P heterogeneity < 0.001 and I(2) = 65.4%). CONCLUSIONS: These meta-analysis results suggest that GSTT1 null genotype is associated with a significantly increased risk of lung cancer in Asian population.

[720]

**TÍTULO / TITLE:** Osteopontin knockdown suppresses non-small cell lung cancer cell invasion and metastasis.

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


**AUTORES / AUTHORS:** Sun BS; You J; Li Y; Zhang ZF; Wang CL

**INSTITUCIÓN / INSTITUTION:** Department of Lung Cancer Surgery, Tianjin Cancer Institute and Hospital, Tianjin Medical University, Tianjin Lung Cancer Center, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin 300060, China.

**RESUMEN / SUMMARY:** BACKGROUND: Osteopontin (OPN) was identified as one of the leading genes that promote the metastasis of malignant tumor. However, the mechanism by which OPN mediates metastasis in non-small cell lung cancer (NSCLC) remains unknown. The aim of the study is to investigate the biological significance and the related molecular mechanism of OPN expression in lung cancer cell line. METHODS: Lentiviral-mediated RNA interference was applied to inhibit OPN expression in metastatic human NSCLC cell line (A549). The invasion, proliferation, and metastasis were evaluated OPN-silenced in A549 cells in vitro and in vivo. The related mechanism was further investigated. RESULTS: Interestingly, OPN knockdown significantly suppressed the invasiveness of A549 cells, but had only a minor effect on the cellular migration and proliferation. Moreover, we demonstrated that OPN knockdown significantly reduced the levels of matrix metalloproteinase (MMP)-2
and urokinase plasminogen activator (uPA), and led to an obvious inhibition of both in vitro invasion and in vivo lung metastasis of A549 cells (P < 0.001).

CONCLUSIONS: Our data demonstrate that OPN contributes to A549 cell metastasis by stimulating cell invasion, independent of cellular migration and proliferation. OPN could be a new treatment target of NSCLC.
between raw garlic consumption and tobacco smoking (Synergy Index (SI) = 0.70, 95% CI = 0.57-0.85; and ROR = 0.78, 95% CI = 0.67-0.90), as well as high-temperature cooking oil fume (ROR = 0.77, 95% CI = 0.59-1.00). In conclusion, protective association between intake of raw garlic and lung cancer has been observed with a dose-response pattern, suggesting that garlic may potentially serve as a chemopreventive agent for lung cancer. Effective components in garlic in lung cancer chemoprevention warrant further in-depth investigation.

[723]
TÍTULO / TITLE: - Therapeutic Delivery of MicroRNA-29b by Cationic Lipoplexes for Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Wu Y; Crawford M; Mao Y; Lee RJ; Davis IC; Elton TS; Lee LJ; Nana-Sinkam SP
INSTITUCIÓN / INSTITUTION: - Center for Affordable Nanoengineering of Polymeric Biomedical Devices, 1012 Smith Lab, The Ohio State University, Columbus, Ohio, USA.
RESUMEN / SUMMARY: - MicroRNA-29b (miR-29b) expression has been shown to be reduced in non-small-cell lung cancer (NSCLC) tissues. Here, we have identified the oncogene cyclin-dependent protein kinase 6 (CDK6) as a direct target of miR-29b in lung cancer. We hypothesized that in vivo restoration of miR-29b and thus targeting of genes important to tumor initiation and progression may represent an option for lung cancer treatment. We developed a cationic lipoplexes (LPs)-based carrier that efficiently delivered miR-29b both in vitro and in vivo. LPs containing miR-29b (LP-miR-29b) efficiently delivered miR-29b to NSCLC A549 cells, reduced the expression of key targets CDK6, DNMT3B, and myeloid cell leukemia sequence 1 (MCL1), as well as cell growth and clonogenicity of A549 cells. In addition, the IC50 for cisplatin in the miR-29b-treated cells was effectively reduced. In a xenograft murine model, LPs efficiently accumulated at tumor sites. Systemic delivery of LP-miR-29b increased the tumor miR-29b expression by approximately fivefold, downregulated the tumor mRNA expression of CDK6, DNMT3B, and MCL1 by ~57.4, ~40.5, and ~52.4%, respectively, and significantly inhibited tumor growth by ~60% compared with LP-miR-NC (negative control). Our results demonstrate that cationic LPs represent an efficient delivery system that holds great potential in the development of miRNA-based therapeutics for lung cancer treatment. Molecular Therapy-Nucleic Acids (2013) 2, e84; doi:10.1038/mtna.2013.14; published online 16 April 2013.
Approximately a third of the patients with non-small cell lung cancer (NSCLC) present with locally advanced disease not amenable to curative resection. Concurrent chemoradiation is currently the treatment of choice for these patients. Outcomes in patients with locally advanced NSCLC treated with concurrent chemoradiation are modest at best. No significant progress has been made over the past decade in this subset of patients with NSCLC. Several trials have examined the role of molecular targeted therapies in this setting. We review the results of these trials and present the outline of a proposed prospective clinical trial to evaluate targeted drugs in molecularly selected group of patients with locally advanced NSCLC.
Efficacy and safety of albumin-bound paclitaxel in treating recurrent advanced non-small-cell lung cancer.

OBJECTIVE: To observe the efficacy and safety of albumin-bound paclitaxel (ABP) monotherapy in treating recurrent advanced non-small-cell lung cancer (NSCLC). METHODS: We retrospectively analyzed the short-term efficacy and toxicities of ABP monotherapy in treating 21 patients who had previously undergone multiple cycles of therapy for their advanced NSCLC in our hospital since 2010. The treatment-related survival was also analyzed. RESULTS: Of these 21 patients, the best overall response was partial response (PR) in 6 patients (28.6%), stable disease (SD) in 10 patients (47.6%), and progressive disease (PD) in 5 patients (23.8%). The overall response rate (ORR) was 28.6% and the disease control rate (DCR) (PR + SD) was 76.2%. The median progression-free survival (PFS) was 4.0 months (95% CI, 5.0-7.0 months). The main grade 3 or 4 toxicities included neutropenia (11.1%), peripheral nerve toxicity (5.6%), muscle and joint aches (5.6%), and fatigue (5.6%). CONCLUSIONS: The ABP monotherapy can achieve good objective response in advanced NSCLC patients who have previously received multiple cycles of treatment and be well tolerated.

A phase II single-arm study of induction chemotherapy with cisplatin and gemcitabine followed by concurrent cisplatin and gemcitabine with thoracic radiation for unresectable locally advanced non-small-cell lung cancer.

OBJECTIVE: To observe the efficacy and safety of albumin-bound paclitaxel (ABP) monotherapy in treating recurrent advanced non-small-cell lung cancer (NSCLC). METHODS: We retrospectively analyzed the short-term efficacy and toxicities of ABP monotherapy in treating 21 patients who had previously undergone multiple cycles of therapy for their advanced NSCLC in our hospital since 2010. The treatment-related survival was also analyzed. RESULTS: Of these 21 patients, the best overall response was partial response (PR) in 6 patients (28.6%), stable disease (SD) in 10 patients (47.6%), and progressive disease (PD) in 5 patients (23.8%). The overall response rate (ORR) was 28.6% and the disease control rate (DCR) (PR + SD) was 76.2%. The median progression-free survival (PFS) was 4.0 months (95% CI, 5.0-7.0 months). The main grade 3 or 4 toxicities included neutropenia (11.1%), peripheral nerve toxicity (5.6%), muscle and joint aches (5.6%), and fatigue (5.6%). CONCLUSIONS: The ABP monotherapy can achieve good objective response in advanced NSCLC patients who have previously received multiple cycles of treatment and be well tolerated.
OBJECTIVES: The aim of this study was to evaluate the efficacy and tolerability of the combination of cisplatin-gemcitabine with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC).

METHODS: This was a phase II, multicenter, open-label, single-arm trial in treatment-naive patients with stage IIIA and IIIB LA-NSCLC. After three induction cycles with gemcitabine 1250 mg/m(2) plus cisplatin 80 mg/m(2), two concurrent chemoradiotherapy cycles with gemcitabine 300 mg/m(2), cisplatin 80 mg/m(2), and radiotherapy (63 Gy) were administered. The primary endpoint was response rate after induction chemotherapy followed by concurrent chemoradiotherapy. Secondary endpoints included time to progressive disease (TtPD), overall survival (OS), and safety.

RESULTS: Overall, 49 patients (median age 63.4 years; 73.5% male; Karnofsky performance status scores of 80, 85, 90, and 100 [16.3%, 2.0%, 49.0%, and 32.7%, respectively]; disease stage IIIA or IIIB 28.6% and 71.4%, respectively) were enrolled and treated. Response rate was 38.8% (95% confidence interval [CI] 25.2-53.8%). Median TtPD was 11.4 months (95% CI 9.4-12.9). Median OS was 21.8 months (95% CI 17.5-26.0), with 1- and 2-year survival rates of 70.8% and 43.7%, respectively. Overall, six patients discontinued from study treatment due to adverse events (AEs), of which two were serious AEs. The most relevant grade ≥3 AEs were neutropenia and thrombocytopenia in induction chemotherapy and chemoradiotherapy, and grade 3 events related to radiation in acute chemoradiotherapy, e.g. dysphagia, radiation pneumonitis, and radiation esophagitis.

CONCLUSIONS: Induction chemotherapy followed by concurrent chemoradiotherapy with gemcitabine (300 mg/m(2)) and cisplatin was associated with acceptable toxicity. The observed median OS time was 21.8 months. Response evaluation was difficult as in many cases it was not possible to differentiate tumor progression from local radiofibrosis.
RESUMEN / SUMMARY: - BACKGROUND: Emerging evidence suggests that single nucleotide polymorphisms (SNPs) in microRNA-coding genes may participate in the pathogenesis of lung cancer by altering the expression of tumor-related microRNAs. Several studies were investigated in recent years to evaluate the association between hsa-miR-196a2 rs11614913 polymorphism and increased/decreased lung cancer risk. In the present study, we performed a meta-analysis to systematically summarize the possible association.

METHODOLOGY PRINCIPAL FINDINGS: We performed a meta-analysis of 4 case-control studies that included 2219 lung-cancer cases and 2232 cancer-free controls. We evaluated the strength of the association using odds ratios (ORs) with 95% confidence intervals (CIs). In the overall analysis, it was found that the rs11614913 polymorphism significantly elevated the risk of lung cancer (CC versus (vs.) TT OR = 1.26, 95% CI 1.07-1.49, P = 0.007; CC/CT vs. TT: OR = 1.13, 95% CI 0.98-1.29, P = 0.007; C vs. T: OR = 1.12, 95% CI 1.03-1.22, P = 0.008). In the subgroup analysis by ethnicity, statistically significantly increased cancer risk was found among Asians (CC vs. TT: OR = 1.30, 95% CI 1.10-1.54, P = 0.003; CT vs. TT: OR = 1.16, 95% CI 1.01-1.34, P = 0.039; CC vs. CT/TT: OR = 1.21, 95% CI 1.04-1.41, P = 0.012; C vs. T: OR = 1.14, 95% CI 1.05-1.25, P = 0.002). For Europeans, a significant association with lung cancer risk was found in recessive model (CC vs. CT/TT: OR = 0.63, 95% CI 0.40-0.98, P = 0.040). No publication bias was found in this study.

CONCLUSION / SIGNIFICANCE: Our meta-analysis suggests that the rs11614913 polymorphism is significant associated with the increased risk of lung cancer, especially in Asians. Besides, the C allele of rs11614913 polymorphism may contribute to increased lung cancer risk.

[729]

TÍTULO / TITLE: - Squamous cell lung carcinoma presenting with erythema annulare centrifugum.

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


AUTORES / AUTHORS: - Atalay AA; Abuaf OK; Dogan B

INSTITUCION / INSTITUTION: - Ayca Alan Atalay, MD, Department of Dermatology and Venereology, GATA Haydarpasa Teaching Hospital, Tibbiye Caddesi, Uskudar, Istanbul, 34668, Turkey; draycaalan@gmail.com.

RESUMEN / SUMMARY: - Erythema annulare centrifugum (EAC) is a permanent or migrating eruption characterized by annular, arcuate, or polycyclic erythematous lesions that expand to the periphery when the medial parts fade. Darier was the first to described it in 1916 (1,2). Defining the incidence and prevalence of EAC is difficult because the literature mostly consists of case reports and brief reviews. Although its etiology is not known for certain, it is assumed to be hypersensitivity reaction to malignancies, infections, and drugs. However, there have not been any underlying factors detected in the majority of
cases. The prognosis for EAC is excellent, except when associated with an underlying malignancy and other systemic disease (1-3). A diagnosis of EAC should be followed by diagnostic work-up because it may result in discovery of an underlying disease. We describe a 52-year-old man affected by EAC, who upon further examination was diagnosed with squamous cell carcinoma of the lung (SCCL). A 52-year-old male patient was admitted to our department with itchy, erythematous, annular, polycyclic plaques, with a trailing scale present on the inner aspect of the advancing edges (Figs. 1 and 2). The plaques had been present on his trunk, extremities, and face for more than 3 months. The patient reported that the itchy lesions had first appeared on his forearms, then spread to his trunk, lower extremities, and face in a few weeks. Skin punch biopsy revealed orthokeratotic, parakeratotic hyperkeratosis observed occasionally on the epidermis, and mild vascular proliferation and perivascular mononuclear cell infiltration on the papillary dermis. The deep dermis, subcutis, and epidermal appendages were normal. The patient was diagnosed as EAC based on histopathologic and clinical findings. There was no history of antecedent infections or recent initiation of a new drug. Routine blood count and other chemistry tests produced normal results. Chest x-ray showed changes in the paracardiac areas of the middle and lower zones of the left lung, nodular opacities with peripheral reticulolinear extensions, and tubular radiolucent areas compatible with bronchiectasis in this region (Fig. 3). Thoracic computed tomography scan revealed a thick-walled, cavitary lesion, 4.5 cm in diameter, centrally located in the suprahilar region of the upper lobe of the left lung, observed to have a subsidiary of the upper lobe bronchus, micronodules and branching linear opacities on the parenchyma, intra-interlobular irregular septal thickening, and tractional bronchiectasis with pleuroparenchymal density increments in peripheral areas (Fig. 4). In consultation with pulmonologist, the patient was diagnosed with lung cancer; laboratory findings: CA 15-3, 32.7 U/mL (reference range: 0-31.3); CEA 7.75 ng/mL (reference range: 0-3); and erythrocyte sedimentation rate 21 mm/h (reference range: 0-15). The patient was hospitalized for treatment at department of pulmonary disease. Tumorous cells were observed on histopathologic examination of the lung biopsy obtained during bronchoscopy, which stained positive for P63 and negative for CYT7-20, CEA, TTF1, and MUC31. Clinical and histopathologic findings, and in consultation with a pulmonologist, indicated SCCL presented with superficial EAC. The patient was referred to thoracic surgery department for surgical treatment. Erythema annulare centrifugum is among diseases of unknown etiology (4). Erythema giratum repens and EAC are figure erythemas associated with malignancy (5). A review of medical literature reveals that malignancies related to EAC are squamous cell carcinoma, nasopharyngeal carcinoma, acute myelocytic leukemia, peritoneal carcinomatosis, primary bronchial carcinoid, Hodgkin’s lymphoma, chronic lymphocytic leukemia, multiple myeloma, prostate carcinoma, malignant histiocyotosis, mucinous
ovarian carcinoma, and breast cancer (3,4,6-9). Monsieur et al. report on EAC, pulmonary osteoarthropathy, palmoplantar hyperkeratosis, inappropriate secretion of antidiuretic hormone, ectopic secretion of adrenocorticotropic hormone and calcitonin in poorly differentiated lung adenocarcinoma (10). Some other publications also report on a random relationship of EAC and malignancy (4). One study of 66 cases identified cutaneous fungal infection as the most important etiologic factor (72%), while other causes included benign internal neoplasm (13%), skin diseases (18%) and internal diseases (21%) (11). A study involving 73 EAC patients revealed neoplasia in 7% of deep type EAC cases (12). Squamous cell carcinoma of the lung accounts for 25%-30% of all lung cancers. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. The need to diagnose lung cancer at an early and potentially curable stage is thus obvious. Approximately 7%-10% of patients with lung cancer are asymptomatic, and their cancers are diagnosed incidentally after a chest radiograph performed for other reasons.

Paraneoplastic syndromes may be the first or most prominent manifestation. Most paraneoplastic syndromes are caused by small cell lung cancer (SCLC). However, many paraneoplastic syndromes also occur in non-small cell lung cancer (NSCLC) patients. The symptoms may be endocrine, neuromuscular, musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature. Cutaneous itching is the most frequent cutaneous manifestation in patients with cancer. Herpes zoster, ichthyosis, flushes, alopecia, acanthosis nigricans, dermic melanosis, or hypertrichosis may also be observed. When a patient is diagnosed as a “typical” paraneoplastic syndrome, a diagnosis of cancer should be considered and investigated (13). Although our patient did not have any symptoms of lung carcinoma, etiologic study of EAC revealed early stages of SCCL. To our knowledge, this is the first case of EAC presented with SCCL. Etiology oriented research performed in EAC patients will help in early diagnosis and treatment of malignancies. This report is presented to emphasize the importance of etiologic research of EAC and EAC association with SCCL.

[730]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hayama M; Chida M; Karube Y; Tamura M; Kobayashi S; Oyaizu T; Honma K
INSTITUCIÓN / INSTITUTION: - Department of General Thoracic Surgery, Dokkyo Medical University.
Objective: Intraoperative diagnosis of lymph node (LN) metastasis is critical in lung cancer patients. The one-step nucleic acid amplification (OSNA) assay is a novel technique using a loop-mediated isothermal amplification method of gene amplification. The objective of this study was to investigate whether the OSNA assay provides sufficient diagnosis of LN metastasis in lung cancer patients.

Methods: A total of 40 LN stations were dissected from the 20 patients, who had curative lobectomy for lung cancer. The cut halves of LNs were used for pathological diagnosis, and other halves were for the OSNA assay. The OSNA assay used cytokeratin (CK) 19 mRNA as a marker. The CK19 mRNA copy number was detected using RD-100i (Sysmex Corp., Hyogo, Japan). One formalin-fixed section with the largest cutting surface of the other halves of LNs was used for pathological examination. When discordance was observed between OSNA assay and usual pathological examination, an additional examination using 1-mm interval sections was performed.

Results: In the forty LN stations, three stations were diagnosed as LN metastasis positive pathologically. In these three, the OSNA assays showed extremely high numbers of CK19 mRNA copies. When the cutoff value was set to 250 copies/mul, 4 stations with relatively low copy numbers were found to be discordant. Of the 4 discordant cases, one was shown to be micro-metastasis positive in the additional pathological assessment. The sensitivity of the OSNA assay was 100.0%, and its specificity was 91.7%.

Conclusions: This method could be applied to intraoperative assessment LNs metastasis.

[731] TÍTULO / TITLE: Malignant Tumor at D-4 Mimicking Wilkie’s Syndrome.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Mandal A; Baig S
INSTITUCIÓN / INSTITUTION: CMRI, Kolkata, India.
RESUMEN / SUMMARY: Primary carcinoma of the duodenum is rare. Here we present a case of megaduodenum due to duodenal adenocarcinoma mimicking Wilkie’s syndrome which was managed by resection and anastomosis.

RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Yumoto R; Suzuka S; Nishimoto S; Nagai J; Takano M
INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutics and Therapeutics, Graduate School of Biomedical & Health Sciences, Hiroshima University.
RESUMEN / SUMMARY: - The clearance of albumin from the alveolar space is a critical process in recovery from the edema. In this study, we investigated the effect of poly(amino acid)s such as poly-L-ornithine (PLO) on albumin uptake in cultured lung epithelial cell line A549. FITC-albumin uptake as well as cell surface binding was markedly stimulated by co-incubation with PLO, and there was a good correlation between them. After taken up by A549 cells, FITC-albumin was predominantly targeted to lysosomes. Interestingly, pretreatment of A549 cells with PLO further stimulated FITC-albumin uptake, even in the absence of PLO in the uptake buffer. FITC-albumin uptake in the presence of PLO was inhibited by a metabolic inhibitor, clathrin-mediated endocytosis inhibitors, and by a macropinocytosis inhibitor, indicating the involvement of clathrin-mediated endocytosis and/or macropinocytosis. Effect of PLO on FITC-albumin clearance was also examined in vivo pulmonary administration method in rats, and co-administration of PLO enhanced fluorescence elimination from the lungs. These findings suggest that pulmonary administration of poly(amino acid)s such as PLO is a possible strategy for enhancing albumin clearance from the alveolar space, and therefore facilitating the recovery from the pulmonary edema.

TÍTULO / TITLE: - Vascular Endothelial Growth Factor Induces CXCL1 Chemokine Release via JNK and PI-3K-Dependent Pathways in Human Lung Carcinoma Epithelial Cells.
RESUMEN / SUMMARY: - El enlace al resumen / Link to its Summary
AUTORES / AUTHORS: - Lo HM; Shieh JM; Chen CL; Tsou CJ; Wu WB
INSTITUCIÓN / INSTITUTION: - School of Medicine, Fu-Jen Catholic University, New Taipei City 24205, Taiwan. wenbin@mail.fju.edu.tw.
RESUMEN / SUMMARY: - El enlace al texto completo (gratuito o de pago) 3390/ijms140510090
Lung cancer cells express different chemokines and chemokine receptors that modulate leukocyte infiltration within tumor microenvironment. In this study we screened several mediators/growth factors on CXCL1 release in human carcinoma epithelial cells. Of the tested mediators, VEGF was found to have a robust increase in causing CXCL1 release. VEGF stimulated CXCL1 release and mRNA expression in a time- and concentration-dependent manner. The release was inhibited by the VEGF receptor antagonists and the JNK, PI-3K, tyrosine kinase, and transcription inhibitors. In parallel, VEGF induced JNK, PI3K and Akt activation. Strikingly, among these...
inhibitors only the JNK inhibitor could reduce VEGF-induced CXCL1 mRNA expression, suggesting that JNK participated in VEGF-induced CXCL1 synthesis, whereas PI-3K was responsible for cellular CXCL1 secretory process. In addition, the steroid dexamethasone and TGF-beta suppressed CXCL1 release through a transcriptional regulation. We also showed that cells stimulated with VEGF significantly attracted monocyte migration, which could be abolished by CXCL1 B/N Ab, CXC receptor 2 antagonist, TGF-beta, and dexamethasone. In summary, we provide here evidence showing JNK activation for VEGF-induced CXCL1 DNA transcription and PI-3K pathway for extracellular CXCL1 release in human carcinoma epithelial cells. The released CXCL1 was functionally linked to recruiting monocytes into lung cancer cell microenvironment.

[734]

TITULO / TITLE: - Acquisition of Chemo- or Radioresistance and Epithelial to Mesenchymal Transition (EMT) Phenotypes in Docetaxel-Resistant Lung Adenocarcinoma Cells was Linked with Downregulation of Let-7c.

RESUMEN / SUMMARY: - MicroRNA (miRNA) expression and functions have been reported to contribute to phenotypic features of tumor cells. Although targets and functional roles for many microRNAs have been described in lung adenocarcinoma (LAD), their pathophysiologic roles in phenotypes of chemoresistant LAD cells are still largely unclear. Previously, docetaxel-resistant LAD cell lines (SPC-A1/DTX and H1299/DTX) were established by our lab and displayed chemoradioresistance and mesenchymal features with enhanced invasiveness and motility. MiRNA microarray data indicated that Let-7c was significantly downregulated in SPC-A1/DTX cells. Ectopic Let-7c expression could increase the in vitro and in vivo chemo- or radiosensitivity of docetaxel-resistant LAD cells by enhancing apoptosis, reverse their EMT phenotypes and inhibit their metastatic potential in vivo by inactivation of Akt phosphorylation, whereas Let-7c inhibitor could decrease the chemo- or radiosensitivity of parental cells. Further investigation suggested that Let-7c could significantly reduce the luciferase activity of a Bcl-xL 3’ untranslated region-based reporter construct and inhibit the endogenous protein level of Bcl-xL. Additionally, siRNA-mediated Bcl-xL knockdown could mimic the same effects of Let-7c precursor and enforced Bcl-xL expression could partially
rescue the effects of Let-7c precursor in docetaxel-resistant LAD cells. Furthermore, we found that Bcl-xL was significantly upregulated in docetaxel-nonresponding LAD tissues, and its expression was inversely correlated with Let-7c expression. This study suggests an important role of Let-7c in the molecular etiology of chemoresistant LAD cells and implicates a potential target to reverse chemoresistance and EMT phenotype in human LADs.

[735]

**TÍTULO / TITLE:** Enhanced heme function and mitochondrial respiration promote the progression of lung cancer cells.

**RESUMEN / SUMMARY:**


**AUTORES / AUTHORS:** Hooda J; Cadinu D; Alam MM; Shah A; Cao TM; Sullivan LA; Brekken R; Zhang L

**INSTITUCIÓN / INSTITUTION:** Department of Molecular and Cell Biology, Center for Systems Biology, University of Texas at Dallas, Richardson, Texas, United States of America.

**RESUMEN / SUMMARY:** Lung cancer is the leading cause of cancer-related mortality, and about 85% of the cases are non-small-cell lung cancer (NSCLC). Importantly, recent advance in cancer research suggests that altering cancer cell bioenergetics can provide an effective way to target such advanced cancer cells that have acquired mutations in multiple cellular regulators. This study aims to identify bioenergetic alterations in lung cancer cells by directly measuring and comparing key metabolic activities in a pair of cell lines representing normal and NSCLC cells developed from the same patient. We found that the rates of oxygen consumption and heme biosynthesis were intensified in NSCLC cells. Additionally, the NSCLC cells exhibited substantially increased levels in an array of proteins promoting heme synthesis, uptake and function. These proteins include the rate-limiting heme biosynthetic enzyme ALAS, transporter proteins HRG1 and HCP1 that are involved in heme uptake, and various types of oxygen-utilizing hemoproteins such as cytoglobin and cytochromes. Several types of human tumor xenografts also displayed increased levels of such proteins. Furthermore, we found that lowering heme biosynthesis and uptake, like lowering mitochondrial respiration, effectively reduced oxygen consumption, cancer cell proliferation, migration and colony formation. In contrast, lowering heme degradation does not have an effect on lung cancer cells. These results show that increased heme flux and function are a key feature of NSCLC cells. Further, increased generation and supply of heme and oxygen-utilizing hemoproteins in cancer cells will lead to intensified oxygen consumption and cellular energy production by mitochondrial...
respiration, which would fuel cancer cell proliferation and progression. The results show that inhibiting heme and respiratory function can effectively arrest the progression of lung cancer cells. Hence, understanding heme function can positively impact on research in lung cancer biology and therapeutics.

[736]

**TÍTULO / TITLE:** - HnRNP A1/A2 and SF2/ASF Regulate Alternative Splicing of Interferon Regulatory Factor-3 and Affect Immunomodulatory Functions in Human Non-Small Cell Lung Cancer Cells.

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


●● Enlace al texto completo (gratuito o de pago)

1371/journal.pone.0062729

**AUTORES / AUTHORS:** - Guo R; Li Y; Ning J; Sun D; Lin L; Liu X

**INSTITUCIÓN / INSTITUTION:** - Department of Geriatrics, Peking University First Hospital, Beijing, China.

**RESUMEN / SUMMARY:** - Heterogeneous nuclear ribonucleoparticule A1/A2 (hnRNP A1/A2) and splicing factor 2/alternative splicing factor (SF2/ASF) are pivotal for precursor messenger RNA (pre-mRNA) splicing. Interferon regulatory factor-3 (IRF-3) plays critical roles in host defense against viral and microbial infection. Truncated IRF-3 proteins resulting from alternative splicing have been identified and characterized as functional antagonists to full-length IRF-3. In this study, we examined the molecular mechanism for splicing regulation of IRF-3 pre-mRNA and first reported the regulatory effect of hnRNP A1/A2 and SF2/ASF on IRF-3 splicing and activation. RNA interference-mediated depletion of hnRNP A1/A2 or SF2/ASF in human non-small cell lung cancer (NSCLC) cells increased exclusion of exons 2 and 3 of IRF-3 gene and reduced expression levels of IRF-3 protein and IRF-3 downstream effector molecules interferon-beta and CXCL10/IP-10. In addition, direct binding of hnRNP A1 and SF2/ASF to specific binding motifs in IRF-3 intron 1 was confirmed by RNA electrophoretic mobility shift assay. Subsequent minigene splicing assay showed that IRF-3 minigenes with mutated hnRNP A1/A2 or SF2/ASF binding motifs increased exclusion of exons 2 and 3. Moreover, knockdown of hnRNP A1/A2 or SF2/ASF in NSCLC cells reinforced phytohemagglutinin-induced tumor necrosis factor-alpha release by peripheral blood mononuclear cells (PBMC) but suppressed that of interleukin-10 in NSCLC/PBMC co-cultures. Taken together, our results suggest that specific knockdown for hnRNP A1/A2 or SF2/ASF increase exclusion of exons 2 and 3 of IRF-3 pre-mRNA and influence immunomodulatory functions of human NSCLC cells.

[737]
Sequencedependent effect of gemcitabine and cisplatin on A549 nonsmall cell lung cancer cells.

Cisdiamminedichloroplatinum (cisplatin, CDDP) containing combination chemotherapy is commonly used for the treatment of nonsmall cell lung cancer (NSCLC). 2',2'Difluorodeoxycytidine (gemcitabine, GEM), an active antineoplastic agent for NSCLC, has been previously reported to be suitable for use in combination with cisplatin in chemotherapy, since their mechanisms may be complementary. In the present study, the sequencedependent effects of GEM and CDDP were investigated in the NSCLC cell line, A549. Significantly increased rates of inhibition and cell cycle arrest were observed in the group treated with GEM followed by CDDP, and this treatment plan was demonstrated to represent the most efficient treatment protocol for the A549 NSCLC cell line. Results of the present study are consistent with previous studies in other cell lines and are likely to provide important insight for subsequent studies.

MicroRNA-449® Enhances Radiosensitivity in CL1-0 Lung Adenocarcinoma Cells.

Lung cancer is the leading cause of cancer-related mortality worldwide. Radiotherapy is often applied for treating lung cancer, but it often fails because of the relative non-susceptibility of lung cancer cells to radiation. MicroRNAs (miRNAs) have been reported to modulate the radiosensitivity of lung cancer cells and have the potential to improve the efficacy of radiotherapy. The purpose of this study was to identify a miRNA that can adjust radiosensitivity in lung adenocarcinoma cells. Two lung adenocarcinoma cell lines (CL1-0 and CL1-5) with different metastatic ability...
and radiosensitivity were used. In order to understand the regulatory mechanisms of differential radiosensitivity in these isogenic tumor cells, both CL1-0 and CL1-5 were treated with 10 Gy radiation, and were harvested respectively at 0, 1, 4, and 24 h after radiation exposure. The changes in expression of miRNA upon irradiation were examined using Illumina Human microRNA BeadChips. Twenty-six miRNAs were identified as having differential expression post-irradiation in CL1-0 or CL1-5 cells. Among these miRNAs, miR-449a, which was down-regulated in CL1-0 cells at 24 h after irradiation, was chosen for further investigation. Overexpression of miR-449a in CL1-0 cells effectively increased irradiation-induced DNA damage and apoptosis, altered the cell cycle distribution and eventually led to sensitization of CL1-0 to irradiation.

[739]

**TITULO / TITLE:** Digoxin Downregulates NDRG1 and VEGF through the Inhibition of HIF-1alpha under Hypoxic Conditions in Human Lung Adenocarcinoma A549 Cells.

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


**AUTORES / AUTHORS:** Wei D; Peng JJ; Gao H; Li H; Li D; Tan Y; Zhang T

**INSTITUCIÓN / INSTITUTION:** Oncology Medicine Centre, General Hospital of Chinese PLA Chengdu Command, Chengdu 610083, China. zhangtao_doctor@163.com.

**RESUMEN / SUMMARY:** Digoxin, an inhibitor of Na+/K+ ATPase, has been used in the treatment of heart-related diseases (such as congestive heart failure and atrial arrhythmia) for decades. Recently, it was reported that digoxin is also an effective HIF-1alpha inhibitor. We investigated whether digoxin could suppress tumor cell growth through HIF-1alpha in non-small cell lung cancer cells (A549 cells) under hypoxic conditions. An MTT assay was used to measure cell viability. RT-PCR and western blotting were performed to analyze the mRNA and protein expression of VEGF, NDRG1, and HIF-1alpha. HIF-1alpha nuclear translocation was then determined by EMSA. Digoxin was found to inhibit the proliferation of A549 cells under hypoxic conditions. Our results showed that hypoxia led to the upregulation of VEGF, NDRG1, and HIF-1alpha both at the mRNA and protein levels. We also found that the hypoxia-induced overexpression of VEGF, NDRG1, and HIF-1alpha was suppressed by digoxin in a concentration-dependent manner. As expected, our EMSA results demonstrated that under hypoxic conditions HIF-1alpha nuclear translocation was also markedly reduced by digoxin in a concentration-dependent manner. Our results suggest that digoxin downregulated hypoxia-induced
overexpression of VEGF and NDRG1 at the transcriptional level probably through the inhibition of HIF-1alpha synthesis in A549 cells.

[740]

**TÍTULO / TITLE:** - CD11b(-)CD27(-) NK cells are associated with the progression of lung carcinoma.

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


**AUTORES / AUTHORS:** - Jin J; Fu B; Mei X; Yue T; Sun R; Tian Z; Wei H

**INSTITUCIÓN / INSTITUTION:** - Institute of Immunology, School of Life Sciences, University of Science and Technology of China, Hefei, Anhui, China.

**RESUMEN / SUMMARY:** - NK cells are a major component of the antitumour immune response that limits tumour progression. However, it has been reported that tumour-infiltrating NK (TINK) cells from patients with non-small-cell lung carcinoma (NSCLC) exhibit profound defects in degranulation and IFN-gamma production. In support of this notion, we report a novel mechanism associated with tumour escape from NK cell-mediated antitumour immunity in lung carcinoma. In this study, we investigated the phenotypic profile of TINK cells based on the expression of the NK-cell maturation markers CD11b and CD27. Interestingly, we found a substantial CD11b(-)CD27(-) (DN) NK-cell population harboured within the tumour tissues. The presence of this CD11b(-)CD27(-) NK subset indicated that the TINK cells were of an immature and inactive phenotype. Remarkably, we determined that the presence of DN NK cells had an impact on the clinical outcomes of patients with NSCLC, as the frequency of tumour-infiltrating DN NK cells was positively correlated with the tumour stage and tumour size. We further used a murine Lewis lung cancer (LLC) model to confirm the correlation between the frequency of tumour-infiltrating DN NK cells and the progression of lung carcinoma. Together, our findings demonstrate that the tumour microenvironment may render TINK cells less tumouricidal and thereby contribute to cancer progression.

[741]

**TÍTULO / TITLE:** - Radiology quiz case 2. Recurrent inverted papilloma (IP) with focal hyperostosis in the right maxillary sinus.

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

**REVISTA / JOURNAL:** - JAMA. Acceso gratuito al texto completo.


**Enlace al texto completo (gratuito o de pago)** 1001/jamaoto.2013.24
[742]

**TÍTULO / TITLE:** - Benign and malignant tumor of the uterine body with broccoli sign: MR imaging features for differential diagnosis.

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


[●●Enlace al texto completo (gratuito o de pago) 1007/s11604-013-0215-7]

**AUTORES / AUTHORS:** - Kozawa E; Takahashi M; Meguro S; Yasuda M; Iwasa N; Fujiwara K; Kimura F

**INSTITUCIÓN / INSTITUTION:** - Department of Imaging Diagnosis, Saitama Medical University, International Medical Center, 1397-1, Yamane, Hidaka, Saitama, 350-1298, Japan, 8kozawa@saitama-med.ac.jp.

**RESUMEN / SUMMARY:** - The characteristic morphology called broccoli sign combines a stalk and prolapsed tumor and is a useful diagnostic indicator of prolapsed tumor of the uterine body. Magnetic resonance (MR) imaging findings of broccoli sign are common for uterine submucosal leiomyomata but not well described for other tumors of the endometrial cavity, such as endometrial polyp, atypical polypoid adenomyoma, endometrial carcinoma, carcinosarcoma, and adenosarcoma. Both benign and malignant masses of the uterine body can show broccoli sign. The MR imaging features of prolapsed uterine tumor with broccoli sign resemble those of usual uterine body tumors, but the location is different. We describe the MR imaging features of prolapsed uterine tumors with broccoli sign.

[743]

**TÍTULO / TITLE:** - Late recurrence of basaloid carcinoma initially treated as a small cell lung cancer.

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


[●●Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2013.03.01]

**AUTORES / AUTHORS:** - Shumaster V; Bae JW; Gettinger SN; Cai G; Kim AW

**INSTITUCIÓN / INSTITUTION:** - Section of Thoracic Surgery, Yale University School of Medicine and Yale-New Haven Hospital, New Haven, CT, USA.

**RESUMEN / SUMMARY:** - We present a patient originally treated with definitive chemoradiation therapy for small cell lung cancer (SCLC) of the right lower lobe. At 8 years post-therapy tumor recurred at the site of the original lesion without evidence of distant disease and was treated with lobectomy. Pathology demonstrated the tumor was a basaloid carcinoma (BC) rather than SCLC. She
is alive and well at 2 years following her resection and 10 years following her definitive chemoradiation therapy.

[744]
**TÍTULO / TITLE:** - Treatment of mesothelioma: still a long way to go!
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 3978/j.issn.1000-9604.2013.01.11
**AUTORES / AUTHORS:** - Van Schil PE
**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Belgium.

[745]
**TÍTULO / TITLE:** - The treatment of pleural carcinosis with malignant pleural effusion.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
  ●●Enlace al texto completo (gratuito o de pago) 3238/arztebl.2013.0313
**AUTORES / AUTHORS:** - Ried M; Hofmann HS
**INSTITUCIÓN / INSTITUTION:** - Department of Thoracic Surgery, University Hospital Regensburg.
**RESUMEN / SUMMARY:** - BACKGROUND: Pleural carcinosis is caused by tumors of the chest (e.g., lung and breast cancer) or elsewhere in the body (e.g., ovarian carcinoma) that metastasize to the visceral and/or parietal pleura. Recurrent malignant pleural effusion due to pleural carcinosis is one of the most common findings in oncology. It affects about 56 000 patients per year in Germany alone. METHODS: This review is based on pertinent literature retrieved by a selective search of the Medline database (key words: malignant pleural effusion, pleural carcinosis) and on the authors’ clinical experience. RESULTS: Although many retrospective studies have been published, there has been only one randomized controlled trial of treatment, in which permanent pleural catheters were compared with talcum pleurodesis. Patients with pleural carcinosis have a median survival of less than 12 months. Many are suffering from progression of their underlying disease, with generalized tumor involvement; thus, the symptomatic treatment of pain and dyspnea is often the main therapeutic issue. The underlying tumor, usually an adenocarcinoma, can be diagnosed either by histology or by cytology. The main complication is progressive respiratory failure. The treatment is palliative, rather than curative. The main approaches are drainage of the effusion (by thoracocentesis or with permanent pleural catheters) and pleurodesis (obliteration of the pleural space...
by causing the visceral and parietal pleura to adhere to each other).

CONCLUSION: Pleural carcinosis with symptomatic malignant pleural effusion is treated palliatively. The appropriate treatment in each case should be determined through discussion with the patient, with the goal of improving the patient’s quality of life.

[746]

**TÍTULO / TITLE:** Two Is Better Than One: Combining IGF1R and MEK Blockade as a Promising Novel Treatment Strategy Against KRAS-Mutant Lung Cancer.

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


- Enlace al texto completo (gratuito o de pago) 1158/2159-8290.CD-13-0128

**AUTORES / AUTHORS:** Chen R; Sweet-Cordero EA

**INSTITUCIÓN / INSTITUTION:** Division of Hematology/Oncology and Stem Cell Transplant, Department of Pediatrics, Stanford University School of Medicine, Stanford, California.

**RESUMEN / SUMMARY:** Summary: A small-molecule inhibitor screen on a panel of human lung cancer cell lines has uncovered an unexpected sensitivity of cells expressing oncogenic KRAS toward insulin-like growth factor 1 receptor (IGF1R) inhibition. Combining IGF1R and MAP-ERK kinase blockade led to significant effects on viability in human non-small cell lung cancer (NSCLC) cell lines and in 2 mouse models of oncogenic KRAS-driven lung cancer. The mechanistic basis for this effect seems to be an increased baseline activation of IGF1R-mediated activation of AKT in cells that express oncogenic KRAS. The studies thus point to a novel approach for treatment of KRAS-driven NSCLC, a particularly difficult subset of patients to treat with existing approaches. Cancer Discov; 3(5); 491-3. ©2013 AACR.

[747]

**TÍTULO / TITLE:** Interstitial Pneumonitis after Treatment with Pemetrexed for Non-small Cell Lung Cancer.

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

**REVISTA / JOURNAL:** Cancer Res. Acceso gratuito al texto completo a partir de 1 año de la fecha de publicación.

- Enlace a la Editora de la Revista http://cancerres.aacrjournals.org/

**AUTORES / AUTHORS:** Kim KH; Song SY; Lim KH; Han SS; Kim SH; Cho JH; Park CW; Lee S; Lee HY

574
INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea.

RESUMEN / SUMMARY: - Pemetrexed is approved as a first-line treatment for advanced non-squamous non-small cell lung cancer (NSCLC) with cisplatin and as a single agent for second-line treatment or for patients who show no disease progression after four cycles of platinum-based doublet induction chemotherapy as maintenance therapy. Pemetrexed has a modest toxicity profile and has not traditionally been regarded as a cause of interstitial pneumonitis. Here, we report on a rare case of pemetrexed-induced pneumonitis in a patient with NSCLC.

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TÍTULO / TITLE: - Present status and upcoming prospects of hedgehog pathway inhibitors in small cell lung cancer therapy.

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


AUTORES / AUTHORS: - Naqvi SH; Naqvi SH; Bandukda MY; Naqvi SM

INSTITUCIÓN / INSTITUTION: - Dow Medical College, Dow University of Health Sciences, Baba-e-Urdu Road, Karachi, Pakistan. sh.abbas.naqvi@gmail.com.

RESUMEN / SUMMARY: - Lung cancer is an important etiology of malignant mortality worldwide with global statistics indicating over 1 million deaths annually. Although there have been advances in cytotoxic chemotherapy, the prognosis after treatment still remains poor.Remarkably, recent studies on the molecular level are creating the possibility to hamper lung cancer by inhibiting the hedgehog pathway. Currently, hedgehog pathway inhibitors include IWP-2, cyclopamine and aprotinin. However, Vismodegib is a new upcoming prospect which has shown positive results while undergoing clinical trials. If approved, it may lead to a novel class of anti-cancer therapy for patients seeking treatment for small cell lung cancer.

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


AUTORES / AUTHORS: - West H; Oxnard GR; Doebele RC
Although the transition to molecularly defined patient subgroups in advanced non-small cell lung cancer (NSCLC) often leads to dramatic and prolonged responses to an inhibitor of an identified oncogenic mutation, acquired resistance eventually ensues. The optimal approach to management in that setting remains the subject of ongoing research, although it is possible to identify several points that distinguish it from traditional tenets based on conventional chemotherapy. Such patients are not equivalent to those who have progressed on first-line chemotherapy, and consideration of initiation of chemotherapy-based regimens as if the patient were being treated first line in the absence of an oncogenic mutation is a reasonable consideration. Acquired resistance is often partial; therefore, continued treatment with the same targeted therapy or another agent against the same target is a strategy favored by many experts, in part to minimize the risk of “rebound progression” that may occur when the targeted therapy is withdrawn. Progression within the central nervous system (CNS) may occur because of poor penetration of the systemic targeted therapy into the CNS, rather than true cellular resistance to the therapy itself; accordingly, local therapy for “brain only” progression with sustained targeted therapy for extracranial disease can be associated with prolonged disease control. Finally, patients with acquired resistance to a targeted therapy are ideal candidates for clinical trials when available, particularly when repeat biopsies of progressing lesions can help elucidate mechanisms of resistance and thereby lead to histologically and molecularly informed treatment decisions.

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

AUTORES / AUTHORS: - Scagliotti GV; Novello S; Rapetti S; Papotti M
INSTITUCIÓN / INSTITUTION: - From the Department of Oncology, University of Torino, San Luigi Hospital, Orbassano, Torino, Italy.
RESUMEN / SUMMARY: - Squamous cell carcinoma (SCC) represents the second most common histologic subtype of lung cancer (preceded only by adenocarcinoma). SSC of the lung is prevalently diagnosed in smokers and has been described as a preferentially centrally located tumor in which the main airways are commonly involved. Clinically, it presents with predominant
locoregional signs and symptoms, but in recent years an increasing frequency of peripheral SCC of the lung has been reported. Pathologic diagnosis can be easily made through light microscopy and immunohistochemistry. The treatment approach for early-stage disease does not differ from that of other histologic subtypes of non-small cell lung cancer; in locally advanced unresectable or metastatic disease, doublet chemotherapy regimens (including cisplatin or carboplatin and a third-generation agent such as gemcitabine, taxanes, or vinorelbine) remain the cornerstone of front-line systemic treatment. Conversely, a single agent, mainly docetaxel, is the preferred treatment in second-line treatment. In unselected patient populations, targeted therapies have been extensively tested in combination with cytotoxic chemotherapy with disappointing results because of increased toxicity or lack of improvement in efficacy outcomes. Genomic alterations in SCC of the lung have not been comprehensively characterized, and no molecularly targeted therapies have been specifically developed for the treatment of this disease, but recently immune checkpoints have emerged as new therapeutic agent.

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[751]

TÍTULO / TITLE: - Secondary malignant peritoneal mesothelioma of the greater omentum after therapy for primary pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Gutzeit A; Reischauer C; Hergan K; Kos S; Roos JE
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Cantonal Hospital Winterthur, Winterthur, Lucerne, Switzerland; Department of Radiology, Research Group, Klinik St. Anna, Lucerne, Switzerland; Department of Radiology, Paracelsus Medical University Salzburg, Salzburg, Austria.

RESUMEN / SUMMARY: - Mesothelioma is the most common malignant primary tumor of the pleura and usually associated with inhalation of asbestos fibers. In contrast, peritoneal mesothelioma is a rare entity whose pathomechanism is not yet fully understood. The coexistence of pleural mesothelioma with secondary involvement of the abdominal cavity has not been addressed in the literature. In this case report, we describe secondary malignant mesothelioma of the greater omentum. A 69-year-old man with histologically proven pleural mesothelioma on the right side and no past medical history of asbestos exposure received palliative treatment consisting of a talc pleurodesis. After a 6-month interval of stable disease, a local progressive tumor of the right pleura was seen on a CT scan. Eleven months later, during follow-up, the patient presented at our emergency department with a sudden onset of diffuse abdominal pain. Abdominal ultrasound revealed a mass within the greater omentum and the coexistence of free fluid. Subsequent abdominal CT scans demonstrated tumor...
infiltration from the right pleura by a transdiaphragmatic route into the abdomen, where diffuse infiltration of the greater omentum was observed. Aspiration of the ascites and the biopsy of the greater omentum confirmed the diagnosis of secondary malignant mesothelioma of the peritoneum. In conclusion, we present the extremely rare diagnosis of secondary malignant mesothelioma of the abdomen, which arose as a result of local progression from the right pleura into the abdomen.
**TÍTULO / TITLE:** - Fer Protein-Tyrosine Kinase Promotes Lung Adenocarcinoma Cell Invasion and Tumor Metastasis.

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

**REVISTA / JOURNAL:** - Mol Cancer Res. 2013 May 22.

**AUTORES / AUTHORS:** - Ahn J; Truesdell P; Meens J; Kadish C; Yang X; Boag AH; Craig AW

**INSTITUCIÓN / INSTITUTION:** - Queen’s University.

**RESUMEN / SUMMARY:** - Epidermal Growth Factor Receptor (EGFR) is frequently amplified or mutated in non-small cell lung cancer (NSCLC).

Although Fer protein-tyrosine kinase signals downstream of EGFR, its role in NSCLC tumor progression has not been reported. Here, we show that Fer levels are elevated in most NSCLC tumors compared to normal lung epithelium. EGFR signaling in NSCLC cell lines led to rapid Fer activation and increased localization to lamellipodia. Stable silencing of Fer in H1299 lung adenocarcinoma cells (Fer KD) caused impaired EGFR-induced lamellipodia formation compared to control cells. Fer-deficient cells showed reduced Vav2 tyrosine phosphorylation and this correlated with direct Fer-mediated phosphorylation of Vav2 on tyrosine-172, which was previously reported to increase the guanine nucleotide exchange factor activity of Vav2. Indeed, Fer KD NSCLC cells displayed defects in RacGTP localization to lamellipodia, cell migration, and cell invasion in vitro. To test the role of Fer in NSCLC progression and metastasis, control and Fer KD H1299 cells were grown as subcutaneous tumors in immune compromised mice. Although Fer was not required for tumor growth, Fer KD tumor-bearing mice had significantly fewer numbers of spontaneous metastases. Taken together, this study identifies Fer as a potential therapeutic target in metastatic lung cancers.

**[754]**

**TÍTULO / TITLE:** - Prognostic value of MET, cyclin D1 and MET gene copy number in non-small cell lung cancer.

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


**AUTORES / AUTHORS:** - Sun W; Song L; Ai T; Zhang Y; Gao Y; Cui J

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, the First Affiliated Hospital of Medical College, Xi’an Jiaotong University, Xi’an, Shaanxi 710061, China.

**RESUMEN / SUMMARY:** - The aim of this study was to analyze the correlation of the expression of MET and cyclin D1 and MET gene copy number in non-small cell lung cancer (NSCLC) tissues and patient clinicopathologic characteristics
and survival. Sixty-one NSCLC tissue specimens were included in the study. The expression of MET and cyclin D1 was evaluated by immunohistochemistry and MET gene copy number was assessed by quantitative real-time polymerase chain reaction (Q-PCR). Positive expression of MET and cyclin D1 protein and increased MET gene copy number occurred in 59.0%, 59.0% and 18.0% of 61 NSCLC tissues, respectively. MET-positivity correlated with poor differentiation (P = 0.009). Increased MET gene copy number was significantly associated with lymph node metastasis (P = 0.004) and advanced tumor stage (P = 0.048), while the expression of cyclin D1 was not associated with any clinicopathologic parameters. There was a significant correlation between the expression of MET and MET gene copy number (P = 0.002). Additionally, the expression of cyclin D1 had a significant association with the expression of MET as well as MET gene copy number (P = 0.002 and P = 0.017, respectively). MET-positivity and increased MET gene copy number were significantly associated with poor overall survival (P = 0.003 and P < 0.001, respectively) in univariate analysis. Multivariate Cox proportional hazard analysis confirmed that the expression of MET and MET gene copy number were prognostic indicators of NSCLC (P = 0.003 and P = 0.001, respectively). The overexpression of MET and the increased MET gene copy number might be adverse prognostic factors for NSCLC patients. The activation of the MET/cyclin D1 signaling pathway may contribute to carcinogenesis and the development of NSCLC, and may represent a target for therapy.
introduction of the most repressed gene JUB into SCLC cell line lead to growth inhibition. Shorter overall survival of clinical SCLC cases correlated to repression of JUB alone, or a set of four genes including H3K27me3(+) genes. Treatment with EZH2 inhibitors, DZNep and GSK126, resulted in growth repression of SCLC cell lines. High PRC2 expression was suggested to contribute to gene repression in SCLC, and may play a role in genesis of SCLC.

[756]

**TÍTULO / TITLE:** - Hypofractionated three-dimensional conformal radiotherapy for medically inoperable early stage non-small-cell lung cancer.

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


**AUTORES / AUTHORS:** - Lee JH; Wu HG; Kim HJ; Park CI; Lee SH; Kim DW; Heo DS

**INSTITUCIÓN / INSTITUTION:** - Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - PURPOSE: The purpose of this study was to assess the clinical outcomes of hypofractionated radiotherapy (HFRT) with three-dimensional conformal technique for medically inoperable patients with early stage non-small-cell lung cancer (NSCLC) and to evaluate prognostic factors. MATERIALS AND METHODS: We performed a retrospective review of 26 patients who underwent HFRT for early stage NSCLC between September 2005 and August 2011. Only clinical stage T1-3N0 was included. The median RT dose was 70 Gy (range, 60 to 72 Gy) and the median biologically equivalent dose (BED) was 94.5 Gy (range, 78.0 to 100.8 Gy). In 84.6% of patients, 4 Gy per fraction was used. Neoadjuvant chemotherapy with paclitaxel and cisplatin was given to 2 of 26 patients. RESULTS: The median follow-up time for surviving patients was 21 months (range, 13 to 49 months). The overall response rate was 53.9%, and the initial local control rate was 100%. The median survival duration was 27.8 months. Rates of 2-year overall survival, progression-free survival (PFS), local control (LC), and locoregional-free survival (LRFS) were 54.3%, 61.1%, 74.6%, and 61.9%, respectively. Multivariate analysis showed that BED (>90 vs. </=90 Gy) was an independent prognostic factor influencing PFS, LC, and LRFS. Severe toxicities over grade 3 were not observed. CONCLUSION: Radical HFRT can yield satisfactory disease control with acceptable rates of toxicities in medically inoperable patients with early stage NSCLC. HFRT is a viable alternative for clinics and patients ineligible for stereotactic ablative radiotherapy. BED over 90 Gy and 4 Gy per fraction might be appropriate for HFRT.

[757]
TÍTULO / TITLE: - Antiestrogen Use and Survival of Women with Non-small Cell Lung Cancer in Manitoba, Canada.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
    ●●Enlace al texto completo (gratuito o de pago) 1007/s12672-013-0149-7
AUTORES / AUTHORS: - Lother SA; Harding GA; Musto G; Navaratnam S; Pitz MW
INSTITUCIÓN / INSTITUTION: - Faculty of Medicine, University of Manitoba, 260 Brodie Centre, 727 McDermot Ave, Winnipeg, MB, R3E3P5, Canada.
RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer death worldwide. Sex differences in lung cancer incidence and survival are known. Female sex is an independent good prognostic factor. Estrogens appear to play a key role in lung cancer outcomes. Accordingly, antiestrogen use may also influence survival in female non-small cell lung cancer (NSCLC) patients. In this study, we compared survival among antiestrogen users and nonusers. We performed a retrospective population-based study. Using the Manitoba Cancer Registry (MCR), we identified all women diagnosed with NSCLC from 2000 to 2007. The population-based Drug Program Information Network was accessed to establish which patients received antiestrogens. Demographic data (e.g., smoking patterns, stage, histology) were gathered from the MCR and by chart review. Survival differences between antiestrogen-exposed and not exposed groups were compared using multivariable Cox regression. Two thousand three hundred twenty women fit our patient criteria, of which 156 had received antiestrogens. Exposure to antiestrogens was associated with a significantly decreased mortality in those exposed both before and after the diagnosis of NSCLC (adjusted hazard ratio, 0.42, p = 0.0006). This association remained consistent across age and stage groups. Antiestrogen use before and after the diagnosis of NSCLC is associated with decreased mortality. This supports previous evidence that estrogens may play a key role in the biology and outcomes of NSCLC and suggests a potential therapeutic use for these agents in this disease.

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[758]
TÍTULO / TITLE: - Pleural mesothelioma presenting as periumbilical metastasis: the first clinical documentation.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
    ●●Enlace al texto completo (gratuito o de pago) 1155/2013/198729
AUTORES / AUTHORS: - Falkenstern-Ge RF; Kimmich M; Bode-Erdmann S; Friedel G; Ott G; Kohlhaufl M
INTITUCIÓN / INSTITUTION: - Division of Pulmonology, Klinik Schillerhoehe, Center for Pulmonology and Thoracic Surgery, Teaching Hospital of the University of Tuebingen, Solitude Street 18, Gerlingen, 70839 Stuttgart, Germany.

RESUMEN / SUMMARY: - Introduction. Pleural mesothelioma with metastasis to the subcutaneous tissue of the abdominal wall at first diagnosis and without penetration into the peritoneum is an extremely rare clinical presentation.

Methods. Patients with pleural mesothelioma have low survival rate. Usually, the disease at presentation is confined to its site of origin (most often the pleural cavity). A 55-year-old man was referred to our center due to increasing dyspnea and a painful periumbilical mass in the anterior abdominal wall. CT scan revealed both advanced mesothelioma of the pleura and a tumor mass confined to the subcutaneous fatty tissue without penetration through the peritoneum. Results. Video-assisted thoracoscopy confirmed the diagnosis of epithelioid pleural mesothelioma, which was also confirmed by a biopsy of the periumbilical mass. Systemic chemotherapy with cisplatin and pemetrexed was initiated. Under the ongoing systemic chemotherapy, the evaluation revealed partial remission of pleura mesothelioma and its subcutaneous manifestation of the abdominal wall. Conclusion. Mesothelioma of the pleura with a simultaneous metastasis to the subcutaneous fatty tissue of the abdominal wall at presentation without penetration of peritoneum is a rare clinical presentation of mesothelioma disease. The knowledge of its natural history is very limited. This is the first ever clinical documentation of a patient with pleura mesothelioma and simultaneous subcutaneous manifestation of abdominal wall.

[759]

TÍTULO / TITLE: - New dilemmas in small-cell lung cancer TNM clinical staging.

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


●●Enlace al texto completo (gratuito o de pago) 2147/OTT.S44201

AUTORES / AUTHORS: - Zarogoulidis K; Latsios D; Porpodis K; Zarogoulidis P; Darwiche K; Antoniou N; Hohenforst-Schmidt W; Eleftheriadou E; Boutsikou E; Kontakiotis T

INSTITUCIÓN / INSTITUTION: - Pulmonary Department-Oncology Unit, “G Papanikolaou” General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.

RESUMEN / SUMMARY: - BACKGROUND: Many patients with limited disease (LD) behave similarly to those with extensive disease (ED) from a prognostic point of view. On the other hand, a proportion of patients with ED small-cell lung cancer (SCLC) behave similarly to those with LD. PATIENTS AND METHODS: In this retrospective study analysis, 764 patients with proven SCLC were included and managed with the same therapeutic protocols. Of these patients,
278 (36.4%) had LD, while 486 (63.6%) had ED. RESULTS: No statistically significant difference was observed for survival for IA and IB disease stages (P = 0.254) and between IIA and IIB stages (P = 0.256) according to the new tumor, node, metastasis (TNM) staging classification classification. In addition, no statistical significant difference was observed for survival between patients with (IIA + IIB) and IIIA (P = 0.951), (IIA + IIIA, P = 0.658), and (IIB + IIIA, P = 0.573) stages. Statistical significant difference was observed for survival among the LD SCLC patients with (IA + IB), (IIA + IIB + IIIA), and IIIB stages (P < 0.001). Similarly, statistical significance was observed for ED SCLC patients with (IIA + IIB + IIIA), IIIB, and IV stages (P < 0.001). CONCLUSIONS: Although stratification of SCLC patients in LD and ED is generally satisfactory, the TNM staging system is recommended for more detailed prognostic information and treatment evaluation in these patients.

[760]
TÍTULO / TITLE: - FER overexpression is associated with poor postoperative prognosis and cancer-cell survival in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kawakami M; Morita S; Sunohara M; Amano Y; Ishikawa R; Watanabe K; Hamano E; Ohishi N; Nakajima J; Yatomi Y; Nagase T; Fukayama M; Takai D
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The University of Tokyo Hospital, Tokyo 113-8655, Japan.
RESUMEN / SUMMARY: - Here, we show that overexpression of fer tyrosine kinase (FER), a non-receptor tyrosine kinase, predicts poor postoperative outcome and might be involved in cancer-cell survival in non-small cell lung cancer (NSCLC). Systematic screening using in silico analyses and quantitative RT-PCR revealed that FER was overexpressed in about 10% of NSCLC patients. Evaluation of FER expression using immunohistochemistry (IHC) on tissue microarrays was consistent with the mRNA level detected using quantitative RT-PCR. In analyses of 135 NSCLC patients who had undergone potential curative resection, we found that FER overexpression detected using IHC had no association with clinicopathological features such as age, sex, smoking history, histological type, disease stage, T factor, N factor, adjuvant chemotherapy history, or EGFR mutation, but was correlated with poor postoperative survival periods. A multivariate Cox regression analysis showed that this prognostic impact was independent of other clinicopathological features. In functional analyses of FER in vitro, FER exhibited a transforming activity, suggesting that it possesses oncogenic functions. We also found that human lung cancer NCI-H661 cells, which exhibited FER-outlier expression, were led to apoptosis by the knockdown of FER using RNA interference. FER
overexpression might serve as a prognostic biomarker and be involved in cancer-cell survival in NSCLC.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 5090/kjtcs.2013.46.2.162
AUTORES / AUTHORS: - Kapoor S
INSTITUCIÓN / INSTITUTION: - Private practice, USA.

[762] TÍTULO / TITLE: - Insulin-like growth factor-1 receptor (IGF-1R) as a biomarker for resistance to the tyrosine kinase inhibitor gefitinib in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s13402-013-0133-9
AUTORES / AUTHORS: - Peled N; Wynes MW; Ikeda N; Ohira T; Yoshida K; Qian J; Ilouze M; Brenner R; Kato Y; Mascaux C; Hirsch FR
INSTITUCIÓN / INSTITUTION: - Departments of Medicine/Medical Oncology and Pathology, University of Colorado Cancer Center, UC Denver, 12801 E 17th Ave; Mail Stop 8177, Aurora, CO, 80045, USA, nirp@post.tau.ac.il.
RESUMEN / SUMMARY: - BACKGROUND: The insulin-like growth factor-1 receptor (IGF-1R) pathway is known to play a role in the acquisition of resistance to epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). However, its exact role in TKI resistance has so far remained unclear. Here, we interrogated the hypothesis that the IGF-1R may serve as a biomarker for, and may play a role in, intrinsic resistance to the EGFR-specific TKI gefitinib in NSCLC. METHODS: Total-IGF-1R and phosphorylated (p)-IGF-1R expression levels were related to gefitinib sensitivity in 23 NSCLC cell lines. This sensitivity was re-evaluated after knocking down IGF-1R expression and after IGF-1R up-regulation through exogenous IGF-1 expression. The utility of IGF-1R expression as a predictive biomarker was also evaluated by immunohistochemistry (IHC) in 98 primary NSCLC samples from patients treated with gefitinib. RESULTS: Seventeen of the cell lines tested were resistant to gefitinib, whereas 3 cell lines were sensitive. The three remaining cell lines showed intermediate values. Thirteen resistant cell lines were found...
to be positive for total-IGF-1R expression, while all the sensitive cell lines were negative, resulting in a positive predictive value (PPV) of 81% for total-IGF-1R to predict resistance. Seven resistant cell lines exhibited high p-IGF-1R levels, whereas all 3 sensitive cell lines were negative for p-IGF-1R, resulting in a PPV of 100% for p-IGF-1R to predict resistance. Neither a knock-down of IGF-1R expression nor an activation of the IGF1-R pathway through exogenous IGF-1 expression affected gefitinib sensitivity. In primary NSCLC tissues, IGF-1R expression was found to be significantly higher in patients with progressive disease, i.e., showing gefitinib resistance, as compared to those with a complete or partial response. CONCLUSIONS: IGF-1R acts as a predictor for resistance to gefitinib in NSCLC cell lines and NSCLC patients, but does not seem to play a role in the intrinsic resistance to this drug. High total-IGF-1R and p-IGF-1R levels may predict such a resistance. Since the underlying mechanism does not appear to be related to proliferation induction, alternative pathways should be explored.

[763]

**TITULO / TITLE:** The presence of old pulmonary tuberculosis is an independent prognostic factor for squamous cell lung cancer survival.

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


**AUTORES / AUTHORS:** Zhou Y; Cui Z; Zhou X; Chen C; Jiang S; Hu Z; Jiang G

**INSTITUCIÓN / INSTITUTION:** Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, 507 Zhengmin Rd, Shanghai, 200433, China. shhuzy@163.com.

**RESUMEN / SUMMARY:** BACKGROUND: Pulmonary tuberculosis (TB) is associated with an increased risk of lung cancer. Our study investigated whether the coexistence of an old pulmonary TB lesion is an independent prognostic factor for lung cancer survival in Chinese non-small cell lung cancer patients. METHODS: We performed a retrospective review of 782 non-small cell lung cancer patients who underwent surgical resection as their primary treatment in 2006 and were followed for 5 years. The associations between lung cancer survival and the presence of old pulmonary TB lesions were assessed using Cox’s proportional hazard regression analysis adjusted for WHO performance status (PS), age, sex, smoking-status, tumor stage, and surgical approach. RESULTS: Sixty-four of the patients had old pulmonary TB lesions. The median survival of squamous cell carcinoma patients with TB was significantly shorter than that of patients without TB (1.7 vs. 3.4 years, p < 0.01). The presence of an old pulmonary TB lesion is an independent predictor of poor survival with a hazard ratio (HR) of 1.72 (95% CI, 1.12-2.64) in the subgroup of squamous cell carcinoma patients studied. CONCLUSION: The presence of an
old pulmonary TB lesion may be an important prognostic factor for predicting the survival of squamous cell carcinoma patients.

[764]

TÍTULO / TITLE: - Rare case of malignant transformation of recurrent respiratory papillomatosis associated with human papillomavirus type 6 infection and p53 overexpression.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Kanazawa T; Fukushima N; Imayoshi S; Nagatomo T; Kawada K; Nishino H; Misawa K; Ichimura K

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology/Head and Neck Surgery, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498 Japan.

RESUMEN / SUMMARY: - Recurrent respiratory papillomatosis (RRP), a chronic upper respiratory condition characterized by diffuse multiple recurring papillomas, is thought to result from human papillomavirus (HPV) type 6 or 11 infection. Although RRP is an intractable disease, malignant transformation of RRP is rare. The underlying mechanism, however, has not been elucidated. We describe the clinical course of a patient who underwent more than 130 operations for RRP associated with HPV type 6 infection and subsequently suffered spontaneous malignant transformation to squamous cell carcinoma. Immunohistochemical analysis revealed that malignant transformation might result from a genomic defect, such as p53 inactivation, leading to stimulation of uncontrolled cell proliferation by HPV type 6 for an extended period, but not directly because of HPV itself. Our results could help in the development of novel therapeutic strategies for severe RRP, although further studies are required before clinical application of molecular targeted therapies.

[765]

TÍTULO / TITLE: - VEGF is an important mediator of tumor angiogenesis in malignant lesions in a genetically engineered mouse model of lung adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Majeti BK; Lee JH; Simmons BH; Shojaei F
RESUMEN / SUMMARY: - BACKGROUND: VEGF is one of the key drivers of physiological or pathological angiogenesis hence several VEGF inhibitors are in different stages of clinical development. To further dissect the role of VEGF in different stages of tumor progression in lung tumors, we utilized KrasG12D-LSL GEMMs (genetically engineered mouse models). METHODS: Intranasal
delivery of adenoviruses expressing cre recombinase in KrasG12D-LSL mice results in the expression of mutant Kras that leads to development of tumor lesions ranging from adenomatous hyperplasia to large adenoma and adenocarcinoma over time in lung. In the current study, we treated KrasG12D-LSL mice at 14 weeks post inhalation with three different angiogenic inhibitors including axitinib and PF-00337210 both of which are selective inhibitors of VEGFR and sunitinib which targets VEGFR, C-SF1-R, PDGFR and KIT.

RESULTS: Pathology findings showed no significant difference in percentage of adenomatous hyperplastic lesions between the vehicle vs. any of the treatments suggesting that angiogenesis may not play a major role at early stages of tumorigenesis. However, each inhibitor suppressed percentage of benign adenoma lesions and almost fully inhibited growth of adenocarcinoma lesions in the recipients which was consistent with a reduction in tumor vasculature. Treatment with sunitinib which is a multi-targeted RTKI did not provide any advantage compared to selective VEGFR inhibitor further emphasizing role of VEGF in tumor angiogenesis in this model. CONCLUSION: Overall, our studies indicate significance of VEGF and angiogenesis in a spontaneous model of lung tumorigenesis and provide a proof of mechanism for anti-cancer activity of VEGF inhibitors in this model.

[766]
TÍTULO / TITLE: Stat3 downstream gene product chitinase 3-like 1 is a potential biomarker of inflammation-induced lung cancer in multiple mouse lung tumor models and humans.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Yan C; Ding X; Wu L; Yu M; Qu P; Du H
INSTITUCIÓN / INSTITUTION: Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.
RESUMEN / SUMMARY: Over-activation of the signal transducers and activators of the transcription 3 (Stat3) pathway in lung alveolar type II (AT II) epithelial cells induces chronic inflammation and adenocarcinoma in the lung of CCSP-rtTA/(tetO)7-CMV-Stat3C bitransgenic mice. One of Stat3 downstream genes products, chitinase 3-like 1 (CHI3L1) protein, showed increased concentration in both bronchoalveolar lavage fluid (BALF) and blood of doxycycline-treated CCSP-rtTA/(tetO)7-CMV-Stat3C bitransgenic mice. When tested in other inflammation-induced lung cancer mouse models, the CHI3L1 protein concentration was also highly increased in BALF and blood of these models with tumors. Immunohistochemical staining showed strong staining of CHI3L1 protein around tumor areas in these mouse models. Analysis of normal objects
and lung cancer patients revealed a significant elevation of CHI3L1 protein concentration in human serum samples from all categories of lung cancers. Furthermore, recombinant CHI3L protein stimulated proliferation and growth of Lewis lung cancer cells. Therefore, secretory CHI3L1 plays an important role in inflammation-induced lung cancer formation and potentially serve as a biomarker for lung cancer prediction. Based on our previous publication and this work, this is the first animal study linking overexpression of CHI3L1 to various lung tumor mouse models. These models will facilitate identification of additional biomarkers to predict and verify lung cancer under various pathogenic conditions, which normally cannot be done in humans.

[767]
TÍTULO/TITLE: - The changing epidemic of lung cancer and occupational and environmental risk factors.
RESUMEN/SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES/AUTHORS: - Dresler C
INSTITUCIÓN/INSTITUTION: - Tobacco Prevention and Cessation Network, Arkansas Department of Health, 4815 West Markham Street, Little Rock, AR 72205, USA. carolyn_dresler@ksg03.harvard.edu
RESUMEN/SUMMARY: - The epidemiology of lung cancer continues to evolve. Since the invention of a machine that could rapidly manufacture cigarettes in the 1880s, tobacco smoking has progressively been the major causative agent for the lung cancer epidemic. Until tobacco inhalation is ceased, globally, there will continue to be readily preventable lung cancers. Because cigarettes and other products the tobacco industry develops or modifies for inhalation are continually changing, the types of lung cancer could continue to change. There are other causes of lung cancer in people who never smoke, which include environmental and occupational. Enough is now known to implement strong policies that could eliminate most lung cancers.

[768]
TÍTULO/TITLE: - Adjuvant chemotherapy in older adults with non-small cell lung cancer.
RESUMEN/SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES/AUTHORS: - Gajra A
INSTITUCIÓN / INSTITUTION: - From SUNY Upstate Medical University, Syracuse, NY.

RESUMEN / SUMMARY: - Platinum-based adjuvant chemotherapy is the standard of care for patients with early-stage non-small cell lung cancer (NSCLC) treated with surgery. There is a paucity of data regarding the appropriate use of adjuvant chemotherapy in the treatment of older adults. In the absence of prospective randomized controlled trials specific to this population, the available evidence is limited to post hoc analyses of prospective studies in age-unselected populations and retrospective reviews of population databases. The available evidence for treatment of older adults with adjuvant therapy using cisplatin- and carboplatin-based therapy is reviewed. Strategies for future research, as well as the role of geriatric assessment in risk stratification, will be addressed.

[769]

TÍTULO / TITLE: - Independent of ErbB1 gene copy number, EGF stimulates migration but is not associated with cell proliferation in non-small cell lung cancer.

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


AUTORES / AUTHORS: - Lauand C; Rezende-Teixeira P; Cortez BA; Niero EL; Machado-Santelli GM

INSTITUCIÓN / INSTITUTION: - Department of Cell and Developmental Biology, Institute of Biomedical Sciences, University of Sao Paulo, Av, Prof, Lineu Prestes, 1524, Butanta, Sao Paulo, SP 05508-000, Brazil. gmmsante@usp.br.

RESUMEN / SUMMARY: - BACKGROUND: Lung cancer often exhibits molecular changes, such as the overexpression of the ErbB1 gene. ErbB1 encodes epidermal growth factor receptor (EGFR), a tyrosine kinase receptor, involved mainly in cell proliferation and survival. EGFR overexpression has been associated with more aggressive disease, poor prognosis, low survival rate and low response to therapy. ErbB1 amplification and mutation are associated with tumor development and are implicated in ineffective treatment. The aim of the present study was to investigate whether the ErbB1 copy number affects EGFR expression, cell proliferation or cell migration by comparing two different cell lines. METHODS: The copies of ErbB1 gene was evaluated by FISH. Immunofluorescence and Western blotting were performed to determine location and expression of proteins mentioned in the present study. Proliferation was studied by flow cytometry and cell migration by wound healing assay and time lapse. RESULTS: We investigated the activation and function of EGFR in the A549 and HK2 lung cancer cell lines, which contain 3 and 6 copies of ErbB1, respectively. The expression of EGFR was lower in the HK2 cell line.
EGFR was activated after stimulation with EGF in both cell lines, but this activation did not promote differences in cellular proliferation when compared to control cells. Inhibiting EGFR with AG1478 did not modify cellular proliferation, confirming previous data. However, we observed morphological alterations, changes in microfilament organization and increased cell migration upon EGF stimulation. However, these effects did not seem to be consequence of an epithelial-mesenchymal transition. CONCLUSION: EGFR expression did not appear to be associated to the ErbB1 gene copy number, and neither of these aspects appeared to affect cell proliferation. However, EGFR activation by EGF resulted in cell migration stimulation in both cell lines.

[770]
TÍTULO / TITLE: - The Motor Protein KIF14 Inhibits Tumor Growth and Cancer Metastasis in Lung Adenocarcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Hung PF; Hong TM; Hsu YC; Chen HY; Chang YL; Wu CT; Chang GC; Jou YS; Pan SH; Yang PC
INSTITUCIÓN / INSTITUTION: - Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan.
RESUMEN / SUMMARY: - The motor protein kinesin superfamily proteins (KIFs) are involved in cancer progression. The depletion of one of the KIFs, KIF14, might delay the metaphase-to-anaphase transition, resulting in a binucleated status, which enhances tumor progression; however, the exact correlation between KIF14 and cancer progression remains ambiguous. In this study, using loss of heterozygosity and array comparative genomic hybridization analyses, we observed a 30% loss in the regions surrounding KIF14 on chromosome 1q in lung adenocarcinomas. In addition, the protein expression levels of KIF14 in 122 lung adenocarcinomas also indicated that approximately 30% of adenocarcinomas showed KIF14 down-regulation compared with the expression in the bronchial epithelial cells of adjacent normal counterparts. In addition, the reduced expression of KIF14 mRNA or proteins was correlated with poor overall survival (P = 0.0158 and <0.0001, respectively), and the protein levels were also inversely correlated with metastasis (P<0.0001). The overexpression of KIF14 in lung adenocarcinoma cells inhibited anchorage-independent growth in vitro and xenograft tumor growth in vivo. The overexpression and silencing of KIF14 also inhibited or enhanced cancer cell migration, invasion and adhesion to the extracellular matrix proteins laminin and collagen IV. Furthermore, we detected the adhesion molecules cadherin 11 (CDH11) and melanoma cell adhesion molecule (MCAM) as cargo on KIF14.
The overexpression and silencing of KIF14 enhanced or reduced the recruitment of CDH11 in the membrane fraction, suggesting that KIF14 might act through recruiting adhesion molecules to the cell membrane and modulating cell adhesive, migratory and invasive properties. Thus, KIF14 might inhibit tumor growth and cancer metastasis in lung adenocarcinomas.

[771]

**TÍTULO / TITLE:** Nrf2 pathway regulates multidrug-resistance-associated protein 1 in small cell lung cancer.

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


**AUTORES / AUTHORS:** Ji L; Li H; Gao P; Shang G; Zhang DD; Zhang N; Jiang T

**INSTITUCIÓN / INSTITUTION:** Department of Pathology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Pathology, Medical School of Nantong University, Nantong, Jiangsu Province, China.

**RESUMEN / SUMMARY:** Although multidrug-resistance-associated protein-1 (MRP1) is a major contributor to multidrug resistance (MDR), the regulatory mechanism of Mrp1 still remains unclear. Nrf2 is a transcription factor that regulates cellular defense response through antioxidant response elements (AREs) in normal tissues. Recently, Nrf2 has emerged as an important contributor to chemo-resistance in tumor tissues. In the present study, the role of Nrf2-ARE pathway on regulation of Mrp1 was investigated. Compared with H69 lung cancer cells, H69AR cells with MDR showed significantly higher Nrf2-ARE pathway activity and expression of Mrp1 as well. When Nrf2 was knocked down in H69AR cells, MRP1’s expression decreased accordingly. Moreover, those H69AR cells with reduced Nrf2 level restored sensitivity to chemo-drugs. To explore how Nrf2-ARE pathway regulates Mrp1, the promoter of Mrp1 gene was searched, and two putative AREs-ARE1 and ARE2 were found. Using reporter gene and ChIP assay, both ARE1 and ARE2 showed response to and interaction with Nrf2. In 40 cases of cancer tissues, the expression of Nrf2 and MRP1 was measured by immunohistochemistry (IHC). As the quantitative data of IHC indicated, both Nrf2 and MRP1 showed significantly higher expression in tumor tissue than adjacent non-tumor tissue. And more important, the correlation analysis of the two genes proved that their expression was correlative. Taken together, theses data suggested that Nrf2-ARE pathway is required for the regulatory expression of Mrp1 and implicated Nrf2 as a new therapeutic target for MDR.

[772]
TÍTULO / TITLE: Pilot Study of CYP2B6 Genetic Variation to Explore the Contribution of Nitrosamine Activation to Lung Carcinogenesis.

RESUMEN / SUMMARY: We explored the contribution of nitrosamine metabolism to lung cancer in a pilot investigation of genetic variation in CYP2B6, a high-affinity enzymatic activator of tobacco-specific nitrosamines with a negligible role in nicotine metabolism. Previously we found that variation in CYP2A6 and CHRNA5-CHRNA3-CHRNB4 combined to increase lung cancer risk in a case-control study in European American ever-smokers (n = 860). However, these genes are involved in the pharmacology of both nicotine, through which they alter smoking behaviours, and carcinogenic nitrosamines. Herein, we separated participants by CYP2B6 genotype into a high vs. low-risk group (*1/*1 + *1/*6 vs. *6/*6). Odds ratios estimated through logistic regression modeling were 1.25 (95% CI 0.68-2.30), 1.27 (95% CI 0.89-1.79) and 1.56 (95% CI 1.04-2.31) for CYP2B6, CYP2A6 and CHRNA5-CHRNA3-CHRNB4, respectively, with negligible differences when all genes were evaluated concurrently. Modeling the combined impact of high-risk genotypes yielded odds ratios that rose from 2.05 (95% CI 0.39-10.9) to 2.43 (95% CI 0.47-12.7) to 3.94 (95% CI 0.72-21.5) for those with 1, 2 and 3 vs. 0 high-risk genotypes, respectively. Findings from this pilot point to genetic variation in CYP2B6 as a lung cancer risk factor supporting a role for nitrosamine metabolic activation in the molecular mechanism of lung carcinogenesis.

[773]
TÍTULO / TITLE: Ectopic activation of germline and placental genes identifies aggressive metastasis-prone lung cancers.

RESUMEN / SUMMARY: We explored the contribution of nitrosamine metabolism to lung cancer in a pilot investigation of genetic variation in CYP2B6, a high-affinity enzymatic activator of tobacco-specific nitrosamines with a negligible role in nicotine metabolism. Previously we found that variation in CYP2A6 and CHRNA5-CHRNA3-CHRNB4 combined to increase lung cancer risk in a case-control study in European American ever-smokers (n = 860). However, these genes are involved in the pharmacology of both nicotine, through which they alter smoking behaviours, and carcinogenic nitrosamines. Herein, we separated participants by CYP2B6 genotype into a high vs. low-risk group (*1/*1 + *1/*6 vs. *6/*6). Odds ratios estimated through logistic regression modeling were 1.25 (95% CI 0.68-2.30), 1.27 (95% CI 0.89-1.79) and 1.56 (95% CI 1.04-2.31) for CYP2B6, CYP2A6 and CHRNA5-CHRNA3-CHRNB4, respectively, with negligible differences when all genes were evaluated concurrently. Modeling the combined impact of high-risk genotypes yielded odds ratios that rose from 2.05 (95% CI 0.39-10.9) to 2.43 (95% CI 0.47-12.7) to 3.94 (95% CI 0.72-21.5) for those with 1, 2 and 3 vs. 0 high-risk genotypes, respectively. Findings from this pilot point to genetic variation in CYP2B6 as a lung cancer risk factor supporting a role for nitrosamine metabolic activation in the molecular mechanism of lung carcinogenesis.

[773]
INSTITUCIÓN / INSTITUTION: - INSERM, U823; Universite Joseph Fourier, Grenoble 1; Institut Albert Bonniot, Grenoble F-38700, France.

RESUMEN / SUMMARY: - Activation of normally silent tissue-specific genes and the resulting cell “identity crisis” are the unexplored consequences of malignant epigenetic reprogramming. We designed a strategy for investigating this reprogramming, which consisted of identifying a large number of tissue-restricted genes that are epigenetically silenced in normal somatic cells and then detecting their expression in cancer. This approach led to the demonstration that large-scale “off-context” gene activations systematically occur in a variety of cancer types. In our series of 293 lung tumors, we identified an ectopic gene expression signature associated with a subset of highly aggressive tumors, which predicted poor prognosis independently of the TNM (tumor size, node positivity, and metastasis) stage or histological subtype. The ability to isolate these tumors allowed us to reveal their common molecular features characterized by the acquisition of embryonic stem cell/germ cell gene expression profiles and the down-regulation of immune response genes. The methodical recognition of ectopic gene activations in cancer cells could serve as a basis for gene signature-guided tumor stratification, as well as for the discovery of oncogenic mechanisms, and expand the understanding of the biology of very aggressive tumors.

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TÍTULO / TITLE: - Quantitative Proteomic Analysis Identifies CPNE3 as a Novel Metastasis-promoting Gene in NSCLC.

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


AUTORES / AUTHORS: - Lin HC; Zhang FL; Geng Q; Yu T; Cui YQ; Liu XH; Li J; Yan MX; Liu L; He XH; Li JJ; Yao M

RESUMEN / SUMMARY: - To discover metastasis-associated proteins within cancer cells, we used the isobaric tags for relative and absolute quantitation (iTRAQ) approach combined with Nano Liquid Chromatography-tandem Mass Spectrometry (NanoLC-MS/MS) analysis to identify proteins that were differentially expressed between lung adenocarcinoma cancer cell lines SPC-A-1sci cells with high metastatic potential and parent SPC-A-1 cells with low metastatic potential. By employing biological and technical replicates, we identified 5818 non-redundant proteins and quantified 5443 proteins, 256 of which were differentially expressed in the two cell lines. Through si-RNA-mediated functional screens, Myosin heavy chain 9 (MYH9) and Copine III (CPNE3) were indicated as positively correlating with the migration and invasion properties of SPC-A1sci cells, and the same function of CPNE3 was confirmed in another lung cancer cell line, H1299. Furthermore, over-expressing CPNE3 promoted non-small-cell lung cancer (NSCLC) cell line (SPC-A-1 and XL-2)
migration and invasion in vitro. Moreover, the targeted knock-down of CPNE3 inhibited the in vivo metastatic abilities of H1299 cells in mouse models. Lastly, immunohistochemistry revealed that the CPNE3 expression level was positively correlated with the clinical stage and TNM classification in NSCLC patients. Taken together, our results indicate that CPNE3 could play a critical role in NSCLC metastasis.

[775]

TÍTULO / TITLE: - Prognostic Significance of Twist and N-Cadherin Expression in NSCLC.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●● Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0062171
AUTORES / AUTHORS: - Hui L; Zhang S; Dong X; Tian D; Cui Z; Qiu X
INSTITUCIÓN / INSTITUTION: - Laboratory Center, The Fourth Affiliated Hospital of China Medical University, Shenyang, China; Center of Laboratory Technology and Experimental Medicine, China Medical University, Shenyang, China.

RESUMEN / SUMMARY: - BACKGROUND: Metastasis is the most common cause of disease failure and mortality for non-small cell lung cancer after surgical resection. Twist has been recently identified as a putative oncogene and a key regulator of carcinoma metastasis. N-cadherin is associated with a more aggressive behavior of cell lines and tumors. The aim of this study was to evaluate the clinical relevance of Twist and N-cadherin expression in NSCLC, and the effects of Twist1 knockdown on lung cancer cells. METHODS: We examined the expressions of Twist and N-cadherin by immunohistochemistry in 120 cases of non-small cell lung cancer (including 68 cases with follow-up records). We also analyzed Twist1 and N-cadherin mRNA expression in 30 non-small cell lung cancer tissues using quantitative reverse transcription polymerase chain reaction. The functional roles of Twist1 in lung cancer cell lines were evaluated by small interfering RNA-mediated depletion of the protein followed by analyses of cell apoptosis and invasion. RESULTS: In lung cancer tissues, the overexpression rate of Twist was 38.3% in lung cancer tissues. Overexpression of N-cadherin was shown in 40.83% of primary tumors. Moreover, Twist1 mRNA expression levels correlated with N-cadherin mRNA levels. Furthermore, overexpression of Twist1 or N-cadherin in primary non-small cell lung cancers was associated with a shorter overall survival (P<0.01, P<0.01, respectively). Depleting Twist expression inhibited cell invasion and increased apoptosis in lung cancer cell lines. CONCLUSIONS: The overexpression of Twist and N-cadherin could be considered as useful biomarkers for predicting the prognosis of NSCLC. Twist1 could inhibit
apoptosis and promote the invasion of lung cancer cells, and depletion of Twist1 in lung cancer cells led to inhibition of N-cadherin expression.

[776]

**TÍTULO / TITLE:** - Does the extent of lymph nodes dissection affect the prognosis of resected stage IA non-small cell lung cancer?
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
**REVISTA / JOURNAL:** - Clin Transl Oncol. 2013 Apr 25.
  - [Enlace al texto completo (gratuito o de pago)](1007/s12094-013-1043-z)

**AUTORES / AUTHORS:** - Xu F; Wang C; Qi L; Yu W; Li Q
**INSTITUCIÓN / INSTITUTION:** - Key Laboratory of Cancer Prevention of Tianjin, Cancer Institute and Hospital of Tianjin Medical University, Huan Hu Xi Road, He Xi District, Tianjin, People’s Republic of China.
**RESUMEN / SUMMARY:** - PURPOSE: Curative surgery remains the priority for treatment of stage IA non-small cell lung cancer (NSCLC). The purpose of this study is to investigate if the extent of lymph node (LN) dissections affect the prognosis of resected stage IA NSCLC. METHODS: A total of 110 stage IA NSCLC patients who underwent curative resections were reviewed. The patients were classified according to the number of lymph nodes dissected (N) and levels sampled (NL, N2). The tumor residuals of 2,251 LNs were detected by immunohistochemistry (IHC). The Flow Cytometry (FACS) of the peripheral blood (PB) and LNs was used to evaluate patients’ immunity. The relationship between the studied factors and the correlation with disease-free survival (DFS) was analyzed. RESULTS: Disease free survival was improved as the extent of dissections increased in terms of N, NL and N2 (p = 0.005, <0.001, <0.001). Multivariate tests suggested N, N2 and NL (p = 0.001, 0.001, <0.001) were independent risk factors. However, the detection of tumor residuals also increased with the extent of dissection (p = 0.023, <0.001) while the presence of micrometastasis (MM) correlated with poor DFS (p = 0.028). Increased N represented weakened innate immunity (p = 0.048). Multivariate tests did not indicate a correlation between immunity and patients’ DFS (p = 0.074).
**CONCLUSION:** The more extensive lymph node dissections achieved better disease control for stage IA NSCLC. Greater retrieval of LNs did not imply enhanced innate immunity; nor did their immunity level affect survival.

[777]

**TÍTULO / TITLE:** - Semi-nested real-time reverse transcription polymerase chain reaction methods for the successful quantitation of cytokeratin mRNA expression levels for the subtyping of non-small-cell lung carcinoma using paraffin-embedded and microdissected lung biopsy specimens.
**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)
●●Enlace al texto completo (gratuito o de pago) 1267/ahc.12024
AUTORES / AUTHORS: - Nakanishi Y; Shimizu T; Tsujino I; Obana Y; Seki T; Fuchinoue F; Ohni S; Oinuma T; Kusumi Y; Yamada T; Takahashi N; Hashimoto S; Nemoto N
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nihon University School of Medicine, Tokyo, Japan.
RESUMEN / SUMMARY: - En pacientes con neoplasias en estadios avanzados de no pequeña célula (NSCLC), la clasificación histológica de las muestras de biopsia es a menudo requerida para determinar las indicaciones de tratamiento con medicamentos. El objetivo de este estudio fue evaluar la utilidad del cuantificación de mRNA sensible para la clasificación histológica de NSCLC avanzadas usando pequeños fragmentos de biopsias FFPE. Las expresiones de CK6, CK7, CK14, CK18, y la transcriptasa tiroidea 1 (TTF-1) se midieron utilizando técnica de reacción en cadena de la polimerasa (RT-PCR) en células microdisectadas de tumores recogidas de 52 biopsias pulmonares. Nuestros resultados muestran una mejoración en la cuantificación de mRNA a partir de muestras FFPE, y la expresión de mRNA usando RT-PCR fue correlacionada con la expresión proteica inmunohistoquímica. CK7, CK18, y TTF-1 mRNA se expresaron a un nivel significativamente más alto (P<0.05) en carcinoma de células escamosas (SQ) que en carcinoma adenocarcinooma (AD), mientras que CK6 y CK14 mRNA expresión fue significativamente más alta (P<0.05) en AD que en SQ. Cada CK histología específica, particularmente CK18 en AD y CK6 en SQ, mostró una correlación con un mal pronóstico (P=0.02, 0.02, respectivamente). Nuestros resultados demostraron que una cuantificación de mRNA de tipo CK de las muestras de biopsia pulmonar puede ser útil para predecir el tipo histológico y el pronóstico de NSCLC avanzada.

[778]
TÍTULO / TITLE: - Myeloid clusters are associated with a pro-metastatic environment and poor prognosis in smoking-related early stage non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0065121
AUTORES / AUTHORS: - Zhang W; Pal SK; Liu X; Yang C; Allahabadi S; Bhanji S; Figlin RA; Yu H; Reckamp KL
INSTITUCIÓN / INSTITUTION: - Department of Cancer Immunotherapy and Immunology, City of Hope Comprehensive Cancer Center, Duarte, California, United States of America.
RESUMEN / SUMMARY: - BACKGROUND: This study aimed to understand the role of myeloid cell clusters in uninvolved regional lymph nodes from early stage non-small cell lung cancer patients. METHODS: Uninvolved regional lymph node sections from 67 patients with stage I-III resected non-small cell lung cancer were immunostained to detect myeloid clusters, STAT3 activity and occult metastasis. Anthracosis intensity, myeloid cluster infiltration associated with anthracosis and pSTAT3 level were scored and correlated with patient survival. Multivariate Cox regression analysis was performed with prognostic variables. Human macrophages were used for in vitro nicotine treatment. RESULTS: CD68(+) myeloid clusters associated with anthracosis and with an immunosuppressive and metastasis-promoting phenotype and elevated overall STAT3 activity were observed in uninvolved lymph nodes. In patients with a smoking history, myeloid cluster score significantly correlated with anthracosis intensity and pSTAT3 level (P<0.01). Nicotine activated STAT3 in macrophages in long-term culture. CD68(+) myeloid clusters correlated and colocalized with occult metastasis. Myeloid cluster score was an independent prognostic factor (P = 0.049) and was associated with survival by Kaplan-Maier estimate in patients with a history of smoking (P = 0.055). The combination of myeloid cluster score with either lymph node stage or pSTAT3 level defined two populations with a significant difference in survival (P = 0.024 and P = 0.004, respectively). CONCLUSIONS: Myeloid clusters facilitate a pro-metastatic microenvironment in uninvolved regional lymph nodes and associate with occult metastasis in early stage non-small cell lung cancer. Myeloid cluster score is an independent prognostic factor for survival in patients with a history of smoking, and may present a novel method to inform therapy choices in the adjuvant setting. Further validation studies are warranted.

TÍTULO / TITLE: - Differentiation of central lung cancer from atelectasis: comparison of diffusion-weighted MRI with PET/CT.

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


AUTORES / AUTHORS: - Yang RM; Li L; Wei XH; Guo YM; Huang YH; Lai LS; Chen AM; Liu GS; Xiong WF; Luo LP; Jiang XQ

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Guangzhou First People's Hospital, Guangzhou Medical College, Guangzhou, China.

RESUMEN / SUMMARY: - OBJECTIVE: Prospectively assess the performance of diffusion-weighted magnetic resonance imaging (DW-MRI) for differentiation of central lung cancer from atelectasis. MATERIALS AND METHODS: 38 consecutive lung cancer patients (26 males, 12 females; age range: 28-71
years; mean age: 49 years) who were referred for thoracic MR imaging examinations were enrolled. MR examinations were performed using a 1.5-T clinical scanner and scanning sequences of T1WI, T2WI, and DWI. Cancers and atelectasis were measured by mapping of the apparent diffusion coefficients (ADCs) obtained with a b-value of 500 s/mm(2). RESULTS: PET/CT and DW-MR allowed differentiation of tumor and atelectasis in all 38 cases, but T2WI did not allow differentiation in 9 cases. Comparison of conventional T2WI and DW-MRI indicated a higher contrast noise ratio of the central lung carcinoma than the atelectasis by DW-MRI. ADC maps indicated significantly lower mean ADC in the central lung carcinoma than in the atelectasis (1.83+/−0.58 vs. 2.90+/−0.26 mm(2)/s, p<0.0001). ADC values of small cell lung carcinoma were significantly greater than those from squamous cell carcinoma and adenocarcinoma (p<0.0001 for both). CONCLUSIONS: DW-MR imaging provides valuable information not obtained by conventional MR and may be useful for differentiation of central lung carcinoma from atelectasis. Future developments may allow DW-MR imaging to be used as an alternative to PET-CT in imaging of patients with lung cancer.

[780]

**TITULO / TITLE:** - Peripheral Blood miR-328 Expression as a Potential Biomarker for the Early Diagnosis of NSCLC.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Ulivi P; Foschi G; Mengozzi M; Scarpi E; Silvestrini R; Amadori D; Zoli W

**INSTITUCION / INSTITUTION:** - Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, 47014 Meldola, Italy. [p.ulivi@irst.emr.it](mailto:p.ulivi@irst.emr.it).

**RESUMEN / SUMMARY:** - Lung cancer is often diagnosed at an advanced stage, with subsequently poor prognosis. There are no biomarkers available to facilitate early diagnosis or to discriminate between benign and malignant nodules. MicroRNAs (miRNAs) are stable molecules that can be found and measured in peripheral blood, thus representing potential diagnostic biomarkers. We evaluated 100 individuals comprising 86 patients with predominantly early-stage non-small cell lung cancer (NSCLC) and 24 healthy donors. RNA was extracted from peripheral blood samples and the expression of a panel of miRNAs was analyzed by Real-Time PCR method. Expression levels of miR-328, miR-18a, miR-339 and miR-140 were significantly higher in NSCLC patients than in healthy donors (p < 0.05). In particular, miR-328 showed good diagnostic accuracy in discriminating between patients with early NSCLC and healthy donors (AUC ROC 0.82, 95% CI 0.72-0.92), with 70%
sensitivity and 83% specificity at the best relative expression cut-off of 300. Moreover, miR-339 was a good discriminant between healthy donors and late-stage NSCLC patients (AUC ROC 0.79, 95% CI 0.68-0.91). In conclusion, miR-328 represents a potential diagnostic biomarker of NSCLC, especially for the identification of early-stage tumors. Its role in discriminating between benign and malignant nodules detected by spiral CT warrants further investigation.

[781]

TÍTULO / TITLE: - Dose-Escalation Study of Three-Dimensional Conformal Thoracic Radiotherapy With Concurrent S-1 and Cisplatin for Inoperable Stage III Non-Small-Cell Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: - Harada H; Nishio M; Murakami H; Ohyanagi F; Kozuka T; Ishikura S; Naito T; Kaira K; Takahashi T; Horike A; Nishimura T; Yamamoto N

INSTITUCIÓN / INSTITUTION: - Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan. Electronic address: h.harada@scchr.jp.

RESUMEN / SUMMARY: - PURPOSE: To determine the recommended dose (RD) in concurrent conformal radiotherapy with S-1 and cisplatin chemotherapy for inoperable stage III non-small-cell lung cancer. PATIENTS AND METHODS: Eligible patients with inoperable stage III non-small-cell lung cancer, age >/= 20 years, performance status 0-1 received 4 cycles of intravenous cisplatin (60 mg/m2, day 1) and oral S-1 (80, 100, or 120 mg based on body surface area, days 1-14) repeated every 4 weeks. Radiation doses were 66, 70, and 74 Gy for arms 1, 2, and 3, respectively. RESULTS: A total of 24 patients were enrolled in our study, including 6 in arm 1, 6 in arm 2, and 12 in arm 3. The patients consisted of 14 men and 10 women, with a median age of 63 years (range, 44-73 years). The median follow-up was 27.3 months (range, 8.5-42.6 months) for all patients and 33.9 months (range, 15.2-42.6 months) for those still alive. Grade 3 febrile neutropenia, lung toxicities, and heart toxicities occurred in 2, 2, and 1 patients, respectively. Dose-limiting toxicity occurred in 2, none, and 1 patient in arms 1, 2, and 3, respectively. The median survival was not reached, and the 2-year survival rate was 70% (95% CI, 51%-89%). Two-year local relapse-free survival and distant metastasis-free survival were 74% (95% CI, 56%-92%) and 45% (95% CI, 25%-65%), respectively. CONCLUSIONS: High-dose radiotherapy with S-1 and cisplatin is feasible, and 74 Gy was determined as the recommended dose.

[782]
TÍTULO / TITLE: - Importance of serum levels of angiopoietin-2 and survivin biomarkers in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fawzy A; Gaafar R; Kasem F; Ali SS; Elshafei M; Eldeib M
INSTITUCIÓN / INSTITUTION: - Clinical Pathology Department, NCI, Cairo University, Egypt. amalfawzy69@hotmail.com
RESUMEN / SUMMARY: - BACKGROUND: Angiogenesis is an essential process in cancer growth maintenance, and metastasis. Angiopoietin-2 promotes tumor angiogenesis by priming the vasculature and potentiating the effects of cytokines at the front of active neovascularization. Enhanced expression of angiopoietin-2 has been reported in lung cancer tissue. Survivin is one of the inhibitors of apoptosis protein that has been shown to play a key role in cancer progression, and in tumor angiogenesis. Also plays a key role in tumor cell resistance to anticancer agents and ionizing radiation. AIM: To measure the serum levels of angiopoietin-2 and survivin as possible angiogenic factors in lung cancer patients with the assessment of their interrelationships and clinical significance. PATIENTS AND METHODS: Patients with lung cancer as NSCLC (n=70) and healthy volunteers (n=10) were enrolled. Serum angiopoietin-2 and survivin concentrations were measured using enzyme-linked immunosorbent assay (ELIZA). RESULTS: Median serum angiopoietin-2 levels with lung cancer (2730pg/mL) ranged from 1171 to 6541pg/mL was higher than the median of the control group (1795pg/mL) ranged from 1076 to 2730/mL, p<0.001. Median serum survivin levels were also higher in patients with lung cancer (53.0pg/mL) ranged from 39.3 to 96.3pg/mL than the median of the control group (48.8pg/mL) ranged from 38.0 to 74.6pg/mL, but did not reach statistical significance p=0.206. In all patients with lung cancer, serum angiopoietin-2 was not significantly correlated with survivin (r=0.073, p=0.657). Neither serum angiopoietin-2 nor survivin showed significant relation with the serum angiopoietin-2 or survivin levels depending on the cell types, stage progression, and metastasis among the patients with NSCLC. CONCLUSIONS: Our study suggests that serum angiopoietin-2 is a useful marker for the diagnosis of NSCLC by ELIZA technique.

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TÍTULO / TITLE: - High Serum CEA and CYFRA21-1 Levels after a Two-Cycle Adjuvant Chemotherapy for NSCLC: Possible Poor Prognostic Factors.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
OBJECTIVE: The aim of this study was to test whether carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (CYFRA21-1) can be used as a prognostic factor for non-small-cell lung cancer (NSCLC) after two cycles of adjuvant chemotherapy in NSCLC patients. METHODS: A total of 169 patients underwent at least two cycles of adjuvant chemotherapy. The serum levels of CEA and CYFRA21-1 were recorded after the second cycle of chemotherapy, and the patient follow-up was conducted. Overall survival (OS) and disease-free survival (DFS) were used as the primary endpoint and the secondary endpoint, respectively. RESULTS: The high levels of CEA and CYFRA21-1 after two cycles of adjuvant chemotherapy were poor prognostic factors for OS, with risk ratios (RR) of 2.003 and 1.702, respectively. A high CEA level was a poor prognostic factor (RR 1.152) for DFS. The median survival time (MST) of the high CEA level group was 26 months, whereas that of the normal group was 61 months (P<0.0001). The median DFS time of the high CEA group and the normal group was 34 and 53 months, respectively (P<0.0001). The MST of the high CYFRA21-1 group and the normal group was 43 and 56 months, respectively (P<0.0001). CONCLUSIONS: The high serum levels of CEA or CYFRA21-1 after two cycles of adjuvant chemotherapy are poor prognostic factors for NSCLC patients.

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TÍTULO / TITLE: Primary cutaneous small cell carcinoma; a case report with differential diagnosis.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Terada T
INSTITUCIÓN / INSTITUTION: Department of Pathology, Shizuoka City Shimizu Hospital Shimizu, Shizuoka, Japan.
RESUMEN / SUMMARY: Primary cutaneous small cell carcinoma (PC-SmCC) is extremely rare; only two cases have been reported in the world literatures. A 79-year-old woman presented a small cutaneous tumor in the face. Physical examination showed a tumor measuring 1.0x.08x0.6 cm in the shallow skin of the face. Excisional skin biopsy was performed. The biopsy showed complete excision of the tumor. The tumor was located in the shallow dermis and no connections to epidermis were seen. The tumor was invasive into subcutaneous tissue and surrounding dermis. The tumor was very hypercellular tumor composed of small cells with scant cytoplasm, hyperchromatic nuclei, negative nucleoli, and molded nuclei. The shapes of tumor cells are round, ovoid or
spindle. The histological appearances fulfilled the criteria of SmCC of WHO. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK34BE12, CD5, CD6, CK8, p63, NSE, NCAM, synaptophysin (focal), chromogranin (focal), p53, KIT, PDGFRA and Ki-67 (labeling index (LI)=86%). They were negative for CK7, CK19, EMA, vimentin, CEA, S100 protein, CA19-9, TTF-1, MUC1, MUC2, MUC5AC and MUC6. Mucin histochemistry revealed no mucins. A molecular genetic analysis of PCR-direct sequencing identified no mutations of KIT (exons 9, 11, 13, and 17) and PDGFRA (exons 12 and 18) genes. The author diagnosed this cutaneous tumor as SmCC. Post-diagnosis whole body examination using various imaging and endoscopic techniques revealed no tumors. This may confirm that the skin tumor was primary. The cutaneous tumor was completely resected with wide margins. The patient is now followed up without therapy 8 months after the diagnosis. No recurrence or metastasis is seen. The differential diagnosis from Merkel cell carcinoma and basal cell carcinoma is very difficult and herein discussed.

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

AUTORES / AUTHORS: - Adulkar N; Radhakrishnan S; Vidhya N; Kim U
INSTITUCIÓN / INSTITUTION: - Department of Orbit, Oculoplasty & Ocular Oncology, Aravind Eye Hospital & Postgraduate Institute, Madurai, Tamil Nadu 625020, India.

RESUMEN / SUMMARY: - Neoplasms of retinal pigment epithelium are rare and must be differentiated from choroidal melanoma. The possibility of a metastatic disease with possible primary sites as lung, breast, or kidney should be ruled out. Herein we report a case of adenocarcinoma arising from the RPE with a lung lesion suspicious of bronchogenic carcinoma. In this paper, ocular symptoms were the first sign of a systemic malignancy.

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

AUTORES / AUTHORS: - Losito NS; Scaffa C; Cantile M; Botti G; Costanzo R; Manna A; Franco R; Greggi S
Metastatic neoplasms to the ovary often cause diagnostic problems, in particular those large ovarian masses mimicking primary tumors. Most of these tumors arise from digestive system or breast, while 37-year-old woman diagnosed as right adnexal complex mass, with a subpleural nodule in the apical part of the left lower lobe, at preoperative chest computed tomography scan. The patient underwent total abdominal hysterectomy with right salpingo-oophorectomy (ovarian mass 220 x 200 mm), total omentectomy, left ovarian biopsy, peritoneal random biopsies, and peritoneal washings for cytology. Pathologic and immunohistochemical examination of ovarian specimen suggested morphology and expression of metastatic lung adenocarcinoma with an intense positivity for Thyroid Transcriptional Factor-1 (TTF-1) and Cytokeratin 7 (CK7) staining. Fine needle biopsy of the lung nodule found epithelioid like malignant cells, confirming the diagnosis of an ovarian metastasis from a primary lung cancer. This report focused on the clinical and pathologic diagnostic challenge of distinguishing secondary from primary ovarian neoplasms. Issues on useful immunohistochemical stains are also discussed.
cisplatin-based chemotherapy should be given in either adjuvant or neoadjuvant settings to patients who are undergoing curative surgical resection and who are candidates for cisplatin therapy. In definitive chemoradiotherapy, cisplatin-based therapy is recommended although a carboplatin-based regimen may be given if patients cannot receive cisplatin. Finally, all patients with stage IIIA NSCLC should be evaluated early in a multidisciplinary setting that includes medical and radiation oncologists and thoracic surgeons with experience in lung cancer therapy.

[788]
TÍTULO / TITLE: Recurrent respiratory papillomatosis: A possible role for the HPV vaccine?
RESUMEN / SUMMARY: [Enlace al Resumen / Link to its Summary]
AUTORES / AUTHORS: Lively JM; Shah RK
INSTITUCIÓN / INSTITUTION: Department of Otolaryngology, Children’s National Medical Center, Washington DC, USA.

[789]
TÍTULO / TITLE: Early detection of lewis lung carcinoma tumor control by irradiation using diffusion-weighted and dynamic contrast-enhanced MRI.
RESUMEN / SUMMARY: [Enlace al Resumen / Link to its Summary]
●●Enlace al texto completo (gratis o de pago) 1371/journal.pone.0062762
AUTORES / AUTHORS: Cheng JC; Yuan A; Chen JH; Lu YC; Cho KH; Wu JK; Wu CJ; Chang YC; Yang PC
INSTITUCIÓN / INSTITUTION: Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan; Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University College of Electrical Engineering and Computer Science, Taipei, Taiwan; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan.
RESUMEN / SUMMARY: PURPOSE: To investigate the correlation between diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) derived parameters and radioresponsiveness of Lewis lung carcinoma (LLC) tumor. MATERIALS AND METHODS: LLC tumor growth in C57BL/6 mouse limb was used for the experiment. The tumors were irradiated with 10 Gy x 5, or 30 Gy x 2 vs. sham irradiation. Fourteen tumors were subjected to DW-MRI and DCE-MRI pre-radiotherapy and weekly imaging after
radiotherapy. The temporal changes in apparent diffusion coefficient (ADC) and DCE-MRI derived parameters (K(\text{trans}), \text{kep}, \text{ve}, \text{vp}) were correlated with tumor size, and were histologically compared with CD31 staining of resected tumors. RESULTS: The 10 Gyx5 dose inhibited tumor growth for a week, while 30 Gyx2 controlled tumor growth for a 3-week observation period. One week after radiotherapy (week 2), irradiated tumors showed significantly higher values of ADC than untreated ones (10 Gyx5, \( p = 0.004 \); 30 Gyx2, \( p = 0.01 \)). Significantly higher values of ve were shown earlier by 30 Gyx2 vs. sham (\( p = 0.01 \)) and 10 Gyx5 vs. sham irradiation (\( p = 0.05 \)). Sustained higher ve from 10 Gyx5 compared to sham irradiated tumors was evident at week 3 (\( p = 0.016 \)) and week 4 (\( p = 0.046 \)). A 13.8\% early increase in ADC for 30 Gyx2 tumor group (\( p = 0.002 \)) and a 16.5\% increase for 10 Gyx5 group were noted (\( p = 0.01 \)) vs. sham irradiation (which showed a 2.2\% decrease). No differences were found for K(\text{trans}), \text{kep}, or \text{vp}. Both radiotherapy groups demonstrated significant reduction in microvessel counts. CONCLUSION: Early increase in ADC and ve correlated with tumor control by irradiation.

[790]

**TÍTULO / TITLE:** - Polymorphisms of microRNA Sequences or Binding Sites and Lung Cancer: A Meta-Analysis and Systematic Review.

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


**AUTORES / AUTHORS:** - Chen Z; Xu L; Ye X; Shen S; Li Z; Niu X; Lu S

**INSTITUCIÓN / INSTITUTION:** - Shanghai Lung Tumor Clinical Medical Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China.

**RESUMEN / SUMMARY:** - OBJECTIVE: Functional single nucleotide polymorphisms (SNPs) of microRNA (miRNA) sequences or binding sites (miRNA-SNPs) are associated with lung cancer risk and survival. The objective of this study was to systematically review genetic association studies about miRNA-SNPs in lung cancer. METHODS: Eligible genetic association studies were retrieved from databases of PubMed, EMBASE, China National Knowledge Infrastructure and SinoMed. Two investigators selected related studies and assessed methodological quality independently. Quantitative data synthesis was conducted for common SNPs of miRNA (miRNA-196\^{a}2 rs11614913, miRNA146a rs2910164, miRNA149 rs2292832, miRNA-605 rs2043556 and miRNA499 rs3746444). GRADE profiler was used to grade the quality of evidence for each miRNA-SNP. RESULTS: 15 eligible studies and 27 miRNA-SNPs were retrieved and 10 miRNA-SNPs were reported with a significant association with susceptibility to or survival of lung cancer. Methodological quality of eligible studies was adequate with an average score
of 8.5. miRNA-196 promoters polymorphism was associated with increased lung cancer risk (homozygote comparison, OR = 1.299, 95% CI: 1.096-1.540; dominant model, OR = 1.217, 95% CI: 1.041-1.421) and decreased survival. And according to GRADE profiler, quality of evidence was moderate for MYCL1 rs3134615, while quality of the other significant associations was low.

CONCLUSIONS: Based on this first systematic review about miRNA-SNPs in lung cancer, quality of evidence was low for most genetic association studies. Polymorphisms of miRNA-196 promoter rs11614913 and MYCL1 rs3134615 could be potential biomarkers of lung cancer.

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[791]

TÍTULO / TITLE: - Use of adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children.

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

REVISTA / JOURNAL: - JAMA. Acceso gratuito al texto completo.

●●Enlace a la Editora de la Revista http://jama.ama-assn.org/search.dtl


●●Enlace al texto completo (gratuito o de pago) 1001/jamaoto.2013.1810

AUTORES / AUTHORS: - Rogers DJ; Ojha S; Maurer R; Hartnick CJ

RESUMEN / SUMMARY: - IMPORTANCE Juvenile recurrent respiratory papillomatosis (RRP) can be an aggressive disease process necessitating frequent trips to the operating room with multiple anesthetics for tumor debulking and airway preservation. Adjuvant therapy, such as that which is reported in this article, may help reduce the number of operative procedures affected children need each year and therefore may also affect their overall quality of life (QOL). OBJECTIVE To describe our experience with intralesional bevacizumab (Avastin) treatment for children with severe RRP by comparing median number of surgical procedures per year, median duration of time between procedures, Derkay staging, and voice QOL before and after bevacizumab treatment. DESIGN Prospective, consecutive case series. SETTING Tertiary care aerodigestive center. PARTICIPANTS Ten children, aged 18 months to 18 years, with severe RRP necessitating more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to intralesional bevacizumab treatment. INTERVENTIONS Intralesional bevacizumab administered at concentration of 2.5 mg/mL for 3 consecutive injections (with 532-nm pulsed KTP [potassium titanyl phosphate] laser when necessary) at intervals of 2 to 3 weeks. MAIN OUTCOME MEASURES Time between surgical procedures, number of procedures per year, Derkay staging, total Pediatric Voice-Related Quality of Life (PVRQOL) score, Emotional PVRQOL score, and Physical PVRQOL score defined by comparing the year leading up to first of 3 bevacizumab injections with the year following the third bevacizumab injection. RESULTS The median duration of time between
surgical procedures increased by 5.9 weeks after bevacizumab (P = .002). The median number of procedures per year decreased by 4 (P = .002). Derkay staging decreased by 6 (P = .03). The median total PVRQOL score increased by 25.5 (P = .02), the median Emotional PVRQOL score increased by 11.3 (P = .047), and the median Physical PVRQOL score increased by 14.3 (P = .047).

CONCLUSIONS AND RELEVANCE Intralesional bevacizumab treatment may increase duration of time between surgical procedures and decrease number of procedures per year, while improving voice QOL.

[792]
TÍTULO / TITLE: - The N-ERC index is a novel monitoring and prognostic marker for advanced malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mori T; Tajima K; Hirama M; Sato T; Kido K; Iwakami S; Sasaki S; Iwase A; Shiomi K; Maeda M; Hino O; Takahashi K
INSTITUCIÓN / INSTITUTION: - Departments of Respiratory Medicine, Juntendo University, Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan;
RESUMEN / SUMMARY: - BACKGROUND: Although N-ERC/mesothelin (N-ERC) is an attractive diagnostic and treatment monitoring biomarker for malignant pleural mesothelioma (MPM), its clinical utility for predicting the prognosis has not yet been clarified. The aim of this study is to investigate whether the serum N-ERC level can accurately predict the outcome in patients with MPM. METHODS: Twenty-six patients with MPM were enrolled. Serum N-ERC level was measured before and after chemotherapy. The N-ERC index was determined by the logarithm of the division of the N-ERC level after two courses of chemotherapy by the prior level. RESULTS: The median N-ERC index in the partial response (PR) group was significantly lower than that in patients with the stable disease (SD) plus the progressive disease (PD) group. The overall survival in the group whose median N-ERC index was lower than its median value was significantly longer than the group whose median N-ERC index was higher than its median value. CONCLUSIONS: The N-ERC index is therefore considered to be a useful biomarker for predicting not only the chemotherapeutic response, but also the prognosis in patients with advanced MPM.

[793]
Enlace al Resumen / Link to its Summary

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


AUTORES / AUTHORS: - Imai K; Minamiya Y; Goto A; Nanjo H; Saito H; Motoyama S; Sato Y; Kudo S; Takashima S; Kawaharada Y; Kurihara N; Orino K; Ogawa J

INSTITUCIÓN / INSTITUTION: - Department of Chest, Breast and Endocrine Surgery, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita City 010-8543, Japan. i-karo@mu.biglobe.ne.jp

RESUMEN / SUMMARY: - BACKGROUND: Adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) with fibrous stromal invasion are newly introduced subtypes of small lung adenocarcinoma. AIS is a small localized adenocarcinoma in which growth is restricted to neoplastic cells along preexisting alveolar structures without fibrous stromal invasion. In MIA, by contrast, tumor cells have infiltrated the myofibroblastic stroma. Transforming growth factor (TGF)-beta is known to be produced by progressor tumors, and excessive TGF-beta contributes to a pathological excess of tissue fibrosis. TGF-beta1 is the most abundant isoform, and its expression is a key event fostering tumor invasion and metastasis. We therefore analyzed the relationship between TGF-beta1 expression and clinicopathological microinvasion in patients with small lung adenocarcinoma.

METHODS: The study participants were 45 patients who underwent curative surgery for AIS and MIA 3 cm or less in size. Those tumors were assessed based on immunohistochemical staining using anti-TGF-beta1 antibody. The TGF-beta1 status was assessed immunohistochemically using the Allred 8-unit system.

RESULTS: The rates of TGF-beta1 positivity in the AIS and MIA groups were 27.3% and 65.2%, respectively (P <0.05). The median of Allred score was 0.5 (range 0-5) in the AIS group and 3.0 (range 0-6) in the MIA group (P = 0.0017).

CONCLUSIONS: We suggest that TGF-beta1 expression is likely to be significantly stronger in patients with MIA than in those with AIS, and the increased expression may be associated with minimal invasion and infiltration of the myofibroblastic stroma.

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[794]

- CASTELLANO -

TÍTULO / TITLE: Ultrassom endobronquico: do diagnostico e estadiamento do cancer de pulmão ate a pesquisa translacional.

TÍTULO / TITLE: - Endobronchial ultrasound: from lung cancer diagnosis and staging to translational research.

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


AUTORES / AUTHORS: - Guarize J
INSTITUCIÓN / INSTITUTION: - Divisao de Cirurgia Toracica, Instituto Europeu de Oncologia, Milao, Italia.

[795]

TÍTULO / TITLE: - Usefulness of transesophageal bronchoscopic ultrasound-guided fine-needle aspiration in the pathologic and molecular diagnosis of lung cancer lesions adjacent to the esophagus.

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


AUTORES / AUTHORS: - Araya T; Demura Y; Kasahara K; Matsuoka H; Yamamura K; Nishitsuji M; Nishi K

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Ishikawa Prefectural Central Hospital, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.

RESUMEN / SUMMARY: - BACKGROUND: The discovery of driver oncogenes has increased the need to obtain a sufficient amount of tissue specimens for lung cancer diagnosis. Although endoscopic ultrasound (with bronchoscope)-guided fine-needle aspiration (EUS-B-FNA) is reportedly a feasible and well-tolerated modality, additional advantages of EUS-B-FNA are yet to be thoroughly investigated. The purpose of this study was to evaluate the ability of EUS-B-FNA to obtain sufficient tissue specimens for pathologic and molecular diagnoses of lung cancer. METHODS: Among lung cancer patients who were diagnosed between December 2010 and December 2012 in our institute, patients who underwent EUS-B-FNA to diagnose lung cancer were enrolled (n=26). EUS-B-FNA was performed when bronchoscopic diagnosis was impossible or difficult to obtain sufficient samples. Epidermal growth factor receptor (EGFR) mutations and echinoderm microtubule-associated protein-like 4 and the anaplastic lymphoma kinase (EML4-ALK) fusion gene were evaluated using EUS-B-FNA samples of non-small cell lung cancer. RESULTS: EUS-B-FNA was performed on 28 lesions in 26 patients. Among the target lesions, 23 were mediastinal lymph nodes including nodal stations 2L, 4L, 7, 8, and 10L. The remaining 5 were intrapulmonary lesions. EUS-B-FNAs were completed without complications in all the patients. The diagnostic yield of EUS-B-FNA in diagnosing lung cancer was 100% (26/26). Additional diagnostic gain of EUS-B-FNA was 69.2% (18/26) as compared to bronchoscopy alone. EGFR mutations and EML4-ALK fusion gene could be evaluated in all patients with non-small cell lung cancer (n=20) using EUS-B-FNA samples. One case with EGFR mutation and 1 case with ALK fusion gene were diagnosed. Six non-small cell carcinomas were also diagnosed by bronchoscopy, but all bronchoscopic samples were insufficient to evaluate mutation analyses. CONCLUSIONS:
EUS-B-FNA is a practical and feasible method to obtain abundant tumorous tissue samples for pathologic diagnosis and molecular analysis, particularly when the target lesions are inaccessible by other modalities because of their locations or because of the patient’s poor physical condition.
TÍTULO / TITLE: - The assessment of the malignant mesothelioma cases and environmental asbestos exposure in Sivas province, Turkey.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s10653-013-9518-y
AUTORES / AUTHORS: - Berk S; Yalcin H; Dogan OT; Epozturk K; Akkurt I; Seyfikli Z
INSTITUCIÓN / INSTITUTION: - Department of Chest Diseases, Faculty of Medicine, Cumhuriyet University, 58140, Sivas, Turkey, serdar_berk@mynet.com.
RESUMEN / SUMMARY: - One of the most significant diseases related to environmental asbestos exposure is malignant mesothelioma (MM). Sivas province is located in the Central Anatolia where asbestos exposure is common. We aimed to study clinical, demographical and epidemiologic features of the patients with MM in Sivas, along with the history of asbestos exposure. In total, 219 patients with MM who were diagnosed in our hospital between 1993 and 2010 were retrospectively analyzed in terms of demographical and clinical features. Rock, soil and house plaster samples were taken from the habitats of those patients and were evaluated with optical microscopy and X-ray diffraction methods. The age of the patients ranged between 18 and 85 years. The male-to-female ratio was 1.4:1. Most of the patients confirmed an asbestos exposure history. The most frequent symptoms of the patients were chest pain (60 %) and dyspnea (50 %). The gap between the start of first symptoms and the diagnosis date was approximately 4 months in average. The plaster materials used in most of the houses were made up of mainly carbonate and silicate minerals and some chrysotile. Ophiolitic units contained fibrous minerals such as serpentine (clino + orthochrysotile) chiefly and pectolite, brucite, hydrotalcite and tremolite/actinolite in smaller amounts. MM is not primarily related to occupational asbestos exposure in our region, and hence, environmental asbestos exposure may be indicted. Yet, single or combined roles and/or interactions of other fibrous and non-fibrous minerals in the etiology of MM are not yet fully understood and remain to be investigated.
[798]

TÍTULO / TITLE: - Urinary bladder urothelial carcinoma with expression of KIT and PDGFRA and showing diverse differentiations into plasmacytoid, clear cell, acantholytic, nested, and spindle variants, and into adenocarcinoma, signet-ring cell carcinoma, small cell carcinoma, large cell carcinoma, and pleomorphic carcinoma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Various tumors can arise in the urinary bladder (UB); most common is urothelial carcinoma (UC). UC of the UB have many variants. Other types of carcinomas such as adenocarcinoma (AC) and small cell carcinoma (SmCC) can occur in UB carcinomas. Expression of KIT and PDGFRA has not been reported. A 66-year-old man admitted to our hospital because of hematuria. Cystoscopy revealed papillary invasive tumor and a transurethral bladder tumorectomy (TUR-BT) was performed. The TUR-BT showed UC, AC, SmCC, large cell carcinoma (LCC), and pleomorphic carcinoma (PC). The UC component showed plasmacytoid, spindle, nested, clear cell, acantholytic variants. The AC element showed tubular adenocarcinoma and signet-ring cell carcinoma (Sig). Immunohistochemically, all of these subtypes were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK34BE12, CK5, CK6, CK7, CK8, CK18, CK19, CK20, EMA, CEA, p63, CA19-9, p53 (positive 45%), MUC1, NSE, NCAM, KIT, PDGFRA, and Ki-67 (87%). They were negative for vimentin, chromogranin, synaptophysin, S100 protein, CD34, CD14, alpha-smooth muscle actin, CD31, caldesmon, CD138, CD45, kappa-chain, lambda-chain, MUC2, MUC5AC and MUC6. Mucin histochemistry revealed mucins in AC element including Sig. A molecular genetic analysis using PCR-direct sequencing method identified no mutations of KIT (exons 9, 11, 13, and 17) and PDGFRA (exons 12 and 18) genes. The carcinoma was highly aggressive and invaded into muscular layer. The nuclear grade was very high, and there were numerous lymphovascular permeations were seen. The surface showed carcinoma in situ involving von-Brunn’s nests. This case shows that carcinoma of UB can show diverse differentiations into numerous histological types and variants, and can express KIT and PDGFRA. The both genes showed no mutations in the present case.

[799]

- Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation.


- Miyanaga A; Shimizu K; Noro R; Seike M; Kitamura K; Kosaithira S; Minegishi Y; Shukuya T; Yoshimura A; Kawamoto M; Tsuchiya S; Hagiwara K; Soda M; Takeuchi K; Yamamoto N; Mano H; Ishikawa Y; Gemma A
RESUMEN / SUMMARY: BACKGROUND: The EML4-ALK (echinoderm microtubule-associated protein-like 4 gene and the anaplastic lymphoma kinase gene) fusion oncogene represents a novel molecular target in a small subset of non-small-cell lung cancers (NSCLCs). The EML4-ALK fusion gene occurs generally in NSCLC without mutations in epidermal growth factor receptor (EGFR) and KRAS. CASE PRESENTATION: We report that a case of EML4-ALK-positive NSCLC with EGFR mutation had a response of stable disease to both an EGFR tyrosine kinase inhibitor (EGFR-TKI) and ALK inhibitor. CONCLUSIONS: We described the first clinical report of a patient with EML4-ALK-positive NSCLC with EGFR mutation that had a response of stable disease to both single-agent EGFR-TKI and ALK inhibitor. EML4-ALK translocation may be associated with resistance to EGFR-TKI, and EGFR signaling may contribute to resistance to ALK inhibitor in EML4-ALK-positive NSCLC.

[800]

TÍTULO / TITLE: Serum HMGB1 as a prognostic marker for malignant pleural mesothelioma.

RESUMEN / SUMMARY: BACKGROUND: Malignant pleural mesothelioma (MPM) is an aggressive malignant tumor of mesothelial origin that shows a limited response to conventional chemotherapy and radiotherapy. Therefore, diagnosing MPM early is very important. Some researchers have previously reported that high-mobility group box 1 (HMGB1) was correlated with pulmonary fibrosis. MPM involves the malignant transformation of mesothelial cells, which originate from mesenchymal cells similar to lung fibroblasts. Here, we investigated serum levels of HMGB1 in patients with MPM and compared them with those of a population that had been exposed to asbestos without developing MPM. METHODS: HMGB1 production from MPM cell lines was measured using ELISA. Serum HMGB1 levels were also examined in 61 MPM patients and 45 individuals with benign asbestos-related diseases. RESULTS: HMGB1 concentrations of 2 out of 4 MPM cell lines were higher than that of...
normal mesothelial cell line, Met-5. We demonstrated that patients with MPM had significantly higher serum levels of HMGB1 than the population who had been exposed to asbestos but had not developed MPM. The difference in overall survival between groups with serum HMGB1 levels that were lower and higher than assumed cut-off values was significant. CONCLUSIONS: Our data suggest that serum HMGB1 concentration is a useful prognostic factor for MPM.
expression in tumorous tissue samples was significantly correlated with tumor aggressiveness. These data suggest that DNA methylation alterations at precancerous stages determine tumor aggressiveness and outcome through silencing of specific genes.
INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Medicine, Affiliated Hospital of Jiangsu University, Zhenjiang, China.

RESUMEN / SUMMARY: - AIM: The diagnostic role of carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen, Cyfra 21-1 and neuron-specific enolase (NSE) in the bronchoalveolar lavage fluid (BALF) for lung cancer is still controversial. The aim of this study was to evaluate the diagnostic value of these four tumor markers in BALF for peripheral lung cancer. METHODS: We measured and compared the levels of CEA, SCC, Cyfra21-1 and NSE in BALF in 42 patients with peripheral lung cancer and 22 patients with benign lung disease. In the patients with peripheral lung cancer, the BAL was separately performed in the bronchus of the tumor-bearing lung and in the corresponding bronchus of the opposite healthy lung. RESULTS: The levels of CEA, SCC, Cyfra21-1 and NSE were significantly elevated in BALF from the tumor-bearing lung compared with the opposite healthy lung in the lung cancer patients (P < 0.001) or the benign lung disease patients (P < 0.005). The diagnostic sensitivities of Cyfra21-1 (86 and 76%), with a specificity of 91%, were the highest among the four tumor markers for the tumor-bearing lung versus the opposite healthy lung and benign lung disease. The combination of Cyfra21-1 and CEA increased the sensitivity to 93 and 86 percent, respectively. CONCLUSION: The assay of these tumor markers in BALF may be used as a diagnostic tool to complement a cytological examination in the diagnosis of peripheral lung cancer.

[805]

- CASTELLANO -

TÍTULO / TITLE: Reaktif Mesotel Hiperplazisi, Malign Mezotelyoma ve Akciger Adenokarsinomu Ayirici Tanisinda Glut-1 ve Koc'un Yeri.


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


ENlace al texto completo (gratuito o de pago) 5146/tjpath.2013.01158

AUTORES / AUTHORS: - Ucer O; Dagli AF; Kilicarslan A; Artas G

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Bingol State Hospital, BINGOL, TURKEY.

RESUMEN / SUMMARY: - Objective: Malignant mesothelioma (MM) is a primary malignant tumor developing from mesothelial cells lining the serosal surfaces and particularly the pleura, and has a very poor prognosis. It may display a variety of histological patterns and has a wide spectrum of cytomorphological characteristics, causing problems in its differential diagnosis from lung adenocarcinomas and sometimes from benign mesothelial proliferations.
Immunohistochemical examination is the most useful method for this distinction. In our study, we aimed to determine the value of glucose transporter isoform-1 (GLUT-1) and K homology domain-containing protein (KOC) markers in the differential diagnosis of reactive mesothelial hyperplasia, malignant mesothelioma and lung adenocarcinoma. Material and Method: Our study included 30 samples of malignant mesothelioma, 30 samples of pulmonary adenocarcinoma and 30 samples of reactive mesothelial hyperplasia selected from the archives of the Firat University Hospital's Pathology Department Laboratory. The samples were applied GLUT-1 and KOC markers by immunohistochemistry and the place of these markers in the differential diagnosis was examined. Results: GLUT-1 was found positive in 80% of malignant mesothelioma cases, 83.3% of adenocarcinoma cases and 6.6% of reactive mesothelial hyperplasia cases. KOC was positive in 83.3% of malignant mesothelioma cases, 76.6% of adenocarcinoma cases and 46.6% of reactive mesothelial hyperplasia cases. There was no statistically significant difference between malignant mesothelioma and lung adenocarcinoma cases in terms of the diffuseness and intensity of staining with GLUT-1, whereas a significant difference was established when these groups were compared with reactive mesothelial hyperplasia cases. However, the KOC staining diffuseness and intensity results were similar to those obtained with GLUT-1. Conclusion: In conclusion, GLUT-1 and KOC markers do not differentiate malignant mesotheliomas from pulmonary adenocarcinomas but can be useful in differentiating reactive mesothelial hyperplasia from malignant mesothelioma and lung adenocarcinoma.
of the chemotherapeutic drug formulations to the lung parenchyma. Acute and latent effects observed in a small number of human trial studies are still under investigation of inhaled chemotherapy administration. This review provides data regarding all up-to-date inhaled chemotherapy studies and presents the methodological parameters of the safety measures incorporated. In addition, a commentary regarding the safety concerns for the medical staff participating in these studies will be presented.

[807]

**Título / Title:** Bronchogenic cyst rupture and pneumonia after endobronchial ultrasound-guided transbronchial needle aspiration: a case report.

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


**Autores / Authors:** Hong G; Song J; Lee KJ; Jeon K; Koh WJ; Suh GY; Chung MP; Kim H; Kwon OJ; Um SW

**Institución / Institution:** Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

**Resumen / Summary:** We report a 54-year-old woman who presented with a well-defined, homogeneous, and non-enhancing mass in the retrobronchial region of the bronchus intermedius. The patient underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for histological confirmation. Serous fluid was aspirated by EBUS-TBNA. Cytological examination identified an acellular smear with negative microbiological cultures. The patient was finally diagnosed with bronchogenic cysts by chest computed tomography (CT) and EBUS-TBNA findings. However, 1 week after EBUS-TBNA, the patient developed bronchogenic cyst rupture and pneumonia. Empirical antibiotics were administered, and pneumonia from the bronchogenic cyst rupture had resolved on follow-up chest CT. To our knowledge, this is the first reported case of pneumonia from bronchogenic cyst rupture after EBUS-TBNA.

[808]

**Título / Title:** Ectopic ikaros expression positively correlates with lung cancer progression.

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


**Autores / Authors:** Zhang Z; Xu Z; Wang X; Wang H; Yao Z; Mu Y; Ma Z; Liu Z
**INSTITUCIÓN / INSTITUTION:** - Department of Lung Cancer, Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, 300060, China.

**RESUMEN / SUMMARY:** - Ikaros, encoded by the IKZF1 gene, is a pivotal transcription factor whose expression and utilization is dynamically altered during hematopoietic development. However, the molecular mechanisms controlling the transcription of the IKZF1 gene are unclear in lung cancer cell lines. Here we show the role of Ikaros in a cohort of grade IIIA lung cancer patients, with particular emphasis on its relationship with clinical outcomes and expression levels. The expression levels of Ikaros were positively correlated with the prognosis in the lung cancer patients. We also demonstrated that Ikaros expression is ectopically activated in a panel of lung cancer cell lines primarily through demethylation of its promoter. Moreover, gain-of-function experiments revealed that Ikaros inhibits migration and invasion of lung cancer cells in vitro. Our results thus shed light on how Ikaros can act as a lineage competency factor to facilitate lung cancer progression. Anat Rec, 296:907-913, 2013. © 2013 Wiley Periodicals, Inc.

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**TÍTULO / TITLE:** - Active Component of Danshen (Salvia miltiorrhiza Bunge), Tanshinone I, Attenuates Lung Tumorigenesis via Inhibitions of VEGF, Cyclin A, and Cyclin B Expressions.

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


**AUTORES / AUTHORS:** - Tung YT; Chen HL; Lee CY; Chou YC; Lee PY; Tsai HC; Lin YL; Chen CM

**INSTITUCIÓN / INSTITUTION:** - Department of Life Sciences, Agricultural Biotechnology Center, National Chung Hsing University, Taichung 402, Taiwan.

**RESUMEN / SUMMARY:** - Tanshinone I (T1) and tanshinone II (T2) are the major diterpenes isolated from Danshen (Salvia miltiorrhiza Bunge). Three human lung adenocarcinoma cell lines, A549, CL1-0, and CL1-5, were treated with T1 and T2 for the in vitro antitumor test. Results showed that T1 was more effective than T2 in inhibiting the growth of lung cancer cells via suppressing the expression of VEGF, Cyclin A, and Cyclin B proteins in a dose-dependent manner. Moreover, a transgenic mice model of the human vascular endothelial growth factor-A165 (hVEGF-A 165) gene-induced pulmonary tumor was further treated with T1 for the in vivo lung cancer therapy test. T1 significantly attenuated hVEGF-A165 overexpression to normal levels of the transgenic mice (Tg) that were pretreated with human monocytic leukemia THP-1 cell-derived conditioned medium (CM). It also suppressed the formation of lung adenocarcinoma tumors (16.7%) compared with two placebo groups (50% for
Tg/Placebo and 83.3% for Tg/CM/Placebo; P < 0.01). This antitumor effect is likely to slow the progression of cells through the S and G2/M phases of the cell cycle. Blocking of the tumor-activated cell cycle pathway may be a critical mechanism for the observed antitumorigenic effects of T1 treatment on vasculogenesis and angiogenesis.

[810]
**TITULO / TITLE:** - Zoledronic acid produces combinatory anti-tumor effects with cisplatin on mesothelioma by increasing p53 expression levels.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary

  ●●Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0060297

**AUTORES / AUTHORS:** - Okamoto S; Jiang Y; Kawamura K; Shingyoji M; Fukamachi T; Tada Y; Takiguchi Y; Tatsumi K; Shimada H; Hiroshima K; Kobayashi H; Tagawa M

**INSTITUCION / INSTITUTION:** - Department of Biochemistry, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba, Japan.
**RESUMEN / SUMMARY:** - We examined anti-tumor effects of zoledronic acid (ZOL), one of the bisphosphonates agents clinically used for preventing loss of bone mass, on human mesothelioma cells bearing the wild-type p53 gene. ZOL-treated cells showed activation of caspase-3/7, -8 and -9, and increased sub-G1 phase fractions. A combinatory use of ZOL and cisplatin (CDDP), one of the first-line anti-cancer agents for mesothelioma, synergistically or additively produced the cytotoxicity on mesothelioma cells. Moreover, the combination achieved greater anti-tumor effects on mesothelioma developed in the pleural cavity than administration of either ZOL or CDDP alone. ZOL-treated cells as well as CDDP-treated cells induced p53 phosphorylation at Ser 15, a marker of p53 activation, and up-regulated p53 protein expression levels. Down-regulation of p53 levels with siRNA however did not influence the ZOL-mediated cytotoxicity but negated the combinatory effects by ZOL and CDDP. In addition, ZOL treatments augmented cytotoxicity of adenoviruses expressing the p53 gene on mesothelioma. These data demonstrated that ZOL-mediated augmentation of p53, which was not linked with ZOL-induced cytotoxicity, played a role in the combinatory effects with a p53 up-regulating agent, and suggests a possible clinical use of ZOL to mesothelioma with anti-cancer agents.

[811]
**TITULO / TITLE:** - Expression of CLDN1 and CLDN10 in lung adenocarcinoma in situ and invasive lepidic predominant adenocarcinoma.
**RESUMEN / SUMMARY:** - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 1186/1749-8090-8-95

AUTORES / AUTHORS: - Zhang Z; Wang A; Sun B; Zhan Z; Chen K; Wang C

RESUMEN / SUMMARY: - BACKGROUND: Non-mucinous bronchioloalveolar carcinoma (BAC) is considered the early stage of lung adenocarcinoma and is classified as the lung adenocarcinoma in situ (AIS) by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society. This study was designed to investigate the gene expression differences between AIS (formerly non—mucinous BAC) and invasive lepidic predominant adenocarcinoma (LPA, formerly non-mucinous BAC pattern with >5 mm invasion, mixed type adenocarcinoma with BAC features) and to investigate the mechanism of the progression of lung adenocarcinoma in situ to invasive adenocarcinoma. METHODS: Gene expression analysis was performed by using Agilent 4 x 44 K Whole Human Genome Oligo Microarray on 10 fresh frozen tissue samples of AIS and LPA, respectively. Real time RT-PCR was used to validate the differential expression of 13 genes selected by cDNA microarray on fresh frozen tissue samples from 41 patients with lung adenocarcinoma and 4 genes were confirmed. These 4 genes were then validated by western blotting. Immunohistochemical staining for these validated genes was performed on formalin-fixed, paraffin-embedded tissue samples from 81 cases of lung adenocarcinoma. RESULTS: We identified a 13 gene expression signature by comparative analysis of gene expression. Expression of these genes strongly differed between AIS and LPA. Four genes (MMP-2, c-fos, claudin 1 (CLDN1) and claudin 10(CLDN10)) were correlated with the results of microarray and real time RT-PCR analyses for the gene-expression data in samples from 41 patients with lung adenocarcinoma. As confirmed by western blotting, the expression levels of MMP-2 and c-fos were higher in LPA than those in AIS; the expression levels of CLDN1 and CLDN10 in LPA were lower than those in AIS. Immunohistochemical staining for these genes in samples from 81 cases of lung adenocarcinoma demonstrated the expressions of CLDN1 and CLDN10 were correlated with overall survival of patients with lung adenocarcinoma. CONCLUSIONS: CLDN1 and CLDN10 may play important roles in the development of AIS to LPA. Overexpression of CLDN1 and CLDN10 indicates a favorable prognosis for overall survival in some patients with lung adenocarcinoma. Expression of CLDN10 may be regulated by the c-fos pathway.

TÍTULO / TITLE: - Rationale and Design of the Japan Molecular Epidemiology for Lung Cancer Study.

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

AUTORES / AUTHORS: - Kawaguchi T; Ando M; Ito N; Isa S; Tamiya A; Shimizu S; Saka H; Kubo A; Koh Y; Matsumura A

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, National Hospital Organization, Kinki-chuo Chest Medical Center, Osaka, Japan. Electronic address: t-kawaguchi@kch.hosp.go.jp.

RESUMEN / SUMMARY: - We present the rationale for the Japan Molecular Epidemiology for Lung Cancer study designed to elucidate molecular mechanisms of carcinogenesis in smokers and never-smokers with non-small-cell lung cancer. This prospective, ongoing, multicenter study is being conducted nationwide in Japan. Although there is no doubt that active smoking is the major cause of lung cancer, the contribution of other possible factors, including environmental tobacco or wood smoke, human papilloma virus, radon, occupational exposures, and genetic susceptibility, is highly likely, based on studies of never-smokers with non-small-cell lung cancer. Because of the predominance of women in the never-smoker subgroup, the role of female hormones in lung cancer development has also been considered. We hypothesize that driver mutations, which are critical for the development of lung cancer, are triggered by the environmental factors with or without the influence of the hormone. The SWOG-led intergroup molecular epidemiology study S0424 was conducted to focus on these issues by using a detailed questionnaire and specimen collection in statistically significant cohorts of smokers and never-smokers from both sexes. The Japan Molecular Epidemiology for Lung Cancer study follows and extends the S0424 molecular epidemiology concept in principle by using a similar approach that will facilitate future comparisons between the studies but with a greater focus on more recently defined driver mutations and broad genomic sequencing.

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


AUTORES / AUTHORS: - Tamura M; Shimizu Y; Hashizume Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Fukui Prefectural Hospital, Yotsui 2-8-1, Fukui 910-8526, Japan. masatamu2007@yahoo.co.jp.

RESUMEN / SUMMARY: - In this report, we describe the surgical resection of a pedunculated solitary fibrous tumor of the pleura (SFTP) by single-incision thoracoscopic surgery (SITS). SITS may be a suitable surgical option for pedunculated SFTPs.

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Ubiquitin ligase Cbl-b is involved in icotinib (BPI-2009H)-induced apoptosis and G1 phase arrest of EGFR mutation-positive non-small-cell lung cancer.

Epidermal growth factor receptor (EGFR) is one of the most promising targets for non-small-cell lung cancer (NSCLC). Icotinib, a highly selective EGFR tyrosine kinase inhibitor (EGFR-TKI), has shown promising clinical efficacy and safety in patients with NSCLC. The exact molecular mechanism of icotinib remains unclear. In this study, we first investigated the antiproliferative effect of icotinib on NSCLC cells. Icotinib significantly inhibited proliferation of the EGFR-mutated lung cancer HCC827 cells. The IC50 values at 48 and 72 h were 0.67 and 0.07 µM, respectively. Flow cytometric analysis showed that icotinib caused the G1 phase arrest and increased the rate of apoptosis in HCC827 cells. The levels of cyclin D1 and cyclin A2 were decreased. The apoptotic process was associated with activation of caspase-3, -8, and poly(ADP-ribose) polymerase (PARP). Further study revealed that icotinib inhibited phosphorylation of EGFR, Akt, and extracellular signal-regulated kinase. In addition, icotinib upregulated ubiquitin ligase Cbl-b expression. These observations suggest that icotinib-induced upregulation of Cbl-b is responsible, at least in part, for the antitumor effect of icotinib via the inhibition of phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase pathways in EGFR-mutated NSCLC cells.

Metabolic and Functional Genomic Studies Identify Deoxycytidylate Kinase as a target in LKB1 Mutant Lung Cancer.

Epidermal growth factor receptor (EGFR) is one of the most promising targets for non-small-cell lung cancer (NSCLC). Icotinib, a highly selective EGFR tyrosine kinase inhibitor (EGFR-TKI), has shown promising clinical efficacy and safety in patients with NSCLC. The exact molecular mechanism of icotinib remains unclear. In this study, we first investigated the antiproliferative effect of icotinib on NSCLC cells. Icotinib significantly inhibited proliferation of the EGFR-mutated lung cancer HCC827 cells. The IC50 values at 48 and 72 h were 0.67 and 0.07 µM, respectively. Flow cytometric analysis showed that icotinib caused the G1 phase arrest and increased the rate of apoptosis in HCC827 cells. The levels of cyclin D1 and cyclin A2 were decreased. The apoptotic process was associated with activation of caspase-3, -8, and poly(ADP-ribose) polymerase (PARP). Further study revealed that icotinib inhibited phosphorylation of EGFR, Akt, and extracellular signal-regulated kinase. In addition, icotinib upregulated ubiquitin ligase Cbl-b expression. These observations suggest that icotinib-induced upregulation of Cbl-b is responsible, at least in part, for the antitumor effect of icotinib via the inhibition of phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase pathways in EGFR-mutated NSCLC cells.
The LKB1/STK11 tumor suppressor encodes a serine/threonine kinase which coordinates cell growth, polarity, motility, and metabolism. In non-small cell lung cancer, LKB1 is somatically inactivated in 25-30% of cases, often concurrently with activating KRAS mutation. Here, we employed an integrative approach to define novel therapeutic targets in KRAS-driven LKB1 mutant lung cancers. High-throughput RNAi screens in lung cancer cell lines from genetically engineered mouse models driven by activated KRAS with or without coincident Lkb1 deletion led to the identification of Dtymk, encoding deoxythymidylate kinase which catalyzes dTTP biosynthesis, as synthetically lethal with Lkb1 deficiency in mouse and human lung cancer lines. Global metabolite profiling demonstrated that Lkb1-null cells had striking decreases in multiple nucleotide metabolites as compared to the Lkb1-wt cells. Thus, LKB1 mutant lung cancers have deficits in nucleotide metabolism conferring hypersensitivity to DTYMK inhibition, suggesting that DTYMK is a potential therapeutic target in this aggressive subset of tumors.

[816]

**TÍTULO / TITLE:** High SOX2 Levels Predict Better Outcome in Non-Small Cell Lung Carcinomas.

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


**AUTORES / AUTHORS:** Velcheti V; Schalper K; Yao X; Cheng H; Kocoglu M; Dhodapkar K; Deng Y; Gettinger S; Rimm DL

**INSTITUCIÓN / INSTITUTION:** Department of Medical Oncology, Yale University School of Medicine, New Haven, Connecticut, United States of America.

**RESUMEN / SUMMARY:** BACKGROUND: SOX2 is an embryonic developmental transcription factor, which is important in the development of the respiratory tract. SOX2 overexpression is associated with aggressive disease in several tumor types. However, SOX2 overexpression and gene amplification associates with favorable outcome in lung squamous cell carcinomas (SCC) and dissimilar results have been reported in lung adenocarcinomas (ADC). The aim of the present study was to evaluate SOX2 expression in NSCLC and determine the relationship with clinico-pathological variables and outcome. METHODS: SOX2 protein levels were measured in tissue microarrays (TMAs) containing FFPE samples from two independent lung cancer cohorts (n = 340 & 307) using automated quantitative immunofluorescence (QIF). Assay validation was
performed using FFPE preparations of cell lines with known SOX2 expression. Associations of SOX2 levels with main clinico-pathological characteristics and with overall survival were studied using uni- and multivariate analysis.

RESULTS: SOX2 levels were higher in patients with SCC than in ADC in both cohorts (p value < 0.0001). In the training cohort, NSCLC patients whose tumors showed high SOX2 (n = 245) had longer survival than those with low SOX2 levels (log rank p = 0.0002). Comparable results were observed in the second independent validation cohort, log rank p = 0.0113. SOX2 positive cases showed a 58% reduction in risk of death in Cox univariate analysis (hazards ratio-HR = 0.42 confidence interval-CI (0.36, 0.73), p = 0.0002). SOX2 was associated with significantly longer survival independent of histology in multivariate analysis (hazards ratio-HR = 0.429 confidence interval-CI (0.295, 0.663), p = <0.001). CONCLUSIONS: SOX2 is an independent positive prognostic marker in NSCLC. Increased SOX2 levels are more frequent in SCC than in ADC, but the association with better survival is independent from the histological subtype.

[817]

TÍTULO / TITLE: Geometrical differences in gross target volumes between 3DCT and 4DCT imaging in radiotherapy for non-small-cell lung cancer.

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


AUTORES / AUTHORS: Li F; Li J; Zhang Y; Xu M; Shang D; Fan T; Liu T; Shao Q

INSTITUCIÓN / INSTITUTION: Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan 250117, China.

RESUMEN / SUMMARY: The aim of this study was to explore the characteristic of 3DCT scanning phases and estimate the comparative amount of respiration motion information included in 3DCT and 4DCT by comparing the volumetric and positional difference between the volumes from 3DCT and 4DCT for the radiotherapy of non-small-cell lung cancer (NSCLC). A total of 28 patients with NSCLC sequentially underwent 3DCT and 4DCT simulation scans of the thorax during free breathing. The 4DCT images with respiratory signal data were reconstructed and sorted into 10 phases throughout a respiratory cycle. GTV-3D from 3DCT, GTV-0%, GTV-20%, GTV-50% and GTV-70% from end-inspiration, mid-expiration, end-expiration and mid-inspiration of 4DCT, and the internal GTV (IGTV-10) from the fused phase of 4DCT were delineated based on the 50% phase image, respectively. The differences in the position, size, matching index (MI) and degree of inclusion (DI) for different volumes were evaluated. The variation in the centroid shifts of GTV-0% and GTV-3D, GTV-20% and GTV-3D, GTV-50% and GTV-3D, and GTV-90% and GTV-3D in the 3D direction was not significant (P = 0.990). The size ratios of GTV-0%, GTV-
20%, GTV-50%, GTV-70% and IGTV-10 to GTV-3D were 0.94 +/- 0.18, 0.95 +/- 0.18, 0.98 +/- 0.15, 1.00 +/- 0.18 and 1.60 +/- 0.55, respectively. DIs of GTV-3D in IGTV-10, and IGTV-10 in GTV-3D were 0.88 +/- 0.14 and 0.59 +/- 0.16 (P < 0.001). The 3DCT scanning phases are irregular. The CTV-to-ITV expansion should be isotropic when defining the ITV on the 3DCT. The internal GTV derived from 4DCT cannot completely include the GTV from 3DCT. An additional margin may be required when defining the ITV-based 4DCT.

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**TÍTULO / TITLE**: Should all cases of lung cancer be presented at Tumor Board Conferences?

**RESUMEN / SUMMARY**: Tumor Board Conferences (TBCs) have been associated with higher adherence of staging and treatment to guidelines. The influence of TBCs on the rate of curative treatments has been established. Patients with lung nodules and tumors of unknown histology should not be presented before surgery, but every patient with malignant histology should be declared to the TBC coordinator and registered at the time of histologic confirmation. This approach allows physicians to deal rapidly with simple cases on a systematic basis, to give more attention to the most complicated situations, and to offer every patient the benefit of a multidisciplinary approach.

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**TÍTULO / TITLE**: Pulmonary sclerosing hemangioma: a unique epithelial neoplasm of the lung (report of 26 cases).

**RESUMEN / SUMMARY**: Pulmonary sclerosing hemangioma (PSH) is a rare lung neoplasm that is composed of pleomorphic epithelial cells and tends to present as a solitary pulmonary nodule. This report presents a series of 26 cases of PSH, with a review of the literature, and discusses the clinical characteristics, imaging findings, histologic features, and treatment options for this uncommon lung tumor.

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**AUTORES / AUTHORS**: Riquet M; Mordant P; Henni M; Wermert D; Fabre-Guillemin E; Cazes A; Le Pimpec Barthes F

**INSTITUCIÓN / INSTITUTION**: Department of General Thoracic Surgery, Georges Pompidou European Hospital, Paris-Descartes University, 20 rue Leblanc, Paris 75015, France. marc.riquet@egp.aphp.fr

**RESUMEN / SUMMARY**: Patients with lung nodules and tumors of unknown histology should not be presented before surgery, but every patient with malignant histology should be declared to the TBC coordinator and registered at the time of histologic confirmation. This approach allows physicians to deal rapidly with simple cases on a systematic basis, to give more attention to the most complicated situations, and to offer every patient the benefit of a multidisciplinary approach.
RESUMEN / SUMMARY: - BACKGROUND: Pulmonary sclerosing hemangioma (SH) is an uncommon tumor. The aim of this study was to identify the origin of pulmonary SH and summarize its clinicopathologic features. METHODS: Data of 26 cases of pulmonary SH were collected and reviewed, including their clinical symptoms, chest radiological examinations, treatments, and pathological findings. RESULTS: Female patients of pulmonary SH were markedly frequent (n=23, 88.46%). Solitary mass or nodule in the lung fields was the most common manifestation (n=24, 92.31%), especially in the right middle lobe (n=9, 34.62%). There were two kinds of tumor cells: lining cells and round cells. All tumors contained a mixture of papillary, solid, sclerotic, and hemorrhagic patterns. Immunohistochemistry with a variable number of antibodies was performed for some cases. All of the detected specimens revealed strong reaction of lining cells with epithelial markers, such as thyroid transcription factor-1 (TTF-1), epithelial membrane antigen (EMA), cytokeratin (CK), pancytokeratin (PCK), and cytokeratin 7 (CK-7), while round cells were positive with TTF-1 and EMA. Until the end of last contact, none of the patients died or suffered from the recurrence of the disease after surgical treatment. CONCLUSIONS: Pulmonary SH is a unique neoplasm of the lung with a characteristic solitary mass or nodule. Pulmonary epithelium might be the primary origin of the tumor cells.

TÍTULO / TITLE: - Endobronchial endometriosis presenting as central-type lung cancer: a case report.

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


AUTORES / AUTHORS: - Yu JH; Lin XY; Wang L; Liu Y; Fan CF; Zhang Y; Wang EH

INSTITUCIÓN / INSTITUTION: - Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China.

RESUMEN / SUMMARY: - A 45-year-old female patient was referred to our hospital for complaining of dyspnea and coughing in the past four months. The computed tomography scanning demonstrated a central lesion in the upper lobe of the left lung close to the hilum, and the subsequent bronchoscopy revealed a polypoid lesion of the distal of the left main bronchus. This patient was diagnosed clinically as “possibly central-type lung cancer”. However, the pathologic result of the surgically excised polypoid lesion was endobronchial endometriosis. VIRTUAL SLIDES: The virtual slide(s) for this article can be found here: http://www.diagnosticpathology.diagnomx.eu/vs/1077439085928525.
**TÍTULO / TITLE:** - A case of synchronous presentation of primary non-small cell lung carcinoma and pheochromocytoma.

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


**AUTORES / AUTHORS:** - Han JW; Kim CH; Jang J; Lee HG; Chung DC; Choi JE; Kim K; Lim AL; Song WJ; Song YK; Woo H; Hyun IG; Shin MK; Lee YS; Shin HS

**INSTITUCIÓN / INSTITUTION:** - Department of Internal Medicine, Hallym University College of Medicine, Seoul, Korea.

**RESUMEN / SUMMARY:** - We report a rare synchronous presentation of primary lung cancer and adrenal pheochromocytoma. A 59-year-old woman was diagnosed with right upper lobe non-small cell lung carcinoma measuring 2.8 cm and a right adrenal gland mass measuring 3.5 cm, which displayed increased metabolic activity on (18)F-fluorodeoxyglucose positron emission tomography-computed tomography. The adrenal lesion was revealed to be asymptomatic. The patient underwent right adrenalectomy and histological examination revealed a pheochromocytoma. Ten days later, right upper lobectomy was performed for lung cancer. This case indicates that incidental adrenal lesions found in cases of resectable primary lung cancer should be investigated.

**TÍTULO / TITLE:** - An unusual case of paratesticular mesothelioma on the site of previously excised epididymal adenomatoid tumour.

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


**AUTORES / AUTHORS:** - Gkentzis A; Sawalem K; Husain J

**INSTITUCIÓN / INSTITUTION:** - Urology Department, Wigan Infirmary, Wigan, United Kingdom. Electronic address: agapiosgkentzis@hotmail.com.

**RESUMEN / SUMMARY:** - INTRODUCTION: Malignant paratesticular tumours are rare. We report a case of paratesticular malignant mesothelioma in a patient who had excision of an adenomatoid tumour on the same site in 2 occasions previously. PRESENTATION OF CASE: A middle aged man who had an adenomatoid tumour excised from his left hemiscrotum fifteen years previously was referred with a suspicious left epididymal lump. This was followed up sonographically for 2 years until it showed signs of enlargement and testicular invasion; it was then managed with radical orchidectomy. The histology showed...
paratesticular epithelioid malignant mesothelioma. The patient was referred to the Oncologists for further management. DISCUSSION: Paratesticular tumours are commonly benign. Scrotal ultrasonography is the preferred diagnostic imaging method. Paratesticular malignant mesotheliomas are very rare and appear to have poor prognosis. The optimal adjuvant treatment post radical orchidectomy is not established yet. In our case there is suggestion of possible malignant transformation from previous adenomatoid tumour. CONCLUSION: In recurrent paratesticular tumours the clinicians should question the possibility of malignant transformation and manage these cases accordingly.

[823]
TÍTULO / TITLE: - A case of synchronous bilateral lung cancers: EML4-ALK positive adenocarcinoma in the right lung and adenocarcinoma in situ (the former bronchioloalveolar carcinoma) in the left lung.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Matsuda I; Takeuchi K; Mizuguchi S; Kaji M; Ueda K; Teramura K; Hirota S
INSTITUCIÓN / INSTITUTION: - Department of Surgical Pathology, Hyogo College of Medicine, Hyogo 663-8501, Japan. hiros@hyo-med.ac.jp.
RESUMEN / SUMMARY: - BACKGROUND: Recently it has been revealed that lung adenocarcinomas with distinct gene mutations or fusions are associated with particular histopathological entities. For example, epidermal growth factor receptor (EGFR) gene mutations are often associated with well differentiated adenocarcinoma of the lung with bronchioloalveolar pattern. On the other hand, echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion gene in a subset of lung adenocarcinoma is related to mucinous cribriform histology. CASE PRESENTATION: Reported herein is a case of synchronous EML4-ALK positive lung adenocarcinoma and adenocarcinoma in situ in the bilateral lungs of a 55-year-old Japanese woman. The woman had EML4-ALK positive lung adenocarcinoma in the right lower lung while adenocarcinoma in situ in the left upper lung, which was EML4-ALK negative. CONCLUSION: To our knowledge, this is the first report of synchronous, bilateral lung adenocarcinomas composed of EML4-ALK positive and negative ones.

[824]
TÍTULO / TITLE: - Pseudomesotheliomatous lung cancer mimicking mesothelioma on F-FDG PET/CT images: report of 2 cases.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Enlace al texto completo (gratuito o de pago) 1007/s11604-013-0210-Z
AUTORES / AUTHORS: - Nakamori T; Kosuda S; Kyoto Y; Fujikawa A; Naoi Y; Nakamori Y
INSTITUCIÓN / INSTITUTION: - Department of Radiology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama, 359-8513, Japan.
RESUMEN / SUMMARY: - The authors report two cases of pseudomesotheliomatous lung cancer (PLC) detected by 18F-FDG PET/CT scan. 18F-FDG PET/CT clearly revealed the extent of the disease in both cases, a case of adenocarcinoma of the lung and a case of squamous cell carcinoma of the lung. Intense 18F-FDG uptake by the diffusely thickened pleurae and primary lesion was observed in both cases, and increased 18F-FDG uptake by a pelvic bone metastasis was observed in the case of squamous cell carcinoma. Although PLC is indistinguishable from malignant pleural mesothelioma on 18F-FDG PET/CT scans, 18F-FDG PET/CT was helpful in identifying the primary focus of the PLCs and in staging the disease. Diagnostic image interpreters should be familiar with the 18F-FDG PET/CT findings in PLC.

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[825]
TÍTULO / TITLE: - A rare case of non-small cell carcinoma of lung presenting as miliary mottling.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Jayaram Subhashchandra B; Ismailkhan M; Chikkaveeraiah Shashidhar K; Gopalakrishna Narahari M
INSTITUCIÓN / INSTITUTION: - Department of General Medicine, JSS Medical College and Hospital, JSS University, Mysore, India.
RESUMEN / SUMMARY: - Miliary mottling on chest radiography is seen in miliary tuberculosis, certain fungal infections, sarcoidosis, coal miner’s pneumoconiosis, silicosis, hemosiderosis, fibrosing alveolitis, acute extrinsic allergic alveolitis, pulmonary eosinophilic syndrome, pulmonary alveolar proteinosis, and rarely in hematogenous metastases from the primary cancers of the thyroid, kidney, trophoblasts, and some sarcomas. Although very infrequent, miliary mottling can be seen in primary lung cancers. Herein, we report the case of a 28-year-old female with chest X-ray showing miliary mottling. Thoracic computed tomography (CT) features were suggestive of tuberculoma with miliary tuberculosis. CT-guided fine needle aspiration cytology confirmed the diagnosis as lower-lobe, left lung non-small cell carcinoma (adenocarcinoma). It is rare for the non-small cell carcinoma of the lung to present as miliary mottling. The rarity of our case lies in the fact that a young, non-smoking female with miliary mottling was diagnosed with non-small cell carcinoma of the lung.

631
[826] TÍTULO / TITLE: - Non small-cell lung cancer with metastasis to thigh muscle and mandible: two case reports.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Giugliano FM; Alberti D; Guida G; Palma GD; Iadanza L; Mormile M; Cammarota F; Montanino A; Fulciniti F; Ravo V; Muto P
INSTITUCIÓN / INSTITUTION: - Radiation Therapy Department, National Cancer Institute, Pascale Foundation, Naples, Italy. francesca_giugliano@hotmail.com.
RESUMEN / SUMMARY: - INTRODUCTION: Lung cancer is the leading cause of cancer-related death in Europe and the US. Isolated metastases to skeletal muscle and the mandible are very uncommon. CASE PRESENTATION: This report presents two cases. Case 1 concerns a 45-year-old Caucasian woman affected by muscle metastasis of the right thigh from non-small-cell lung cancer. Case 2 concerns a 61-year-old Caucasian man affected by mandible metastasis from non-small-cell lung cancer. Both metastases were detected by diagnostic imaging studies. Both patients were treated with radiation therapy with palliative and antalgic intent. CONCLUSION: Radiation therapy was effective and well tolerated in both cases. Both our patients are alive, with follow-up of 18 months and five months, respectively.

[827] TÍTULO / TITLE: - Diagnostic delay in malignant pleural mesothelioma due to physicians fixation on history with non-exposure to asbestos.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Madsen PH; Laursen CB; Davidsen JR
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark.
RESUMEN / SUMMARY: - To establish the diagnosis of virtually any disease, the clinician must combine a variety of information. Often emphasised in this context is thorough medical history-taking including information on exposure to factors leading to or being associated with the disease in question. Continuous assessment of all available information is of utmost importance, as fixation on single details can be misleading with inappropriate consequences in both the
diagnostic and therapeutic approach. This case report presents how an atypical medical history led to a delay in the diagnosis of malignant pleural mesothelioma due to a low a priori likelihood of the disease because of non-exposure to asbestos. We highlight the fact that postrationalisation and attempts to renew a diagnostic approach must be carried out each time diagnostic dilemmas emerge, and when some or all diagnostic clues disagree.

[828]

**TÍTULO / TITLE:** - The frequency of EGFR and KRAS mutations in non-small cell lung cancer (NSCLC): routine screening data for central Europe from a cohort study.

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

**REVISTA / JOURNAL:** - British Medical J (BMJ). Acceso gratuito al texto completo.

- Enlace a la Editora de la Revista [http://bmj.com/search.dtl](http://bmj.com/search.dtl)
- Enlace al texto completo (gratuito o de pago) [1136/bmjopen-2013-002560](1136/bmjopen-2013-002560)

**AUTORES / AUTHORS:** - Boch C; Kollmeier J; Roth A; Stephan-Falkenau S; Misch D; Gruning W; Bauer TT; Mairinger T

**INSTITUCIÓN / INSTITUTION:** - Klinik fur Pneumologie, Lungenklinik Heckeshorn, HELIOS Klinikum Emil von Behring, Berlin, Berlin, Germany.

**RESUMEN / SUMMARY:** - OBJECTIVES: Owing to novel therapy strategies in epidermal growth factor receptor (EGFR)-mutated patients, molecular analysis of the EGFR and KRAS genome has become crucial for routine diagnostics. Till date these data have been derived mostly from clinical trials, and thus collected in pre-selected populations. We therefore screened ‘allcomers’ with a newly diagnosed non-small cell lung carcinoma (NSCLC) for the frequencies of these mutations. DESIGN: A cohort study. SETTING: Lung cancer centre in a tertiary care hospital. PARTICIPANTS: Within 15 months, a total of 552 cases with NSCLC were eligible for analysis. PRIMARY AND SECONDARY OUTCOME MEASURES: Frequency of scrutinising exons 18, 19 and 21 for the presence of activating EGFR mutation and secondary codon 12 and 13 for activating KRAS mutations. RESULTS: Of the 552 patients, 27 (4.9%) showed a mutation of EGFR. 19 of these patients (70%) had deletion E746-A750 in codon 19 or deletion L858R in codon 21. Adenocarcinoma (ACA) was the most frequent histology among patients with EGFR mutations (ACA, 22/254 (8.7%) vs non-ACA, 5/298 (1.7%); p<0.001). Regarding only ACA, the percentage of EGFR mutations was higher in women (16/116 (14%) women vs 6/138 (4.3%) men; p=0.008). Tumours with an activating EGFR mutation were more likely to be from non-smokers (18/27; 67%) rather than smoker (9/27; 33%). KRAS mutation was present in 85 (15%) of all cases. In 73 patients (86%), the
mutation was found in exon 12 and in 12 cases (14%) in exon 13. Similarly, ACA had a higher frequency of KRAS mutations than non-ACA (67/254 (26%) vs 18/298 (6.0%); p<0.001). CONCLUSIONS: We found a lower frequency for EGFR and KRAS mutations in an unselected Caucasian patient cohort as previously published. Taking our results into account, clinical trials may overestimate the mutation frequency for EGFR and KRAS in NSCLC due to important selection biases.

[829]
TITULO / TITLE: Scalp metastases—an unusual presentation of non-small cell lung cancer prognosis of cutaneous metastases in the current era.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Rachakonda KM; George MK; Peek RD
INSTITUCIÓN / INSTITUTION: Medical Oncology, Tamworth Base Hospital, Dean Street, Tamworth, NSW 2340, Australia. kmrachakonda@gmail.com

RESUMEN / SUMMARY: We report a case of metastatic lung cancer presenting as scalp metastases. Immunohistochemistry and radiological investigations helped in making the diagnosis. We also report better survival as seen in our present case using newer chemotherapeutic agents. The report emphasizes the need to look carefully for skin lesions as they provide easily accessible tissue for histopathology and also aid in proper staging as they can be missed out on routine radiological investigations. The case also reflects improvement in cancer care and outcomes in recent times.

[830]
TITULO / TITLE: Multiple Reaction Monitoring of Multiple Low-Abundance Transcription Factors in Whole Lung Cancer Cell Lysates.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: Kim JS; Lee Y; Lee MY; Shin J; Han JM; Yang EG; Yu MH; Kim S; Hwang D; Lee C
INSTITUCIÓN / INSTITUTION: Theragnostic Research Center, Korea Institute of Science and Technology, Seoul, Korea.
RESUMEN / SUMMARY: Lung cancer-related transcription factors (TFs) were identified by integrating previously reported genomic, transcriptomic, and proteomic data and were quantified by multiple reaction monitoring (MRM) in various cell lines. All experiments were performed without affinity depletion or subfractionation of cell lysates. Since the target proteins were expected to be present in low abundance, we experimentally optimized MRM transition
parameters with chemically synthesized peptides. Quantitation was based on stable isotope-labeled standard peptides (SIS peptides). Out of 288 MRM measurements (36 peptides representing 28 TFs x 8 cell lines), 241 were successfully obtained within a quantitation limit of 15 amol, 221 measurements (91.7%) showed coefficients of variation (CVs) of <=20%, and 149 (61.8%) showed CVs of <=10%, quantifying as low as 19.4 amol/mg protein for STAT2 with a CV of 6.3% in an A549 cell. Comparisons between MRM measurements and levels of the corresponding mRNAs revealed linear, nonlinear, or no relationship between protein and mRNA levels, indicating the need for an MRM assay. An integrative analysis of MRM and gene expression profiles from doxorubicin-resistant H69AR and sensitive H69 cells further showed that 14 differentially expressed TFs, such as STAT1 and SMAD4, regulated genes associated with drug resistance and cell differentiation-related processes. Thus, the analytical performance of MRM for the quantitation of low abundance TFs suggests its usefulness for biological application.

[831]
TÍTULO / TITLE: - Determination of standard number, size and weight of mediastinal lymph nodes in postmortem examinations: reflection on lung cancer surgery.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ziyade S; Pinarbasili NB; Ziyade N; Akdemir OC; Sahin F; Soysal O; Toker A
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Faculty of Medicine, Bezmialem Vakif University, Merkezefendi Mah, Mevlana Cad, Sedeftepe Evleri No:96/15 Zeytinburnu, Istanbul, Turkey. sedatziyade@gmail.com.
RESUMEN / SUMMARY: - BACKGROUND: Mediastinal lymph node dissection is an essential component of lung cancer surgery. Literature lacks established information regarding the number and size of the healthy lymph nodes. In this postmortem autopsy study, we aim to define the number, size and weight of the lymph nodes in each mediastinal lymph node station. To implement the data for the clinical practice, we analyzed the possible number of nodes to be dissected in a systematic mediastinal lymph node dissection from the right and left sides during lung cancer surgery. METHODS: Sixty-two samples obtained from cadavers who did not die from chest malignancies, extrathoracic malignancies, any kind of infections or previous hospitalization before the death were included to the study. The locations of the nodes were recorded according to the American Thoracic Society Mediastinal Lymph Node Map. The number, size and weight of the nodes were determined at each station. RESULTS: Median
age of the cadavers was 39 years. Primary causes of death were asphyxia in 10 (16.1%) subjects, trauma in 29 (46.8%) subjects, cardiovascular problems in 10 (16.1%) subjects, and undetermined in 13 (21%) subjects. The median number of lymph nodes resected from each patient was 23 (range: 11-54). The right sided paratracheal lymph nodes (Station 2R and 4R) were more frequent, heavier and longer than left sided lymph nodes (Station 2L and 4L) at the paratracheal region. Right sided inferior mediastinal lymph nodes were heavier and longer than the left ones; however, their availability was more often on the left. CONCLUSIONS: The properties of mediastinal lymph nodes at particular stations are different for number, size and weight. Station 4R and 7 have the highest number of nodes followed by stations 5 and 6. We recommend removing the lymph nodes of these stations completely in lung cancer patients to rule out the possibility of micrometastatic disease. Diameter of normal lymph node may be 1 cm for the stations other than 4R and 7, but the definition of normal diameter of a lymph node at the stations 4R and 7 may be changed as 1.5 cm and 2.0 cm, respectively. Weight of the nodes may be a new subject to study and may be defined as a new modality to define a staging to be more accurate and the issue needs further investigations.

[832]

**TÍTULO / TITLE:** - Performance of integrated positron emission tomography/computed tomography for mediastinal nodal staging in non-small cell lung carcinoma.

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


**AUTORES / AUTHORS:** - Broderick SR; Patterson GA

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**RESUMEN / SUMMARY:** - Integrated positron emission tomography (PET)/CT is routinely used for mediastinal nodal staging of non-small cell lung carcinoma in centers throughout the world. This modality is the most accurate noninvasive means by which to identify metastatic disease in mediastinal lymph nodes. This article reviews the evidence supporting the use of PET/CT and discusses the clinical applicability of this modality.

[833]
Efficacy of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in evaluating lung cancer recurrence.

Asai N; Ohkuni Y; Shoji K; Kaneko N

Kameda Medical Center, Kamogawa, Japan.

Antitumor effects of inductive hyperthermia using magnetic ferucarbotran nanoparticles on human lung cancer xenografts in nude mice.

Araya T; Kasahara K; Nishikawa S; Kimura H; Sone T; Nagae H; Ikehata Y; Nagano I; Fujimura M

Department of Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.

BACKGROUND: The effects of inductive hyperthermia on lung cancer have yet to be fully investigated. Magnetic nanoparticles used in inductive hyperthermia are made-to-order and expensive. This study was performed to investigate the use of ferucarbotran in inductive hyperthermia and to clarify whether inductive hyperthermia using ferucarbotran promotes antitumor effects in vivo using a lung cancer cell line.

METHODS: We injected A549 cells subcutaneously into the right thighs of BALB/c nu/nu nude mice. Forty mice with A549 xenografts were then classified into three groups. Group 1 was the control group. All mice in groups 2 and 3 had ferucarbotran injected into their tumors, and mice in group 3 were then subjected to alternating magnetic field irradiation. We evaluated tumor temperature during the hyperthermic procedure, the time course of tumor growth, histologic findings in tumors after hyperthermic treatment, and adverse events.

RESULTS: Intratumor temperature rose rapidly and was maintained at 43 degrees C-45 degrees C for 20 minutes in an alternating magnetic field. Tumor volumes in groups 1 and 2 increased exponentially, but tumor growth in group 3 was significantly suppressed. No severe adverse events were observed. Histologic findings for the tumors in group 3 revealed mainly necrosis.

CONCLUSION: Inductive hyperthermia using ferucarbotran is a beneficial and promising approach in the treatment of lung cancer. Ferucarbotran is a novel tool for further development of inductive hyperthermia.
Contribution of immunohistochemistry in the differential diagnosis of non-small cell lung carcinomas on small biopsy samples.

Purpose: Targeted therapy increases survival and the quality of life of non-small cell lung cancer (NSCLC) patients but it needs precise histological subtyping. The present study evaluated 6 monoclonal antibodies for the differential diagnosis of NSCLC on small-sized tissue samples. Methods: 50 small-sized tissue samples were obtained by bronchoscopy or fine needle aspiration biopsy (FNAB). According to morphology before immunohistochemistry 2 squamous cell carcinomas (SCC), 6 adenocarcinomas (AC), 9 NSCLC-probably SCC, 11 NSCLC-probably AC and 22 unclassified NSCLCs were diagnosed. Thyroid transcription factor-1 (TTF-1), cytokeratin 5/6, cytokeratin 7, p63, and the neuroendocrine markers CD56 and synaptophysin were used in the differential diagnosis of NSCLC. Results: After immunohistochemistry 13 (26.0%) SCC, 27 (54.0%) AC, 3 (6.0%) NSCLC with neuroendocrine differentiation (NSCLC-NE) and 7 (14.0%) NSCLC-unclassified were diagnosed. Twenty-two NSCLC-unclassified were further diagnosed as SCC (n=7), AC (n=7) NSCLC-NE (n=2) and 6 remained NSCLC-unclassified. Significant difference was found between definitely diagnosed 8 NSCLCs and 15 ACs (20.5 vs. 38.57; p=0.008). TTF-1 and cytokeratin 7 were expressed in 85.2% (23/27) of AC, and cytokeratin 5/6 and p63 in 100% (13/13) of SCC. Positivity of CD56 and synaptophysin in 3 NSCLC determined NSCLC-NE. Conclusion: No one monoclonal antibody is totally specified for one histological type of tumor and its origin. Combination of TTF-1, cytokeratin 7, p63, cytokeratin 5/6, CD56 and synaptophysin allows for differentiation of NSCLC but Napsin-A for AC differentiation and chromogranin A for NSCLC-NE differentiation should be added in an optimal panel.

Predictors of radiation pneumonitis and pulmonary function changes after concurrent chemoradiotherapy of non-small cell lung cancer.


Enlace al texto completo (gratis o de pago) 3857/roj.2013.31.1.34

Park YH; Kim JS
INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the predictive factors of radiation pneumonitis (RP) and associated changes in pulmonary function after definitive concurrent chemoradiotherapy (CCRT) in patients with non-small cell lung cancer (NSCLC). MATERIALS AND METHODS: Medical records of 60 patients with NSCLC who received definitive CCRT were retrospectively reviewed. Dose volumetric (DV) parameters, clinical factors, and pulmonary function test (PFT) data were analyzed. RP was graded according to the CTCAE ver. 4.0. Percentage of lung volume that received a dose of threshold (Vdose) and mean lung dose (MLD) were analyzed for potential DV predictors. PFT changes were calculated as the difference between pre-RT and post-RT values at 3, 6, and 12 months after RT. RESULTS: Twenty-two patients (37%) developed grade >/=2 RP. Among clinical factors, tumor location in lower lobe was associated with RP. Among the DV parameters, only MLD >15 Gy was associated with grade >/=2 RP. There were statistically significant decreases in PFT at all points compared with pre-RT values in grade >/=2 RP group. MLD was associated with forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) changes at 6 and 12 months. V10 was associated with FVC changes at 12 months. V20 and V30 were associated with FEV1 changes at 6 months and FVC changes at 12 months. CONCLUSION: After definitive CCRT in patients with NSCLC, MLD >15 Gy and lower lobe tumor location were predictors of grade >/=2 RP. Pulmonary functions were decreased after CCRT and the magnitude of changes was associated with DV parameters.


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


AUTORES / AUTHORS: - Sun T; Zhang R; Wang J; Li X; Guo X

INSTITUCIÓN / INSTITUTION: - School of Public Health, Capital Medical University, Beijing, China.

RESUMEN / SUMMARY: - BACKGROUND: Lung cancer is one of the most common forms of cancer resulting in over a million deaths per year worldwide. Typically, the problem can be approached by developing more discriminative diagnosis methods. In this paper, computer-aided diagnosis was used to facilitate the prediction of characteristics of solitary pulmonary nodules in CT of lungs to diagnose early-stage lung cancer. METHODS: The synthetic minority
over-sampling technique (SMOTE) was used to account for raw data in order to balance the original training data set. Curvelet-transformation textural features, together with 3 patient demographic characteristics, and 9 morphological features were used to establish a support vector machine (SVM) prediction model. Longitudinal data as the test data set was used to evaluate the classification performance of predicting early-stage lung cancer. RESULTS: Using the SMOTE as a pre-processing procedure, the original training data was balanced with a ratio of malignant to benign cases of 1:1. Accuracy based on cross-evaluation for the original unbalanced data and balanced data was 80% and 97%, respectively. Based on Curvelet-transformation textural features and other features, the SVM prediction model had good classification performance for early-stage lung cancer, with an area under the curve of the SVMs of 0.949 (P<0.001). Textural feature (standard deviation) showed benign cases had a higher change in the follow-up period than malignant cases. CONCLUSIONS: With textural features extracted from a Curvelet transformation and other parameters, a sensitive support vector machine prediction model can increase the rate of diagnosis for early-stage lung cancer. This scheme can be used as an auxiliary tool to differentiate between benign and malignant early-stage lung cancers in CT images.

[838]
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Midthun DE
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RESUMEN / SUMMARY: A large randomized controlled trial, The National Lung Screening Study (NLST), has demonstrated that screening with low-dose spiral computed tomography saved lives from lung cancer when compared with screening with chest radiographs. This is the first test showing efficacy in screening for lung cancer as previous trials of chest radiographs and sputum cytology failed to result in fewer deaths with screening. This review will examine the problem of lung cancer, the issues presented by screening, and the results of computed tomography (CT) studies for lung cancer screening. Now that CT screening has been shown to be effective, implementation of screening becomes the next step.

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[839]
TÍTULO / TITLE: Rare mutations in non-small-cell lung cancer.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary
In the last decade, new insights in molecular biology have changed the therapeutic landscape of non-small-cell lung cancer. Since 2004, when activating mutations of the EGFR were firstly identified, several genetic aberrations have been discovered, mainly in adenocarcinoma. EGFR mutations are a relatively frequent event in non-small-cell lung cancer, generally consisting of exon 19 deletion or exon 21 substitution. In adenocarcinoma, additional rare mutations are detectable in the EGFR gene, as well as in other genes, including ALK, ROS1, RET, HER2 and BRAF. Recent studies in squamous cell carcinoma identified TP53 as the most frequent mutation, followed by additional more rare mutations, including PI3KCA, PTEN, DDR2 and FGFR. The aim of the present review is to analyze the potential prognostic and predictive role of rare mutations.

[840]


RESUMEN / SUMMARY: We previously reported novel quinuclidinone analogs which induced apoptosis in lung and breast cancer cells. In this study, we designed and synthesized novel quinuclidinone analogs that showed cytotoxicity in lung cancer cells. The effects of these analogs were studied in H1299 human large cell lung carcinoma cells that are null for p53 and normal lung epithelial cell lines (NL-20). The effects of the analogs were investigated by MTT assay, ELISA based apoptotic assay, TUNEL assay, sphingomyelinase activity, flow cytometry and western blot analysis. Our data indicated that derivatives 4 and 6 decreased cell proliferation and induced apoptosis in H1299 cells more than NL-20 cells. Derivatives 4 and 6 reduced percent of cells in G2/M phase in H1299 cells more than NL-20 cells and these results were confirmed by increased expression levels of cyclin E. Furthermore, derivatives 4 and 6 increased sphingomyelinase activity, caspase-8, and caspase-9 and JNK-1 expression level in H1299. Additionally, derivatives 4 and 6 induced Procasparase-3, PARP-1 cleavage, and increased caspase-3 activity. All these
results confirm that our quinuclidinone derivatives provoke cytotoxicity in lung cancer cells through the interplay of key apoptosis molecules in different compartments of the cell beginning with an increase in sphingomyelinase activity.

[841]
TÍTULO / TITLE: - Minimally invasive pulmonary surgery for lung cancer, up to date.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1007/s11748-013-0260-2
AUTORES / AUTHORS: - Iwata H
INSTITUCIÓN / INSTITUTION: - Department of General and Cardiothoracic Surgery, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu City, Gifu, 501-1194, Japan, ihisashi@gifu-u.ac.jp.
RESUMEN / SUMMARY: - Recently, the minimally invasive surgical approach is an important issue in the pulmonary surgery. In this review, we present the current fashion of video-assisted thoracic surgery (VATS) and new approach including robotic lobectomy. There is no clear definition or standard for this surgical procedure regarding VATS lobectomy. Therefore, no randomized controlled trial of VATS and conventional lobectomy can be set up. Although the definition of VATS lobectomy is not straightforward, VATS lobectomy showed the technical feasibility of conventional lobectomy in mortality and postoperative complication as well as lymph node dissection. VATS procedure for advanced lung cancer is unclear whether such observations can be developed into a standardized approach. There are no reports to evaluate the advantages of robotic lobectomy in terms of treatment outcomes for lung cancer compared with VATS lobectomy. However, we believe that robotic lobectomy has clear potential to improve the quality of minimally invasive surgery.

[842]
TÍTULO / TITLE: - The role of thoracic surgery in octogenarians with non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ●●Enlace al texto completo (gratuito o de pago) 1093/icvts/ivt158
AUTORES / AUTHORS: - Rizzi A; De Simone M; Raveglia F; Cioffi U
INSTITUCIÓN / INSTITUTION: - Thoracic Unit, Ospedale San Paolo Milano, University of Milan, Milan, Italy.
**TÍTULO / TITLE:** - Video-assisted thoracic surgery lobectomy versus lobectomy by thoracotomy for lung cancer: pilot study.

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


**AUTORES / AUTHORS:** - Papiashvilli M; Sasson L; Azzam S; Hayat H; Schreiber L; Ezri T; Priel IE

**INSTITUCIÓN / INSTITUTION:** - Department of Cardiothoracic Surgery, Edith Wolfson Medical Center, Holon, Israel. fredicag@asaf.health.gov.il

**RESUMEN / SUMMARY:** - **OBJECTIVE:** Video-assisted thoracic surgery lobectomy (VATS-L) has become accepted as a safe and effective procedure to treat early-stage non-small cell lung carcinoma (NSCLC). However, the advantages of VATS-L compared with lobectomy by thoracotomy (TL) remain controversial. The aim of this study was to compare the outcomes of patients who underwent VATS-L with those who underwent TL. **METHODS:** We studied 103 patients who underwent surgery for operable NSCLC between October 2009 and March 2012. All operations were performed by a single surgeon. The inclusion and exclusion criteria for VATS-L and TL were formulated before the study was initiated. Data on age, sex, preoperative comorbidities, intraoperative and postoperative complications, hospital stay, morbidity, mortality, and other characteristics were recorded preoperatively, in real time intraoperatively, and during hospitalization and were statistically compared. Comorbidities were scaled according to the Charlson Comorbidity Index, and propensity scores between the patients who underwent TL and VATS-L were compared. **RESULTS:** Sixty-three VATS-L operations and 40 TL operations were performed. There were no postoperative complications in 39 patients (61.9%) who underwent VATS-L compared with 25 patients (62.5%) who underwent TL. The patients who underwent TL were significantly younger than the patients who underwent VATS-L (mean +/- SD, 64.7 +/- 12.6 vs 70.9 +/- 8.4; P = 0.003). Hospital stay was not found to be related to the type of surgery (mean +/- SD, 8.43 +/- 3.15 days vs 8.32 +/- 4.13 days; P = 0.888). There were no significant differences when comparing postoperative complications. **CONCLUSIONS:** Our initial data suggest that VATS-L is a safe procedure in patients with resectable IA/IB NSCLC and may be the preferred strategy for treatment of the older patient population.

[844]

**TÍTULO / TITLE:** - New molecular insights in tobacco-induced lung cancer.

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

Enlace al texto completo (gratuito o de pago) 2217/fon.13.32

AUTORES / AUTHORS: Tonini G; D’Onofrio L; Dell’aquila E; Pezzuto A
INSTITUCIÓN / INSTITUTION: Department of Oncology, University Campus Bio-Medico Roma, Rome, Italy.

RESUMEN / SUMMARY: We know that cigarette smoking is a leading preventable cause of carcinogenesis in lung cancer. Cigarette smoke is a mixture of more than 5000 chemical compounds, among which more than 60 are recognized to have a specific carcinogenic potential. Carcinogens and their metabolites (i.e., N-nitrosamines and polycyclic aromatic hydrocarbons) can activate multiple pathways, contributing to lung cell transformation in different ways. Nicotine, originally thought only to be responsible for tobacco addiction, is also involved in tumor promotion and progression with antiapoptotic and indirect mitogenic properties. Lung nodules are frequent in smokers and can be transformed into malignant tumors depending on persistent smoking status. Even if detailed mechanisms underlying tobacco-induced cancerogenesis are not completely elucidated, this report collects the emergent body of knowledge in order to simplify the extremely complex framework that links smoking exposure to lung cancer.

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[TÍTULO / TITLE: Honokiol inhibits non-small cell lung cancer cell migration by targeting PGE(2)-mediated activation of beta-catenin signaling.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Singh T; Katiyar SK
INSTITUCIÓN / INSTITUTION: Department of Dermatology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America.
RESUMEN / SUMMARY: Lung cancer remains a leading cause of death due to its metastasis to distant organs. We have examined the effect of honokiol, a bioactive constituent from the Magnolia plant, on human non-small cell lung cancer (NSCLC) cell migration and the molecular mechanisms underlying this effect. Using an in vitro cell migration assay, we found that treatment of A549, H1299, H460 and H226 NSCLC cells with honokiol resulted in inhibition of migration of these cells in a dose-dependent manner, which was associated with a reduction in the levels of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). Celecoxib, a COX-2 inhibitor, also inhibited cell migration. Honokiol inhibited PGE2-enhanced migration of NSCLC cells, inhibited the activation of NF-kappaB/p65, an upstream regulator of COX-2, in A549 and H1299 cells, and treatment of cells with caffeic acid phenethyl ester, an inhibitor of NF-kappaB, also inhibited migration of NSCLC cells. PGE2 has been shown to activate
beta-catenin signaling, which contributes to cancer cell migration. Therefore, we checked the effect of honokiol on beta-catenin signaling. It was observed that treatment of NSCLC cells with honokiol degraded cytosolic beta-catenin, reduced nuclear accumulation of beta-catenin and down-regulated matrix metalloproteinase (MMP)-2 and MMP-9, which are the down-stream targets of beta-catenin and play a crucial role in cancer cell metastasis. Honokiol enhanced: (i) the levels of casein kinase-1alpha, glycogen synthase kinase-3beta, and (ii) phosphorylation of beta-catenin on critical residues Ser(45), Ser(33/37) and Thr(41). These events play important roles in degradation or inactivation of beta-catenin. Treatment of celecoxib also reduced nuclear accumulation of beta-catenin in NSCLC cells. FH535, an inhibitor of Wnt/beta-catenin pathway, inhibited PGE2-enhanced cell migration of A549 and H1299 cells. These results indicate that honokiol inhibits non-small cell lung cancer cells migration by targeting PGE2-mediated activation of beta-catenin signaling.

[846]

TITULO / TITLE: - TGF-beta1 exposure induces epithelial to mesenchymal transition both in CSCs and non-CSCs of the A549 cell line, leading to an increase of migration ability in the CD133(+) A549 cell fraction.

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


AUTORES / AUTHORS: - Tirino V; Camerlingo R; Bifulco K; Irollo E; Montella R; Paino F; Sessa G; Carriero MV; Normanno N; Rocco G; Pirozzi G

INSTITUCION / INSTITUTION: - Department of Experimental Medicine, Second University of Naples, Naples, Italy.

RESUMEN / SUMMARY: - Metastasis is the leading cause of death by cancer. Non-small-cell lung cancer (NSCLC) represents nearly 85% of primary malignant lung tumours. Recent researches have demonstrated that epithelial-to-mesenchymal transition (EMT) plays a key role in the early process of metastasis of cancer cells. Transforming growth factor-beta1 (TGF-beta1) is the major inductor of EMT. The aim of this study is to investigate TGF-beta1’s effect on cancer stem cells (CSCs) identified as cells positive for CD133, side population (SP) and non-cancer stem cells (non-CSCs) identified as cells negative for CD133, and SP in the A549 cell line. We demonstrate that TGF-beta1 induces EMT in both CSC and non-CSC A549 sublines, upregulating the expression of mesenchymal markers such as vimentin and Slug, and downregulating levels of epithelial markers such as e-cadherin and cytokeratin. CSC and non-CSC A549 sublines undergoing EMT show a strong migration and strong levels of MMP9 except for the CD133(-) cell fraction. OCT4 levels are strongly upregulated in all cell fractions except CD133(-) cells. On the contrary, wound size reveals that TGF-beta1 enhances motility in wild-type
A549 as well as CD133(+) and SP(+) cells. For CD133(-) and SP(-) cells, TGF-beta1 exposure does not change the motility. Finally, assessment of growth kinetics reveals major colony-forming efficiency in CD133(+) A549 cells. In particular, SP(+) and SP(-) A549 cells show more efficiency to form colonies than untreated corresponding cells, while for CD133(-) cells no change in colony number was observable after TGF-beta1 exposure. We conclude that it is possible to highlight different cell subpopulations with different grades of stemness. Each population seems to be involved in different biological mechanisms such as stemness maintenance, tumorigenicity, invasion and migration.

[847]
TÍTULO / TITLE: - Initial Experience With a Free, High-Volume, Low-Dose CT Lung Cancer Screening Program.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - McKee BJ; McKee AB; Flacke S; Lamb CR; Hesketh PJ; Wald C
INSTITUCIÓN / INSTITUTION: - Department of Radiology, Lahey Hospital & Medical Center, Burlington, Massachusetts, USA.
RESUMEN / SUMMARY: - The National Lung Screening Trial demonstrated a significant mortality benefit for patients at high risk for lung cancer undergoing serial low-dose CT. Currently, the National Comprehensive Cancer Network and several United States-based professional associations recommend CT lung screening for high-risk patients. In the absence of established reimbursement, the authors modeled and implemented a free low-dose CT lung cancer screening program to provide equitable access to all eligible patients. Elements of the program reported in this article include a decentralized referral network, centralized program coordination, structured reporting, and a patient data management system. The experience and initial results observed in this clinical setting closely match the performance metrics of the National Lung Screening Trial with regard to cancer detection and incidental findings rates. To eliminate health care disparities a vigorous lobbying effort will be needed to expedite reimbursement and make CT lung screening equally available to all patients at high-risk.

[848]
TÍTULO / TITLE: - Lung cancer: ALK status of NSCLC reflected in CTCs.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Xiao Z; Jiang Q; Willette-Brown J; Hu Y
INSTITUCIÓN / INSTITUTION: - Laboratory of Experimental Immunology, Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, Frederick Maryland.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Chen KC; Chen JS
INSTITUCIÓN / INSTITUTION: - The Institute of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, Taipei, Taiwan; ; Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Lococo F; Cesario A; Attili F; Chiappetta M; Leuzzi G; Costamagna G; Granone P; Larghi A
INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Catholic University, Rome, Italy.
RESUMEN / SUMMARY: - OBJECTIVESThe efficacy of endoscopic ultrasound (EUS) for evaluating mediastinal adenopathy in lung cancer is nowadays proven. However, its accuracy for detection of malignant pleural effusion per se has not been yet investigated. Herein we report our experience with EUS for detecting pleural effusion during the staging procedure of non-small cell lung cancer (NSCLC) patients.METHODSBetween January 2009 and December 2011, we performed endoscopic ultrasound-guided fine needle aspiration (EUS-
FNA) on 92 selected NSCLC patients to evaluate the T and N factors and to acquire biopsy material and when this was detected, to sample the pleural effusion. RESULTS In 10 patients (8 males and 2 females, mean age 66.9 +/- 9.2 years) a pleural effusion was detected and sampled. In 7 out of the 10 cases, the cytological examination of the fluid obtained by EUS-FNA tested positive for malignant cells, thereby upgrading the case to Stage IV, irrespective of T and N statuses. In 3 cases the cytology on the EUS-FNA material was proven to be negative for malignancy thereby allowing patients to be treated with curative intent without further delay. CONCLUSION EUS-FNA of the pleural fluid is a safe and simple procedure. Our data, albeit stemming from a limited study population, show that it can be efficient in selected NSCLC cases for obtaining useful material and information with significant impact on the staging and, therefore, on the planning of the optimum therapeutic strategy.

[852] TÍTULO / TITLE: mTOR Inhibitors Control the Growth of EGFR Mutant Lung Cancer Even after Acquiring Resistance by HGF.
RESUMEN / SUMMARY: Enlace al Resumen / Link to its Summary

AUTORES / AUTHORS: Ishikawa D; Takeuchi S; Nakagawa T; Sano T; Nakade J; Nanjo S; Yamada T; Ebi H; Zhao L; Yasumoto K; Nakamura T; Matsumoto K; Kagamu H; Yoshizawa H; Yano S
INSTITUCIÓN / INSTITUTION: Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Japan; Department of Medicine (II), Niigata University Medical and Dental Hospital, Niigata City, Japan.
RESUMEN / SUMMARY: Resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), gefitinib and erlotinib, is a critical problem in the treatment of EGFR mutant lung cancer. Several mechanisms, including bypass signaling by hepatocyte growth factor (HGF)-triggered Met activation, are implicated as mediators of resistance. The mammalian target of rapamycin (mTOR), is a downstream conduit of EGFR and MET signaling, and is thus considered a therapeutically attractive target in the treatment of various types of cancers. The purpose of this study was to examine whether 2 clinically approved mTOR inhibitors, temsirolimus and everolimus, overcome HGF-dependent resistance to EGFR-TKIs in EGFR mutant lung cancer cells. Both temsirolimus and everolimus inhibited the phosphorylation of p70S6K and 4E-BP1, which are downstream targets of the mTOR pathway, and reduced the viability of EGFR mutant lung cancer cells, PC-9, and HCC827, even in the presence of HGF in vitro. In a xenograft model, temsirolimus suppressed the growth of PC-9 cells overexpressing the HGF-gene; this was associated with...
suppression of the mTOR signaling pathway and tumor angiogenesis. In contrast, erlotinib did not suppress this signaling pathway or tumor growth. Multiple mechanisms, including the inhibition of vascular endothelial growth factor production by tumor cells and suppression of endothelial cell viability, contribute to the anti-angiogenic effect of temsirolimus. These findings indicate that mTOR inhibitors may be useful for controlling HGF-triggered EGFR-TKI resistance in EGFR mutant lung cancer, and they provide the rationale for clinical trials of mTOR inhibitors in patients stratified by EGFR mutation and HGF expression status.

[853]

**TITULO / TITLE:** - Characteristics of local recurrence of lung cancer and possibilities for surgical management.

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


**AUTORES / AUTHORS:** - Stojiljkovic D; Mandaric D; Miletic N; Stojisic J; Markovic I; Gavrilovic D; Pupic G; Stojiljkovic T; Lukac B; Dzodic R

**INSTITUCION / INSTITUTION:** - Institute of Oncology and Radiology of Serbia, Department of Surgery, Belgrade, Serbia.

**RESUMEN / SUMMARY:** - Purpose: To investigate the correlation between stage and histopathological characteristics of patients with lung cancer and local recurrence, as well as the incidence and the characteristics of local recurrence along with the possibility of surgical retreatment. Methods: Studied were 51 patients with locally relapsing lung cancer, initially treated surgically from 2003 to 2007. The operations performed ranged from conservative wedge resections, standard lobectomies and pneumonectomies to extensive resections of the entire lung and chest wall. All patients underwent regular follow-up including thoracic CT scan every 3 months. Results: All patients were diagnosed with local recurrence after a median of 10 months (range 1-30) after primary surgery with curative intent. There was no statistically significant link between type of surgery and time to local recurrence. Patients with pathological stage I,II, and IIIa had a significantly longer time to local recurrence than those with stage IIIb and IV. Local recurrence sites were the bronchial stump, mediastinal lymph nodes, the remaining lung parenchyma, chest wall and a combination of these. Surgical retreatment was possible in 20 of 51 patients (39.27%) of patients. Squamous cell cancer (SCC) was the predominant histological type (38 of 51; 74.5%), followed by adenocarcinoma (9 of 51; 17.7%). Conclusion: SCC is the commonest locally relapsing lung cancer. The type of the initial surgical procedure didn’t have any impact on the incidence of local recurrence, but the extent and completeness of surgery did. The time to local recurrence heavily depended on the primary tumor pathological stage. Chest wall was the commonest relapse
site, and the most suitable for surgical retreatment, which was related to the quality of surgery.

[854]

**TÍTULO / TITLE:** - QSAR and Docking Based Semi-Synthesis and In Vitro Evaluation of 18 beta-Glycyrrhetinic Acid Derivatives against Human Lung Cancer Cell Line A-549.

**RESUMEN / SUMMARY:** - For the prediction of anticancer activity of glycyrrhetinic acid (GA-1) analogs against the human lung cancer cell line (A-549), a QSAR model was developed by forward stepwise multiple linear regression methodology. The regression coefficient (r^2) and prediction accuracy (rCV^2) of the QSAR model were taken 0.94 and 0.82, respectively in terms of correlation. The QSAR study indicates that the dipole moments, size of smallest ring, amine counts, hydroxyl and nitro functional groups are correlated well with cytotoxic activity. The docking studies showed high binding affinity of the predicted active compounds against the lung cancer target EGFR. These active glycyrrhetinic acid derivatives were then semi-synthesized, characterized and in-vitro tested for anticancer activity. The experimental results were in agreement with the predicted values and the ethyl oxalyl derivative of GA-1 (GA-3) showed equal cytotoxic activity to that of standard anticancer drug paclitaxel.

[855]

**TÍTULO / TITLE:** - Gli1 mediates lung cancer cell proliferation and sonic hedgehog-dependent mesenchymal cell activation.

**RESUMEN / SUMMARY:** - Non-Small-Cell-Lung-Cancer (NSCLC) represents approximately 85% of all lung cancers and remains poorly understood. While
signaling pathways operative during organ development, including Sonic Hedgehog (Shh) and associated Gli transcription factors (Gli1-3), have recently been found to be reactivated in NSCLC, their functional role remains unclear. Here, we hypothesized that Shh/Gli1-3 could mediate NSCLC autonomous proliferation and epithelial/stromal signaling in the tumoral tissue. In this context, we have investigated the activity of Shh/Gli1-3 signaling in NSCLC in both, cancer and stromal cells. We report here that inhibition of Shh signaling induces a significant decrease in the proliferation of NSCLC cells. This effect is mediated by Gli1 and Gli2, but not Gli3, through regulation of cyclin D1 and cyclin D2 expression. While exogenous Shh was unable to induce signaling in either A549 lung adenocarcinoma or H520 lung squamous carcinoma cells, both cells were found to secrete Shh ligand, which induced fibroblast proliferation, survival, migration, invasion, and collagen synthesis. Furthermore, Shh secreted by NSCLC mediates the production of proangiogenic and metastatic factors in lung fibroblasts. Our results thus provide evidence that Shh plays an important role in mediating epithelial/mesenchymal crosstalk in NSCLC. While autonomous Gli activity controls NSCLC proliferation, increased Shh expression by NSCLC is associated with fibroblast activation in tumor-associated stroma. Our study highlights the relevance of studying stromal-associated cells in the context of NSCLC regarding new prognosis and therapeutic options.

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**TÍTULO / TITLE:** - Over-Expression of Deubiquitinating Enzyme USP14 in Lung Adenocarcinoma Promotes Proliferation through the Accumulation of beta-Catenin.

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


**AUTORES / AUTHORS:** - Wu N; Liu C; Bai C; Han YP; Cho WC; Li Q

**INSTITUCIÓN / INSTITUTION:** - Department of Respiratory Medicine, Shanghai Hospital, Second Military Medical University, Shanghai 200433, China. qiangli20122012@126.com.

**RESUMEN / SUMMARY:** - The deubiquitinating enzyme USP14 has been identified and biochemically studied, but its role in lung cancer remains to be elucidated. The aim of this study was to evaluate the prognostic significance of USP14 in patients with lung adenocarcinoma and to define its role in lung cancer cell proliferation. USP14 mRNA levels in different non-small cell lung cancer (NSCLC) cell lines were detected by real-time qPCR. USP14 protein levels in surgically resected samples from NSCLC patients, and in NSCLC cell lines, were detected by immunohistochemistry or Western blot. The correlation of USP14 expression with clinical characteristics and prognosis was determined.
by survival analysis. After silencing USP14, cell proliferation was assessed by MTT assay and the cell cycle was measured by FACS assay. It was found that USP14 expression was upregulated in NSCLC cells, especially in adenocarcinoma cells. Over-expression of USP14 was associated with shorter overall survival of patients. Downregulation of USP14 expression arrested the cell cycle, which may be related to beta-catenin degradation. Over-expression of USP14 was associated with poor prognosis in NSCLC patients and promoted tumor cell proliferation, which suggests that USP14 is a tumor-promoting factor and a promising therapeutic target for NSCLC.

[857]

TÍTULO / TITLE: - Collision tumors of hepatocellular carcinoma and malignant peritoneal mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1007/s00795-013-0041-0
AUTORES / AUTHORS: - Uemoto J; Hoshi N; Hirabayashi K; Hoshi S; Onodera K; Nishi T; Tomikawa M; Igarashi S
INSTITUCION / INSTITUTION: - Department of Palliative Medicine, Okayama Saiseikai General Hospital, 1-17-18 Ifuku-chou, Kita-ku, Okayama, Okayama, 700-8511, Japan, uemotoj@gmail.com.
RESUMEN / SUMMARY: - We report a case of synchronous hepatocellular carcinoma (HCC) and malignant peritoneal mesothelioma (MM-per). A 56-year-old man with no past history of asbestos exposure, chronic viral hepatitis, or alcoholic liver injury was admitted to our hospital with left flank pain and abdominal tumor. Partial hepatectomy, splenectomy, partial diaphragm resection, and partial gastrectomy were performed. The tumor in the lateral segment of the liver was gray to white, massive in appearance, and contained focal bile-producing nodules and extensive fibrous firm lesion. It had directly invaded the spleen and diaphragm. Liver cirrhosis was not found. The peritoneum contained multiple small nodules especially around the diaphragm, which mimicked carcinoma dissemination. After histological examination, the liver tumor was diagnosed as HCC. It had trabecular and scirrhous patterns and positive immunoreactivities for Hep-Par-1 and alpha-fetoprotein. The peritoneal nodules were diagnosed as MM-per, epithelioid type, with positive immunoreactivities for calretinin and cytokeratin 5/6. The two tumors collided around the diaphragm. Cases of MM synchronous with other primary malignant tumors have been reported, but most had a history of asbestos exposure unlike the present case. The carcinogenic background was unclear for two tumors in this case. This is an extremely rare and valuable case.

[858]
LIMITED RESSECTION AND TWO-STAGED LOBECTOMY FOR NON- Small cell lung cancer with ground-glass opacity.

BACKGROUND: Lung tumors showing ground-glass opacities on high-resolution computed tomography indicate the presence of inflammation, atypical adenomatous hyperplasia, or localized bronchioloalveolar carcinoma. We adopted a two-staged video-assisted thoracoscopic lobectomy strategy involving completion lobectomy for localized bronchioloalveolar carcinoma with an invasive component according to postoperative pathological examination by permanent section after partial resection.

METHODS: Forty-one patients with undiagnosed small peripheral ground-glass opacity lesions underwent partial resection from 2001 to 2007 in Hokkaido University Hospital. Localized bronchioloalveolar carcinoma was classified according to the Noguchi classification for adenocarcinoma. Malignant lesions other than Noguchi types A and B were considered for completion lobectomy and systemic mediastinal lymphadenectomy. Perioperative data of completion video-assisted thoracoscopic lobectomies were compared with data of 67 upfront video-assisted thoracoscopic lobectomies for clinical stage IA adenocarcinoma performed during the same period.

RESULTS: Postoperative pathological examination revealed 35 malignant and 6 non-malignant diseases. Histologically, all of the malignant diseases were adenocarcinomas of Noguchi type A (n = 7), B (n = 9), C (n = 18), and F (n = 1). Eleven of 19 patients (58%) with Noguchi type C or F underwent two-staged video-assisted thoracoscopic lobectomy. Three patients refused a second surgery. There was no cancer recurrence. The two-staged lobectomy group had a significantly longer operative time and more blood loss than the upfront lobectomy group. There was no surgical mortality or cancer recurrence.

CONCLUSIONS: Two-staged lobectomy for undiagnosed small peripheral ground-glass opacity lesions showed satisfactory oncological results. However, low compliance for and invasiveness of the second surgery are concerns associated with this strategy.
BACKGROUND: Simian virus 40 (SV40), a polyomavirus, was discovered as a contaminant of a human polio vaccine in the 1960s. It is known that malignant mesothelioma (MM) is associated with SV40, and that the virus works as a cofactor to the carcinogenic effects of asbestos. However, the reports about the correlation between SV40 and MM have not been consistent. The purpose of this study is to identify SV40 in MM tissue in Korea through detection of SV40 protein and DNA.

METHODS: We analyzed 62 cases of available paraffin-blocks enrolled through the Korean Malignant Mesothelioma Surveillance System and performed immunohistochemistry for SV40 protein and real-time polymerase chain reaction (PCR) for SV40 DNA.

RESULTS: Of 62 total cases, 40 had disease involving the pleura (64.5%), and 29 (46.8%) were found to be of the epithelioid subtype. Immunostaining demonstrated that all examined tissues were negative for SV40 protein. Sufficient DNA was extracted for real-time PCR analysis from 36 cases. Quantitative PCR of these samples showed no increase in SV40 transcript compared to the negative controls. CONCLUSIONS: SV40 is not associated with the development of MM in Korea.

RESUMEN / SUMMARY: Simian virus 40 (SV40), a polyomavirus, was discovered as a contaminant of a human polio vaccine in the 1960s. It is known that malignant mesothelioma (MM) is associated with SV40, and that the virus works as a cofactor to the carcinogenic effects of asbestos. However, the reports about the correlation between SV40 and MM have not been consistent. The purpose of this study is to identify SV40 in MM tissue in Korea through detection of SV40 protein and DNA. METHODS: We analyzed 62 cases of available paraffin-blocks enrolled through the Korean Malignant Mesothelioma Surveillance System and performed immunohistochemistry for SV40 protein and real-time polymerase chain reaction (PCR) for SV40 DNA. RESULTS: Of 62 total cases, 40 had disease involving the pleura (64.5%), and 29 (46.8%) were found to be of the epithelioid subtype. Immunostaining demonstrated that all examined tissues were negative for SV40 protein. Sufficient DNA was extracted for real-time PCR analysis from 36 cases. Quantitative PCR of these samples showed no increase in SV40 transcript compared to the negative controls. CONCLUSIONS: SV40 is not associated with the development of MM in Korea.

[860]

TÍTULO / TITLE: Chemoprevention of lung squamous cell carcinoma by ginseng.

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


Enlace al texto completo (gratuito o de pago) 1158/1940-6207.CAPR-12-0366

AUTORES / AUTHORS: Pan J; Zhang Q; Li K; Liu Q; Wang Y; You M

INSTITUCIÓN / INSTITUTION: Corresponding Author: Ming You, Medical College of Wisconsin Cancer Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. Phone: 414-955-2565; Fax: 414-955-6058; E-mail: myou@mcw.edu.

RESUMEN / SUMMARY: Ginseng has been used as a medicinal herb to maintain physical vitality for thousands of years, and it has also been shown to be a nonorgan-specific cancer preventive agent by several epidemiologic studies.
However, the chemopreventive effects of Korea white ginseng (KWG) in lung squamous cell carcinoma (SCC) have not been tested. In this study, we investigated the chemopreventive activity of KWG in a mouse lung SCC model. N-nitroso-trischloroethylurea (NTCU) was used to induce lung tumors in female Swiss mice, and KWG was given orally. KWG significantly reduced the percentage of lung SCCs from 26.5% in the control group to 9.1% in the KWG group and in the meantime, increased the percentage of normal bronchial and hyperplasia. KWG was also found to greatly reduce squamous cell lung tumor area from an average of 9.4% in control group to 1.5% in the KWG group. Treatment with KWG decreased Ki-67 staining, suggesting that the lung tumor inhibitory effects of KWG were partly through inhibition of proliferation. High-performance liquid chromatography/mass spectrometry identified 10 ginsenosides from KWG extracts, Rb1 and Rd being the most abundant as detected in mouse blood and lung tissue. The tumor inhibitory effects of KWG are mediated by inhibition of activator protein (AP-1), as showed by in vitro study conducted on AP-1/NF-kappaB-dependent mouse non-small cell lung carcinoma cell lines. Western blotting of lung tissues also indicated that NTCU upregulated AP-1 through phosphorylation of c-jun-NH2-kinase, which was downregulated by KWG in concurrence with its chemoprevention function. These results suggest that KWG could be a potential chemopreventive agent for lung SCC. Cancer Prev Res; 6(6); 530-9. ©2013 AACR.

[861] TÍTULO / TITLE: - In-flight arterial gas emboli from a ruptured bronchogenic cyst.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Mak E; Wai Cheung K; Mondor F

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   ● Enlace al texto completo (gratuito o de pago) 1371/journal.pone.0062082
AUTORES / AUTHORS: - Chen JY; Tang YA; Li WS; Chiou YC; Shieh JM; Wang YC
INSTITUCIÓN / INSTITUTION: - Institute of Basic Medical Sciences, National Cheng Kung University, Tainan, Taiwan, R.O.C.
RESUMEN / SUMMARY: - Some potent chemotherapy drugs including tubulin-binding agents had been developed from nature plants, such as podophyllotoxin
and paclitaxel. However, poor cytotoxic selectivity, serious side-effects, and limited effectiveness are still the major concerns in their therapeutic application. We developed a fully synthetic podophyllotoxin derivative named Ching001 and investigated its anti-tumor growth effects and mechanisms in lung cancer preclinical models. Ching001 showed a selective cytotoxicity to different lung cancer cell lines but not to normal lung cells. Ching001 inhibited the polymerization of microtubule resulting in mitotic arrest as evident by the accumulation of mitosis-related proteins, survivin and aurora B, thereby leading to DNA damage and apoptosis. Ching001 also activated pro-apoptotic ER stress signaling pathway. Intraperitoneal injection of 2 mg/kg Ching001 significantly inhibited the tumor growth of A549 xenograft, while injection of 0.2 mg/kg Ching001 decreased the lung colonization ability of A549 cells in experimental metastasis assay. These anti-tumor growth and lung colonization inhibition effects were stronger than those of paclitaxel treatment at the same dosage. The xenograft tumor tissue stains further confirmed that Ching001 induced mitosis arrest and tumor apoptosis. In addition, the hematology and biochemistry tests of blood samples as well as tissue examinations indicated that Ching001 treatment did not show apparent organ toxicities in tested animals. We provided preclinical evidence that novel synthetic microtubule inhibitor Ching001, which can trigger DNA damage and apoptosis by inducing mitotic arrest and ER stress, is a potential anti-cancer compound for further drug development.

[863]

TÍTULO / TITLE: - Simultaneous bilateral spontaneous hydropneumothorax: a rare presentation of bilateral malignant pleural mesothelioma.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
   • Enlace a la Editora de la Revista http://bmj.com/search.dtl
   • Enlace al texto completo (gratuito o de pago) 1136/bcr-2013-009350
AUTORES / AUTHORS: - Fayed HE; Woodcock VK; Grayez J
INSTITUCIÓN / INSTITUTION: - Department of Medicine, Oxford University Hospitals, Banbury, UK.
RESUMEN / SUMMARY: - This is a case of a 69-year-old man with a history of asbestos exposure who presented with acute shortness of breath. His chest x-ray showed bilateral hydropneumothorax. Further investigations including CT chest and video-assisted thoracoscopic surgery revealed bilateral pleural thickening and histology confirmed epithelioid mesothelioma. This case highlights the need for clinicians to be aware of atypical presentations of malignant pleural mesothelioma as well as the importance of considering
underlying secondary causes such as malignancy in the older patient presenting with spontaneous pneumo/hydropneumothorax.

[864]

**TITULO / TITLE:** - Lung cancer in 2013.

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


●●Enlace al texto completo (gratuito o de pago) 1200/EdBook_AM.2013.33.339

**AUTORES / AUTHORS:** - Shepherd FA; Bunn PA; Paz-Ares L

**INSTITUCIÓN / INSTITUTION:** - From the Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; University of Colorado Denver, Aurora, CO; Medical Oncology Department, Instituto de Biomedicina de Sevilla and Hospital Universitario Virgen del Rocio, Seville, España.

**RESUMEN / SUMMARY:** - Lung cancer is the leading worldwide cause of cancer death and the majority of patients present with metastatic stage IV disease. At diagnosis, clinical, histologic, and molecular features must be considered in therapeutic decision-making for systemic therapy. Molecular testing for at least epidermal growth factor receptor (EGFR) and ALK should be performed in all patients before therapy. Platinum doublet chemotherapy may be considered for “fit” patients who do not have a molecular driver genetic abnormality. Bevacizumab can be considered for addition to the doublet in patients with nonsquamous cancers who have no contraindications. A pemetrexed combination is considered only in nonsquamous histology. Patients with EGFR mutations or ALK fusions should be treated with erlotinib or crizotinib, respectively, even in patients with tumor-related poor performance. The tyrosine-kinase inhibitors (TKIs) may be continued until multisite, symptomatic progression. For patients initially treated with a platinum doublet, maintenance chemotherapy with pemetrexed, erlotinib, gemcitabine, or possibly docetaxel is an option with selection based on clinical features, histology, type of initial therapy, and response to first-line therapy.

[865]

**TITULO / TITLE:** - Identification of proteomic signatures associated with lung cancer and COPD.

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


●●Enlace al texto completo (gratuito o de pago) 1016/j.jprot.2013.04.037

**AUTORES / AUTHORS:** - Pastor MD; Nogal A; Molina-Pinelo S; Melendez R; Salinas A; Gonzalez De la Pena M; Martin-Juan J; Corral J; Garcia-Carbonero R; Carnero A; Paz-Ares L
INSTITUCIÓN / INSTITUTION: - Instituto de Biomedicina de Sevilla (IBIS), (HUVR, CSIC, Universidad de Sevilla), Sevilla, España.

RESUMEN / SUMMARY: - Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) commonly coexist in smokers, and the presence of COPD increases the risk of developing LC. The aim of this study was to identify distinct proteomic profiles able to discriminate these two pathological entities. Protein content was assessed in the bronchoalveolar lavage (BAL) of 60 patients classified in four groups: COPD, COPD and LC, LC without COPD, and control with neither COPD nor LC. Proteins were separated into spots by bidimensional polyacrylamide gel electrophoresis (2D-PAGE) and examined by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF/TOF). A total of 40 proteins were differentially expressed in the LC and/or COPD groups as compared with the control group. Distinct protein profiles were identified and validated for each pathological entity (LC and COPD). The main networks involved were related to inflammatory signalling, free radical scavenging and oxidative stress response, and glycolysis and gluconeogenesis pathways. The most relevant signalling link between LC and COPD was through the NF-kappaB pathway. In conclusion, the protein profiles identified contribute to elucidate the underlying pathogenic pathways of both diseases, and provide new tools of potential use as biomarkers for the early diagnosis of LC. BIOLOGICAL SIGNIFICANCE: Sequence coverage. The protein sequence coverage (95%) was estimated for specific proteins by the percentage of matching amino acids from the identified peptides having confidence greater than or equal to 95% divided by the total number of amino acids in the sequence. Ingenuity Pathways Analysis. Mapping of our proteins onto biological pathways and disease networks demonstrated that 22 proteins were linked to inflammatory signalling (p-value: 1.35 *10^-08-1.42 *10^-02), 15 proteins were associated with free radical scavenging and oxidative stress response (p-value: 4.93 *10^-11-1.27 *10^-02), and 9 proteins were related with glycolysis and gluconeogenesis pathways (p-value: 7.39 *10^-09-1.58 *10^-02).

A 57-year-old man presented with abdominal pain and backache, weight loss of 10 kg and irregular bowel movements. He was previously diagnosed with Stage IB squamous cell carcinoma of lung and had undergone lobectomy 12 months previously. Investigations including imaging revealed a cystic mass in the body and tail of the pancreas which was biopsied and it was confirmed to be a recurrence of the squamous lung cancer involving the pancreas. He was treated with systemic chemotherapy and has shown a partial response on repeat imaging. This case illustrates a rare and unusual site of relapse in lung cancer after adjuvant therapy and a key message for follow-up surveillance for these patients.

Enrichment strategies in glycomics based lung cancer biomarker development.

PURPOSE: There is a need to identify better glycan biomarkers for diagnosis, early detection and treatment monitoring in lung cancer using biofluids such as blood. Biofluids are complex mixtures of proteins dominated by a few high abundance proteins that may not have specificity for lung cancer. Therefore two methods for protein enrichment were evaluated; affinity capturing of IgG and enrichment of medium abundance proteins, thus allowing us to determine which method yields the best candidate glycan biomarkers for lung cancer. EXPERIMENTAL DESIGN: N-glycans isolated.
from plasma samples from 20 cases of lung adenocarcinoma and 20 matched controls were analyzed using nLC-PGC-chip-TOF-MS. N-glycan profiles were obtained for five different fractions: total plasma, isolated IgG, IgG depleted plasma, and the bound and flow-through fractions of protein enrichment.

RESULTS: Four glycans differed significantly (FDR<0.05) between cases and controls in whole unfractionated plasma, while four other glycans differed significantly by cancer status in the IgG fraction. No significant glycan differences were observed in the other fractions. CONCLUSIONS AND CLINICAL RELEVANCE: These results confirm that the N-glycan profile in plasma of lung cancer patients is different from healthy controls and appears to be dominated by alterations in relatively abundant proteins. This article is protected by copyright. All rights reserved.

[869]

TÍTULO / TITLE: - Genome-wide identification of bone metastasis-related microRNAs in lung adenocarcinoma by high-throughput sequencing.

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


AUTORES / AUTHORS: - Xie L; Yang Z; Li G; Shen L; Xiang X; Liu X; Xu D; Xu L; Chen Y; Tian Z; Chen X

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The Third Affiliated Hospital of Kunming Medical University, Tumor Hospital of Yunnan Province, Kunming, PR China.

RESUMEN / SUMMARY: - BACKGROUND: MicroRNAs (miRNAs) are a class of small noncoding RNAs that regulate gene expression at the post-transcriptional level. They participate in a wide variety of biological processes, including apoptosis, proliferation and metastasis. The aberrant expression of miRNAs has been found to play an important role in many cancers. RESULTS: To understand the roles of miRNAs in the bone metastasis of lung adenocarcinoma, we constructed two small RNA libraries from blood of lung adenocarcinoma patients with and without bone metastasis. High-throughput sequencing combined with differential expression analysis identified that 7 microRNAs were down-regulated and 21 microRNAs were up-regulated in lung adenocarcinoma with bone metastasis. A total of 797 target genes of the differentially expressed microRNAs were identified using a bioinformatics approach. Functional annotation analysis indicated that a number of pathways might be involved in bone metastasis, survival of the primary origin and metastatic angiogenesis of lung adenocarcinoma. These include the MAPK, Wnt, and NF-kappaB signaling pathways, as well as pathways involving the matrix metalloproteinase, cytoskeletal protein and angiogenesis factors.
CONCLUSIONS: This study provides some insights into the molecular mechanisms that underlie lung adenocarcinoma development, thereby aiding the diagnosis and treatment of the disease.

[870]
TÍTULO / TITLE: - The role of estrogen, progesterone and aromatase in human non-small-cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Kazmi N; Marquez-Garban DC; Aivazyan L; Hamilton N; Garon EB; Goodglick L; Pietras RJ
INSTITUCIÓN / INSTITUTION: - UCLA Geffen School of Medicine, Department of Medicine, Division of Hematology/Oncology, Factor Building 11-934, 700 Tiverton Avenue, Los Angeles, CA 90095-16781, USA.
RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer-related deaths in both men and women worldwide. Despite advances in treatment, patients have few effective therapeutic options and survival rates remain low. Emerging evidence suggests that the hormones estrogen and progesterone play a key role in the progression of non-small-cell lung cancer (NSCLC). The aromatase enzyme, which is responsible for a key step in estrogen biosynthesis, elicits higher levels of estrogen in lung tumors as well as in metastases compared with nonmalignant tissues. Thus, aromatase may prove to be a key predictive biomarker for treatment of NSCLC. Epidemiologic and preclinical data show estrogens play a critical role in lung tumor development and progression. Two estrogen receptors, alpha and beta, are expressed in normal and in cancerous lung epithelium, and estrogen promotes gene transcription that stimulates cell proliferation and inhibits cell death. Furthermore, expression of both forms of estrogen receptor, progesterone receptor and aromatase in NSCLC specimens has been correlated with worse clinical outcomes. Combination therapies that include estrogen receptor downregulators and aromatase inhibitors are currently being assessed in Phase I-II clinical trials among patients with advanced NSCLC. Results will help guide future lung cancer management decisions, with a goal of achieving more effective and less toxic treatments for patients.

[871]
TÍTULO / TITLE: - Hypersensitivity reactions to carboplatin and cisplatin in non-small cell lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Non-small cell lung cancer (NSCLC) treatment has changed in the past ten years due to the acceptance of platinum-based adjuvant chemotherapy. In the event of relapse, patients are often retreated with platinum agents. Hypersensitivity reactions to carboplatin are well documented among gynecologic oncology patients. Now that adjuvant chemotherapy is a component of NSCLC treatment, platinum hypersensitivity is also a concern in the lung cancer population. A 74-year-old male developed relapsed NSCLC two years after a lobectomy and adjuvant chemotherapy including carboplatin. He was treated with a carboplatin containing regimen, and experienced hypersensitivity during his 2(nd) cycle (post-relapse). We briefly report four additional cases of platinum sensitivity in NSCLC patients, to highlight the increasing likelihood of platinum hypersensitivity in this “at risk” group. Hypersensitivity reactions to platinum chemotherapeutics occur in NSCLC patients, and patients and treating medical staff should be aware of this serious, treatment-related complication.

[872]

MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1.

Dysregulation of microRNAs has a critical role in cancer progression. Here we identify an intronic microRNA, miR-135b that is upregulated in highly invasive non-small-cell lung cancer cells. Expression of miR-135b enhances cancer cell invasive and migratory abilities in vitro and promotes cancer metastasis in vivo, while specific inhibition of miR-135b by a miR-135b-specific molecular sponge and antagonirs suppresses cancer cell invasion, orthotopic lung tumour growth and metastasis in a mouse model. miR-135b targets multiple key components in the Hippo pathway, including LATS2, beta-TrCP and NDR2, as well as LZTS1. Expression of miR-135b, LZTS1, LATS2 and nuclear TAZ predicts poor outcomes of non-small-cell lung cancer. We find that miR-135b is dually regulated by DNA demethylation and nuclear
factor-kappaB signalling, implying that abnormal expression of miR-135b in cancer may result from inflammatory and epigenetic modulations. We conclude that miR-135b is an oncogenic microRNA and a potential therapeutic target for non-small-cell lung cancer.

[873]
TÍTULO / TITLE: - Thyroid gland metastasis from small cell lung cancer: an unusual site of metastatic spread.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 3978/j.issn.2072-1439.2012.06.03
AUTORES / AUTHORS: - Katsenos S; Archondakis S; Vaias M; Skoulikaris N
INSTITUCIÓN / INSTITUTION: - Department of Pneumonology, Army General Hospital of Athens, Athens, Greece;
RESUMEN / SUMMARY: - Metastasis to the thyroid gland is uncommon compared with the frequency of primary thyroid tumors. The primary sites of metastatic thyroid tumors usually include the breast, lung, kidney and stomach. Among lung cancer types metastasizing to the thyroid, adenocarcinomas are the commonest followed by squamous and large cell carcinomas. Small cell lung carcinoma has not been frequently reported to cause thyroid metastatic deposits. Herein, we describe a patient with small cell lung cancer who developed metastatic lesions to the thyroid and brain simultaneously. Thyroid ultrasonography-guided fine-needle aspiration cytology (US-FNAC) and particularly immunocytochemistry documented metastasis from primary lung cancer. Clinical, cytopathological and therapeutic aspects of this unusual site of extrathoracic metastatic disease are discussed laying special emphasis on the paramount importance of the immunocytochemistry in distinguishing primary thyroid tumors from thyroid metastasis due to lung cancer.

[874]
- CASTELLANO -
TÍTULO / TITLE: Dermatomiosite como primeira manifestacao de uma neoplasia pulmonar.
TÍTULO / TITLE: - Dermatomyositis as the first manifestation of a lung tumor.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1016/j.rppneu.2012.11.002
AUTORES / AUTHORS: - Castro AS; Barroso A; Parente B

RESUMEN / SUMMARY: - Dermatomyositis (DM) is a rare disease characterised by proximal muscle weakness and a typical cutaneous rash. The muscle biopsy shows inflammatory lesions consistent with myositis, being related to an increased risk of cancer, often considered as a paraneoplastic syndrome. The authors present a case of a 63-year-old man, with progressive proximal muscle weakness and cutaneous rash, appearing in two months. The muscle and skin biopsies were consistent with DM. Chest tomography showed a nodular image in the lingular region and bronchy biopsy confirmed the diagnosis of small cell lung carcinoma (SCLC). This clinical case intends to enhance the importance of a thorough diagnostic study in patients with DM, as it is often a paraneoplastic syndrome.

TÍTULO / TITLE: - Peritoneal mesothelioma.

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


AUTORES / AUTHORS: - Kindler HL

INSTITUCIÓN / INSTITUTION: - From the Gastrointestinal Oncology and Mesothelioma Programs, Section of Hematology/Oncology, University of Chicago, Chicago, IL.

RESUMEN / SUMMARY: - The etiology, gender distribution, pathology, natural history, and treatment options for mesothelioma (MM) differ substantially depending on the site of origin. Peritoneal mesothelioma (MPeM) is a rare disease, comprising only approximately 10% to 15% of the 2,500 cases of MM diagnosed in the United States each year. Patients with MPeM are younger than patients with pleural MM, and a higher proportion, mostly women, are long-term survivors. Most MPeM is caused by asbestos exposure. Germ-line mutations of BAP1 (BRCA associated protein 1) can predispose to MM, uveal melanoma, and potentially other cancers. MPeM can be challenging to diagnose, and cytology is rarely helpful. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is essential. The three major pathologic subtypes are epithelial, sarcomatoid, and biphasic. Most cases are epithelial; the others have a dismal prognosis. Two indolent subtypes of borderline malignant potential-well-differentiated papillary mesothelioma and benign multicystic mesothelioma-are more common in the peritoneum and are treated surgically. In highly selected patients receiving treatment at experienced referral centers, an aggressive
 locoregional strategy that combines cytoreductive surgery to remove all gross
disease and hyperthermic intraperitoneal chemotherapy to treat residual
microscopic tumors yields a 3-year survival of 60% and a median survival
approaching 5 years, far better than expected from historic controls. This
approach also provides durable palliation of malignant ascites in nearly all
patients. Pemetrexed is the only U.S. Food and Drug Administration (FDA)-
approved systemic chemotherapy for pleural MM. Largely on the basis of data
from pharmaceutical registry studies, the activity of pemetrexed-based
chemotherapy appears to be similar in pleural MM and MPeM.

[876]

TÍTULO / TITLE: - Ovarian metastasis from lung cancer: a rare entity.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

●●Enlace al texto completo (gratuito o de pago) 1155/2013/378438

AUTORES / AUTHORS: - Cengiz H; Yildiz S; Kaya C; Senyurek E; Ekin M; Yasar

INSTITUCIÓN / INSTITUTION: - Bakirkoy Dr. Sadi Konuk Teaching and Research
Hospital, Tevfik Saglam Street, No. 11, Zuhuratbaba, Bakirkoy, 34147 Istanbul,
Turkey.

RESUMEN / SUMMARY: - This paper describes a case of ovarian metastasis from
lung carcinoma along with its diagnostic challenges, clinical management, and
review of the literature. A 49-year-old woman was admitted to our emergency
department with complaints of abdominal pain and vomiting. A laparoscopic
appendectomy was performed due to acute appendicitis, and a unilateral
oophorectomy (left side) via laparoscopy was performed due to the detection of
an ovarian mass. Immunohistochemical staining of the ovarian mass revealed
that it was reactive to cytokeratin-7 (CK-7) but negative for CK-20. The
immunohistochemical and pathological features of the tumor indicated an
ovarian metastasis of non-small-cell lung cancer. The patient underwent
chemotherapy and was followed up by the oncology department. Her
postoperative regular followup of 6 months showed that her condition was
stable with no recurrence. The management of female patients with acute
abdominal pain and pelvic masses should consist of a multidisciplinary
approach to include the diagnosis of any distant organ metastasis.

[877]

TÍTULO / TITLE: - Metastatic small-cell lung cancer presenting as fulminant
hepatic failure.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
REVISTA / JOURNAL: - British Medical J (BMJ). Acceso gratuito al texto
completo.
AUTORES / AUTHORS:  - Ke E; Gomez JD; Tang K; Sriram KB

INSTITUCIÓN / INSTITUTION:  - Department of Respiratory Medicine, Gold Coast Hospital, Gold Coast, Queensland, Australia.

RESUMEN / SUMMARY:  - We report a case of a 75-year-old woman with fulminant hepatic failure due to metastatic small-cell lung cancer (SCLC). The patient was hospitalised for the management of rapidly progressive hepatic failure. Thoracic radiology identified a widened mediastinum, and prior to hospitalisation she had received antibiotics for a urinary tract infection. Consequently, her hepatic failure was deemed to be due to either sarcoidosis with hepatic involvement or an antibiotic-related adverse event and was treated with prednisolone. However, the patient’s clinical condition continued to deteriorate and a liver biopsy was obtained. Histopathology and immunohistochemistry tests demonstrated almost complete parenchymal replacement with metastatic SCLC. The patient was considered to be too unwell to receive chemotherapy and hence received best supportive care instead, and died shortly thereafter.

[878]


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


AUTORES / AUTHORS:  - Li G

[879]

TÍTULO / TITLE:  - Preferential killing of human lung cancer cell lines with mitochondrial dysfunction by nonthermal dielectric barrier discharge plasma.

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


AUTORES / AUTHORS:  - Panngom K; Baik KY; Nam MK; Han JH; Rhim H; Choi EH

RESUMEN / SUMMARY: - The distinctive cellular and mitochondrial dysfunctions of two human lung cancer cell lines (H460 and HCC1588) from two human lung normal cell lines (MRC5 and L132) have been studied by dielectric barrier discharge (DBD) plasma treatment. This cytotoxicity is exposure time-dependent, which is strongly mediated by the large amount of H2O2 and NOx in culture media generated by DBD nonthermal plasma. It is found that the cell number of lung cancer cells has been reduced more than that of the lung normal cells. The mitochondrial vulnerability to reactive species in H460 may induce distinctly selective responses. Differential mitochondrial membrane potential decrease, mitochondrial enzymatic dysfunction, and mitochondrial morphological alteration are exhibited in two cell lines. These results suggest the nonthermal plasma treatment as an efficacious modality in lung cancer therapy.

[880]

TÍTULO / TITLE: - Early detection of NSCLC with scFv selected against IgM autoantibody.

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


AUTORES / AUTHORS: - Pedchenko T; Mernaugh R; Parekh D; Li M; Massion PP

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Vanderbilt Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America. tetyana.v.pedchenko@vanderbilt.edu

RESUMEN / SUMMARY: - Survival of patients with lung cancer could be significantly prolonged should the disease be diagnosed early. Growing evidence indicates that the immune response in the form of autoantibodies to developing cancer is present before clinical presentation. We used a phage-displayed antibody library to select for recombinant scFvs that specifically bind to lung cancer-associated IgM autoantibodies. We selected for scFv recombinant antibodies reactive with circulating IgM autoantibodies found in the serum of patients with early stage lung adenocarcinoma but not matched controls. Discriminatory performance of 6 selected scFvs was validated in an independent set of serum from stage 1 adenocarcinoma and matching control groups using two independent novel methods developed for this application. The panel of 6 selected scFvs predicted cancer based on seroreactivity value with sensitivity of 0.8 and specificity of 0.87. Receiver Operative Characteristic curve (ROC) for combined 6 scFv has an AUC of 0.88 (95%CI, 0.76-1.0) as determined by fluorometric microvolume assay technology (FMAT). The ROC curve generated using a homogeneous bridging Mesa Scale Discovery (MSD)
The assay had an AUC of 0.72 (95% CI, 0.59-0.85). The panel of all 6 antibodies demonstrated better discriminative power than any single scFv alone. The scFv panel also demonstrated the association between a high score - based on seroreactivity - with poor survival. Selected scFvs were able to recognize lung cancer associated IgM autoantibodies in patient serum as early as 21 months before the clinical presentation of disease. The panel of antibodies discovered represents a potential unique non-invasive molecular tool to detect an immune response specific to lung adenocarcinoma at an early stage of disease.

[881]
TÍTULO / TITLE: - Lung cancer in developing countries.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Ferreira CG
INSTITUCIÓN / INSTITUTION: - From the Brazilian National Cancer Institute, Rio de Janeiro, Brazil.
RESUMEN / SUMMARY: - The era of personalized medicine has come to the treatment of non-small cell lung cancer, and now molecular testing is part of the daily clinical decision, at least for patients with adenocarcinoma. Nevertheless, access to those tests is still very limited in the developing world. Developing countries must adapt their health care system to address that and grant access of patients with lung cancer to those tests. Because of several differences among developing countries, strategies will certainly vary from country to country. Issues such as generation of local molecular epidemiology data, quality control, education of health care professionals, development of innovative local and regional strategies, interconnection between regulatory pathways for the approval of drugs, and companion molecular tests are required.

[882]
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Goldkorn T; Chung S; Filosto S
INSTITUCIÓN / INSTITUTION: - Center for Comparative Respiratory Biology and Medicine, Genome and Biomedical Sciences Facility, University of California School of Medicine, Davis, CA, 95616, USA, tgoldkorn@ucdavis.edu.
RESUMEN / SUMMARY: - Sphingolipids play key roles in cancer, yet our current understanding of sphingolipid function in lung cancer is limited to a few key players. The best characterized of these are sphingosine-1-phosphate and ceramide which are described for their opposing roles in cell fate. However, because sphingolipids as a whole are readily interconverted by a complex enzymatic machinery, no single sphingolipid appears to have exactly one role. Instead, the roles of specific sphingolipids appear to be context specific as demonstrated by findings that ceramide-1-phosphatase has both proliferative and apoptotic effects depending on its concentration. Therefore, we present herein several years of research on ceramide, a sphingolipid linked to apoptotic signaling, that is emerging in cancer research for its potential roles in proliferation and cell-to-cell communication via exosomes. Ceramide is a well-studied sphingolipid in both normal and pathological conditions ranging from skin development to lung cancer. Interestingly, several groups have previously reported its increased levels in emphysema patients who are smokers, a patient subpopulation greatly susceptible to lung cancer. However, the molecular mechanisms through which cigarette smoke (CS) and ceramide accumulation lead to lung cancer, non-small cell lung cancer (NSCLC) specifically, are unknown. Interestingly, recent studies clearly establish that two signaling pathways are activated during CS exposure in the lung airway. One centers on the activation of neutral sphingomyelinase2 (nSMase2), an enzyme that hydrolyzes sphingomyelin to ceramide. The other pathway focuses on the oncogenic EGF receptor (EGFR), which becomes aberrantly activated but not degraded, leading to prolonged proliferative signaling. Recent studies show that these two signaling pathways may actually converge and integrate. Specifically, Goldkorn et al. demonstrated that during CS exposure, EGFR is favorably co-localized in ceramide-enriched regions of the plasma membrane, proposing that nSMase2/ceramide plays a role in the aberrant EGFR activation, leading to augmented tumorigenic signaling. Moreover, new findings indicate that CS exposure may induce resistance to the tyrosine kinase inhibitors (TKIs), used for treatment of NSCLC, merely through posttranslational molecular alterations. Furthermore, structural anomalies of the CS-activated EGFR appear to be supported by the excess ceramide produced by the CS-activated nSMase2 in the plasma membrane of lung epithelial cells. We present in this chapter the progression of the sphingolipid field in lung cancer using ceramide as an example. However, many crucial questions remain to be answered regarding the role of sphingolipids in lung cancer because of the glut of promising observations.

[883]
TITULO / TITLE: - TrkB is responsible for EMT transition in malignant pleural effusions derived cultures from adenocarcinoma of the lung.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary

669
Lung cancer is the leading cause of cancer-related mortality worldwide. Recent evidence indicates that tumors contain a subpopulation of cancer stem cells (CSCs) that are responsible for tumor maintenance and spread. CSCs have recently been linked to the occurrence of epithelial-to-mesenchymal transition (EMT). Neurotrophins (NTs) are growth factors that regulate the biology of embryonic stem cells and cancer cells, but still little is known about the role NTs in the progression of lung cancer. In this work, we investigated the role of the NTs and their receptors using as a study system primary cell cultures derived from malignant pleural effusions (MPEs) of patients with adenocarcinoma of the lung. We assessed the expression of NTs and their receptors in MPE-derived adherent cultures vs. spheroids enriched in CSC markers. We observed in spheroids a selectively enhanced expression of TrkB, both at the mRNA and protein levels. Both K252a, a known inhibitor of Trk activity, and a siRNA against TrkB strongly affected spheroid morphology, induced anoikis and decreased spheroid forming efficiency. Treatment with neurotrophins reversed the inhibitory effect of K252a. Importantly, TrkB inhibition caused loss of vimentin expression as well as that of a set of transcription factors known to be linked to EMT. These ex vivo results nicely correlated with an inverse relationship between TrkB and E-cadherin expression measured by immunohistochemistry in a panel of lung adenocarcinoma samples. We conclude that TrkB is involved in full acquisition of EMT in lung cancer, and that its inhibition results in a less aggressive phenotype.
to estimate risk of the 4 most numerous specific cell types: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and bronchioloalveolar carcinoma. RESULTS: Smoking 1 or more cigarette packs per day was a powerful predictor (p < 0.0001) of all cell types, with hazard ratios ranging from 5.8 for bronchioloalveolar to 62.7 for squamous cell carcinoma. Other hazard ratio ranges included male/female from 0.6 (bronchioloalveolar, p < 0.05) to 2.0 (squamous, p < 0.001); black/white from 0.8 (small cell, p < 0.05) to 1.7 (squamous, p < 0.001); Asian/white from 0.8 (small cell) to 1.9 (bronchioloalveolar); and alcohol intake of 3 or more drinks per day from 1.0 (squamous) to 1.5 (adenocarcinoma, p < 0.01). College graduation and increasing body mass index were inversely related to risk of several cell types. Noteworthy sex-specific associations included increased risk of Asian vs white women for adenocarcinoma, squamous cell carcinoma and bronchioloalveolar carcinoma and substantially increased risk of adenocarcinoma in women with alcohol intake of 3 or more drinks per day. CONCLUSIONS: These risk factor disparities for lung cancer cell types presumably reflect biologic differences. Future investigation may contribute to increased understanding of tumorigenesis and optimal treatment.
carried out. The antimicrobial activity was assessed using broth micro dilution technique. RESULTS: Ethyl acetate extract showed activity against bacteria such as Bacillus subtilis, Klebsiella pneumoniae (K. pneumoniae), Pseudomonas aeruginosa, Salmonella typhimurium, Shigella flexneri, Enterobacter aerogenes, Staphylococcus aureu and Staphylococcus epidermidis (S. epidermidis) and fungi such as, Candida albicans and Trichophyton rubrum. The lowest minimum inhibitory concentrations were: 250 microg/mL against S. epidermidis and 250microg/mL against K. pneumonia. The isolate had the ability to produce enzymes such as protease. The exyract showed cytotoxic effect in human adenocarcinoma cancer cell line (A549). GC-MS analysis showed the presence of isovaleric acid (3.64%), 2-Methylbutanoic acid (5.03%), isobutyramide (5.05%), N,N-oimethylformamide-di-t-butylacetal (9.79%), benzeneacetamide (15.56%), octyl butyl phthalate (3.59%) and diisooctyl phthalate (5.79) in the extract. CONCLUSIONS: Methylobacterium sp. (ERI-135) showed promising antibacterial and cytotoxic activity. This is the first report in the antimicrobial and cytotoxic effect of Methylobacterium sp.

[886]

TÍTULO / TITLE: - The involvement of NRF2 in lung cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Bauer AK; Hill T 3rd; Alexander CM
INSTITUCIÓN / INSTITUTION: - Department of Environmental and Occupational Health, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA. alison.bauer@ucdenver.edu
RESUMEN / SUMMARY: - Nuclear factor, erythroid-derived 2, like 2 (NRF2) is a key regulator of antioxidants and cellular stress responses. The role of NRF2 in pulmonary neoplasia, a diverse disease for which few biomarkers exist, is complicated and appears to depend on several main factors including the existence of activating mutations in NRF2 and/or loss of function mutations in KEAP1 and the stage of carcinogenesis studied, particularly in the mouse models tested. Therapeutic strategies for lung cancer targeting NRF2 have observed mixed results, both anti- and protumorigenic effects; however, these differences seem to reflect the mutation status of NRF2 or KEAP1. In this paper, we will discuss the studies on human NRF2 and the mechanisms proposed, several mouse models using various mice deficient in NRF2, as well as xenograft models, and the chemotherapeutic strategies using the NRF2 pathway.

[887]

TÍTULO / TITLE: - Tobacco and lung cancer.
RESUMEN / SUMMARY: - Tobacco use, primarily associated with cigarette smoking, is the largest preventable cause of cancer mortality, responsible for approximately one-third of all cancer deaths. Approximately 85% of lung cancers result from smoking, with an additional fraction caused by secondhand smoke exposure in nonsmokers. The risk of lung cancer is dose dependent, but can be dramatically reduced with tobacco cessation, especially if the person discontinues smoking early in life. The increase in lung cancer incidence in different countries around in the world parallels changes in cigarette consumption. Lung cancer risks are not reduced by switching to filters or low-tar/low-nicotine cigarettes. In patients with cancer, continued tobacco use after diagnosis is associated with poor therapeutic outcomes including increased treatment-related toxicity, increased risk of second primary cancer, decreased quality of life, and decreased survival. Tobacco cessation in patients with cancer may improve cancer treatment outcomes, but cessation support is often not provided by oncologists. Reducing the health related effects of tobacco requires coordinated efforts to reduce exposure to tobacco, accurately assess tobacco use in clinical settings, and increase access to tobacco cessation support. Lung cancer screening and coordinated international tobacco control efforts offer the promise to dramatically reduce lung cancer mortality in the coming decades.

TÍTULO / TITLE: - Multiple cutaneous nodules as the presenting sign of small cell lung cancer.

[888]

TITULO / TITLE: - Multiple cutaneous nodules as the presenting sign of small cell lung cancer.
INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Mercy University Hospital, Cork, Ireland.

RESUMEN / SUMMARY: - We describe a 67-year-old male smoker who presented with an 8 week history of productive cough, dyspnoea on minimal exertion, weight loss of 8 kg and multiple painful cutaneous nodules of varying size and morphology. A chest radiograph showed a mass at the right hilum. A CT examination showed extensive mediastinal lymphadenopathy with encasement of the lower trachea, carina and left main bronchus. The left main bronchus was 95% stenosed and there were multiple liver metastases. Innumerable cutaneous nodules were also seen. A biopsy of one of the cutaneous nodules confirmed metastases from a neuroendocrine lung primary tumour, consistent with extensive stage small cell lung cancer. The patient died soon after diagnosis.

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

●●Enlace al texto completo (gratuito o de pago) 4103/1477-3163.109033
AUTORES / AUTHORS: - Hanna JM; Onaitis MW
INSTITUCIÓN / INSTITUTION: - Department of Surgery, Duke University Medical Center, Durham.
RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer deaths worldwide, and current therapies are disappointing. Elucidation of the cell(s) of origin of lung cancer may lead to new therapeutics. In addition, the discovery of putative cancer-initiating cells with stem cell properties in solid tumors has emerged as an important area of cancer research that may explain the resistance of these tumors to currently available therapeutics. Progress in our understanding of normal tissue stem cells, tumor cell of origin, and cancer stem cells has been hampered by the heterogeneity of the disease, the lack of good in vivo transplantation models to assess stem cell behavior, and an overall incomplete understanding of the epithelial stem cell hierarchy. As such, a systematic computerized literature search of the MEDLINE database was used to identify articles discussing current knowledge about normal lung and lung cancer stem cells or progenitor cells. In this review, we discuss what is currently known about the role of cancer-initiating cells and normal stem cells in the development of lung tumors.

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RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
Because of dramatic tumor regressions reported with the anti-programmed death-1 (PD-1) and anti-programmed death ligand-1 (PDL-1) antibodies inhibiting the PD-1 immune checkpoint, non-small cell lung cancer (NSCLC) is now recognized as an immune-modifiable disease. As responses were observed in smaller numbers in phase I trials, the immunologic profiles and unique toxicities of these agents have not been fully established in NSCLC. Moreover, PD-1 checkpoint inhibitors in development by different companies may demonstrate diverse spectrums of activity and toxicity. Although the cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors in earlier phase studies appeared to have less impressive responses in NSCLC, their safety profile has been more broadly defined. The anti-CTLA-4 antibody, ipilimumab, has the best characterized immune-related toxicities (predominantly skin, gastrointestinal, hepatic, and endocrine) and management strategies in melanoma. Despite the lack of studies directly comparing these agents, toxicities from PD-1 inhibition seem milder than those of CTLA-4 inhibition, with distinct toxicities of pneumonitis infrequently observed with the BMS-936558 anti-PD-1 antibody, nivolumamb, and frequent mild infusion reactions reported with the BMS-936559 anti-PDL-1 antibody. As lungs are critical organs often already compromised in NSCLC patients, immune-mediated pneumonitis can cause worrisome morbidity and mortality. Even though immune checkpoint inhibitors are being rapidly developed in a multitude of trials, optimal immune-mediated toxicity management has not been determined, is evolving, and will be further explored. Early diagnosis and symptom management with corticosteroids form the basis of treatment. Assessment of new immune-response criteria and use of primary endpoints of overall survival (OS) will be important in the development of these immunotherapies in NSCLC.
INSTITUCIÓN / INSTITUTION: - Thoracic Oncology Laboratory, Department of Surgery, University of California, San Francisco, San Francisco, California 94115, USA.

RESUMEN / SUMMARY: - Analysis of gene expression patterns in normal tissues and their perturbations in tumours can help to identify the functional roles of oncogenes or tumour suppressors and identify potential new therapeutic targets. Here, gene expression correlation networks were derived from 92 normal human lung samples and patient-matched adenocarcinomas. The networks from normal lung show that NKX2-1 is linked to the alveolar type 2 lineage, and identify PEBP4 as a novel marker expressed in alveolar type 2 cells. Differential correlation analysis shows that the NKX2-1 network in tumours includes pathways associated with glutamate metabolism, and identifies Vaccinia-related kinase (VRK1) as a potential drug target in a tumour-specific mitotic network. We show that VRK1 inhibition cooperates with inhibition of poly (ADP-ribose) polymerase signalling to inhibit growth of lung tumour cells. Targeting of genes that are recruited into tumour mitotic networks may provide a wider therapeutic window than that seen by inhibition of known mitotic genes.

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TÍTULO / TITLE: - Lung cancer screening update.

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


AUTORES / AUTHORS: - Dhillon SS; Loewen G; Jayaprakash V; Reid ME

INSTITUCIÓN / INSTITUTION: - Department of Medicine Pulmonology, Elm and Carlton Streets, Roswell Park Cancer Institute, Buffalo, New York, USA.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer-related mortality globally and the American cancer society estimates approximately 226,160 new cases and 160,340 deaths from lung cancer in the USA in the year 2012. The majority of lung cancers are diagnosed in the later stages which impacts the overall survival. The 5-year survival rate for pathological st age IA lung cancer is 73% but drops to only 13% for stage IV. Thus, early detection through screening and prevention are the keys to reduce the global burden of lung cancer. This article discusses the current state of lung cancer screening, including the results of the National Lung Cancer Screening Trial, the consideration of implementing computed tomography screening, and a brief overview of the role of bronchoscopy in early detection and potential biomarkers that may aid in the early diagnosis of lung cancer.

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[893]
The EGFR family members sustain the neoplastic phenotype of ALK+ lung adenocarcinoma via EGR1.

In non-small cell lung cancer (NSCLC), receptor tyrosine kinases (RTKs) stand out among causal dominant oncogenes, and the ablation of RTK signaling has emerged as a novel tailored therapeutic strategy. Nonetheless, long-term RTK inhibition leads invariably to acquired resistance, tumor recurrence and metastatic dissemination. In ALK+ cell lines, inhibition of ALK signaling was associated with coactivation of several RTKs, whose pharmacological suppression reverted the partial resistance to ALK blockade. Remarkably, ERBB2 signaling synergized with ALK and contributed to the neoplastic phenotype. Moreover, the engagement of wild-type epidermal growth factor receptor or MET receptors could sustain cell viability through early growth response 1 (EGR1) and/or Erk1/2; Akt activation and EGR1 overexpression prevented cell death induced by combined ALK/RTK inhibition. Membrane expression of ERBB2 in a subset of primary naive ALK+ NSCLC could be relevant in the clinical arena. Our data demonstrate that the neoplastic phenotype of ALK-driven NSCLC relays ‘ab initio’ on the concomitant activation of multiple RTK signals via autocrine/paracrine regulatory loops. These findings suggest that molecular and functional signatures are required in de novo lung cancer patients for the design of efficacious and multi-targeted ‘patient-specific’ therapies.

Nicotine and lung cancer.

In non-small cell lung cancer (NSCLC), nicotine and lung cancer.
Institute, Buffalo, NY, USA; Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston, SC, USA and Roswell Park Cancer Institute, Buffalo, NY, USA.

RESUMEN / SUMMARY: - Tobacco use in cancer patients is associated with increased cancer treatment failure and decreased survival. Nicotine is one of over 7,000 compounds in tobacco smoke and nicotine is the principal chemical associated with addiction. The purpose of this article is to review the tumor promoting activities of nicotine. Nicotine and its metabolites can promote tumor growth through increased proliferation, angiogenesis, migration, invasion, epithelial to mesenchymal transition, and stimulation of autocrine loops associated with tumor growth. Furthermore, nicotine can decrease the biologic effectiveness of conventional cancer treatments such as chemotherapy and radiotherapy. Common mechanisms appear to involve activation of nicotinic acetylcholine receptors and beta-adrenergic receptors leading to downstream activation of parallel signal transduction pathways that facilitate tumor progression and resistance to treatment. Data suggest that nicotine may be an important mechanism by which tobacco promotes tumor development, progression, and resistance to cancer treatment.

[895]

TÍTULO / TITLE: - Primary Pulmonary Adenocarcinoma Mimicking Papillary Thyroid Carcinoma.

RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Zhu YZ; Li WP; Wang ZY; Yang HF; He QL; Zhu HG; Zheng GJ

RESUMEN / SUMMARY: - We herein reported a primary pulmonary papillary carcinoma with colloid-like luminal content in the glandular cavity and classic nuclear features such as pseudo-inclusions, intranuclear grooves in the tumor cell nuclei and ground glass nuclei which closely mimics papillary thyroid carcinoma. Meanwhile, lymph node in the left pulmonary hilum was involved and showed similar features to the primary pulmonary papillary carcinoma. This specific histopathological presentation caused a diagnostic dilemma. The patient didn’t show previous concomitant or subsequent evidence of a thyroid tumor. Immunohistochemistry further confirmed pulmonary origin and excluded a metastasis from the thyroid, as it was thyroglobulin negative, thyroid transcription factor 1 and surfactant apoprotein A positive, which was consistent with the imageology and history. Based on the above features, the diagnosis of primary pulmonary papillary carcinoma was confirmed. Understanding the existence of papillary thyroid carcinoma-like pulmonary papillary carcinoma will avoid misdiagnosis or unnecessary clinical and radiologic investigations in future.
[896] **TÍTULO / TITLE:** - Plasma cell myeloma initially presenting as lung cancer.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Cho SY; Jeong JH; Lee WI; Lee J; Hong IK; Suh JT; Lee HJ; Yoon HJ; Park TS

**INSTITUCIÓN / INSTITUTION:** - Department of Laboratory Medicine, School of Medicine, Kyung Hee University, Seoul, Korea.

[897] **TÍTULO / TITLE:** - Chromatin patterns associated with lung adenocarcinoma progression.

**RESUMEN / SUMMARY:** - [Enlace al Resumen / Link to its Summary](#)


**AUTORES / AUTHORS:** - Druliner BR; Fincher JA; Sexton BS; Vera DL; Roche M; Lyle S; Dennis JH

**INSTITUCIÓN / INSTITUTION:** - Department of Biological Science; Florida State University; Tallahassee, FL USA.

**RESUMEN / SUMMARY:** - The development and progression of lung adenocarcinoma, one of the most common cancers, is driven by the interplay of genetic and epigenetic changes and the role of chromatin structure in malignant transformation remains poorly understood. We used systematic nucleosome distribution and chromatin accessibility microarray mapping platforms to analyze the genome-wide chromatin structure from normal tissues and from primary lung adenocarcinoma of different grades and stages. We identified chromatin-based patterns across different patients with lung adenocarcinoma of different cancer grade and stage. Low-grade cancers had nucleosome distributions very different compared with the corresponding normal tissue but had nearly identical chromatin accessibility. Conversely, nucleosome distributions of high-grade cancers showed few differences. Substantial disruptions in chromosomal accessibility were seen in a patient with a high-grade and high-stage tumor. These data imply that chromatin structure changes during the progression of lung adenocarcinoma. We have therefore developed a model in which low-grade lung adenocarcinomas are linked to changes in nucleosome distributions, whereas higher-grade tumors are linked to large-scale chromosomal changes. These results provide a foundation for the development of a comprehensive framework linking the general and locus-specific roles of chromatin structure to lung cancer progression. We propose that this strategy has the potential to
identify a new class of chromatin-based diagnostic, prognostic and therapeutic markers in cancer progression.

[898]
**TÍTULO / TITLE:** Genome-wide analysis of runs of homozygosity identifies new susceptibility regions of lung cancer in Han Chinese.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 7555/JBR.27.20130017
**AUTORES / AUTHORS:** Wang C; Xu Z; Jin G; Hu Z; Dai J; Ma H; Jiang Y; Hu L; Chu M; Cao S; Shen H
**INSTITUCIÓN / INSTITUTION:** Department of Epidemiology and Biostatistics and Ministry of Education (MOE) Key Lab for Modern Toxicology, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 210029, China;
**RESUMEN / SUMMARY:** Runs of homozygosity (ROHs) are a class of important but poorly studied genomic variations and may be involved in individual susceptibility to diseases. To better understand ROH and its relationship with lung cancer, we performed a genome-wide ROH analysis of a subset of a previous genome-wide case-control study (1,473 cases and 1,962 controls) in a Han Chinese population. ROHs were classified into two classes, based on lengths, intermediate and long ROHs, to evaluate their association with lung cancer risk using existing genome-wide single nucleotide polymorphism (SNP) data. We found that the overall level of intermediate ROHs was significantly associated with a decreased risk of lung cancer (odds ratio = 0.63; 95% confidence interval: 0.51-0.77; P = 4.78x10(-6)), while the long ROHs seemed to be a risk factor of lung cancer. We also identified one ROH region at 14q23.1 that was consistently associated with lung cancer risk in the study. These results indicated that ROHs may be a new class of variation which may be associated with lung cancer risk, and genetic variants at 14q23.1 may be involved in the development of lung cancer.

[899]
**TÍTULO / TITLE:** Glutathione s-transferase mu2 suppresses cancer cell metastasis in non-small cell lung cancer.
**RESUMEN / SUMMARY:** Enlace al Resumen / Link to its Summary
●●Enlace al texto completo (gratuito o de pago) 1158/1541-7786.MCR-12-0488
**AUTORES / AUTHORS:** Tang SC; Wu CH; Lai CH; Sung WW; Yang WJ; Tang LC; Hsu CP; Ko JL
INSTITUCIÓN / INSTITUTION: - Institute of Medicine, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Rd., Taichung City 40203,Taiwan. jiko@csmu.edu.tw.

RESUMEN / SUMMARY: - Glutathione-S-transferase mu2 (GST-M2) is a phase II detoxification enzyme. Low expression of GST-M2 in lung cancers is due to hypermethylation of its promoter. Lung cancer with the GST mu-null genotype is associated with shorter survival. However, a correlation between GST-M2 and important clinical parameters, as well as the migration of GST-M2-defective cells in lung cancer, has not been established. In the present study, we investigate the role of GST-M2 in cell migration and actin disassembly in lung cancer cells. GST-M2 and CCN2 mRNA levels were significantly reduced in non-small cell lung cancer (NSCLC) tumors when compared with matched normal lung tissues in 82 patients with NSCLC. We found that high expressions of both GST-M2 and CCN2 are correlated with favorable survival of patients with lung cancer when compared with similar patients without GST-M2 or CCN2 expression. GST-M2 can induce CCN2 expression by driving the CCN2 proximal promoter. Overexpression of GST-M2 decreases the formation of filopodia, resulting in remodeling of the reorganized cytoskeletons.

Overexpression of GST-M2 significantly suppressed cancer cell migration on wound-healing assay. In addition, overexpression of GST-M2 dramatically reduced tumor growth and metastasis in a xenograft mouse model. These data highlight the potential of GST-M2 as a novel tumor suppressor. GST-M2 increases the expression of CCN2 in lung cancer cells, which inhibits cancer cell migration in lung cancer and animal models. Mol Cancer Res; 11(5); 518-29. ©2013 AACR.

[900]

TÍTULO / TITLE: - Desmoplastic malignant mesothelioma.

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


● Enlace al texto completo (gratuito o de pago)

1097/LBR.0b013e31828e1aa2

AUTORES / AUTHORS: - Baccioglu A; Kaba E; Ozmen SA; Demirci M

INSTITUCIÓN / INSTITUTION: - Immunology and Allergy Clinic, Erzurum Region Training and Research Hospital, Ministry of Health, Erzurum, Turkey.

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RESUMEN / SUMMARY: - Desmoplastic mesothelioma is a rare subtype of diffuse malignant mesothelioma. A 72-year-old woman from East Anatolia presented with chest pain. The images of body positron emission tomography revealed irregular, left pleural thickening involving mediastinal and diaphragmatic surfaces with hypermetabolic characterization. The diagnosis of desmoplastic malignant mesothelioma was confirmed by minithoracotomy and
immunohistochemical staining with pan-cytokeratin, cytokeratin 5/6, calretinin, carcinoembryonic antigen, thyroid transcription factor-1, CD15, and HMB-45 on the biopsy specimen. This case is unique in terms of the reporting patient being from a nonendemic area for asbestos-related diseases and in terms of its rare histopathology.

[901]
TÍTULO / TITLE: - Reliability of Family Proxy Data for Studies of Malignant Mesothelioma: Results from the ATSDR Pilot Surveillance.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Melnikova N; Wu J; Kaye W; Orr M
INSTITUCIÓN / INSTITUTION: - Agency for Toxic Substances and Disease Registry, Division of Toxicology and Health Sciences, Buford Highway, Atlanta, GA 30341, USA.
RESUMEN / SUMMARY: - Objective. To evaluate the validity of proxy interviews in obtaining information on persons with rapidly fatal diseases such as malignant mesothelioma (MM). Methods. Persons with MM diagnosed in 2002 through 2005 in New York and New Jersey and 1997-2004 in Wisconsin were eligible for inclusion in the project. Persons with MM and their family member proxy were interviewed using the same questionnaire designed by ATSDR to collect information on potential direct or indirect occupational and environmental exposure to asbestos, genetic, and health related malignancy predisposition, and exposure to tobacco products. Descriptive statistics and the McNemar/Durkalski test were used to analyze 33 matched pairs. Results. The overall study confirmed a generally high ability of proxies to give interviews of comparable quality and completeness when asked dichotomous questions. The reliability of information collected from proxies varied by topic and family relationship. Conclusions. Family proxy interviews, using dichotomous responses, can serve as an acceptable source of information about health and exposure-related risk factors for MM.

[902]
TÍTULO / TITLE: - Vertebral and Pulmonary Actinomycosis Mimicking Metastatic Lung Cancer.
RESUMEN / SUMMARY: - Enlace al Resumen / Link to its Summary
AUTORES / AUTHORS: - Fichte S; Brodhun M; Gottinger S; Rosahl S; Klisch J; Gerlach R
Actinomycosis of the spine with spinal cord compression is rare. Only 22 cases are reported in the literature. The authors describe a remarkable case of a large lesion leading to bony destruction and spinal cord compression in the cervicothoracic junction with a large intrathoracic extension, which was considered to be a metastatic pulmonary disease but turned out to be actinomycosis.

Clinical Presentation A 55-year-old man presented with acute tetraparesis. Magnetic resonance imaging (MRI) and computed tomography (CT) imaging showed vertebral body collapse of T1 and partially C7 with spinal cord compression as well as a mass in the right upper lobe with multiple intrapulmonary nodules. Moreover, dorsal elements (laminae and spinous process) were also involved and partially destructed. Differential diagnosis favored metastatic pulmonary disease.

Intervention Decompression surgery was performed by anterior corpectomy of T1, stabilization with an expandable titanium cage and additional anterior plate C7-T2. Histology revealed typical sulfur granules. Microbiology exams were positive for Actinobacillus actinomycetemcomitans. There was no proof of malignancy in thoracic biopsy in the late diagnostic work-up. To prevent instrumentation failure, an external immobilization (halo fixation) was applied until complete fusion was documented in CT during the postoperative course. After an 11-month course of ampicillin/sulbactam, there was complete resolution of the intrapulmonary and spinal pathology.

Conclusion Thoracic actinomycosis with spinal involvement is a rare disease. Therefore, diagnosis may be difficult. Surgical intervention, correct diagnosis, and specific long-term antibiotic treatment resulted in favorable outcome.

[903]

**TÍTULO / TITLE:** Advances in cytopathology for lung cancer: the impact and challenges of new technologies.

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


**AUTORES / AUTHORS:** Sekhon HS; Souza CA; Gomes MM

**INSTITUCIÓN / INSTITUTION:** Department of Pathology and Laboratory Medicine, The Ottawa Hospital, University of Ottawa, 501 Smyth Road, Ottawa, Ontario, Canada K1H 8L6.

**RESUMEN / SUMMARY:** Despite recent advances in treatment modalities, the survival rate of patients with lung cancer has not significantly improved. Therefore, new avenues are being explored in the era of evolving personalized patient management by early detection. Cytology is now the mainstay to
address the diagnostic needs of pulmonary malignancies. Cytology specimens deliver diagnostic results equivalent to tissue biopsies. Fine-needle aspirations are equally useful to perform diagnostic, predictive, and prognostic immunohistochemical markers and molecular analysis. This article reviews the main new technologies that produced this revolution. The new role of the cytopathologist in this time of interdisciplinary care is also discussed.

[904]

**Título / Title:** - The role of VATS in the staging of non small cell lung cancer.
**Resumen / Summary:** - Enlace al Resumen / Link to its Summary

**Autores / Authors:** - Bagheri R; Tavassoli A; Haghi SZ; Sahebi MA; Bigdeli N
**Institución / Institution:** - Department of Thoracic Surgery, Cardiothoracic Surgery and Transplant Research Center, Imam Reza Hospital, Mashhad, Iran.

**Resumen / Summary:** - INTRODUCTION: Since determining of prognosis and treatment method is related to accurate evaluation of TNM staging of non small cell lung cancer (NSCLC), we aimed to evaluate the role of Video-assisted thoracic surgery (VATS) in staging of NSCLC. MATERIALS AND METHODS: This study was performed on 40 patients with NSCLC who had undergone preoperative staging and were candidate for curative surgery between 2008-2010. They underwent VATS immediately before the surgery. After performing VATS, the patients underwent thoracotomy by posterolateral incision unless any criteria of inoperability were present. Diagnostic accuracy of VATS for confirmation or modification of preoperative staging was evaluated. RESULTS: M/F ratio was 21/19. Mean age of the patients was 57.2 +/- 16.64 yrs. The most common symptom was coughing in 90% of patients. 72.5% of the patients had endobronchial mass and only for 27.5% tissue sample was obtained by transthoracic needle biopsy (TTNB) method. After performing VATS, 6 patients were excluded from surgery (3 cases (7.5%) due to seeding plural metastasis, 2 cases (5%) due to N2 involvement and one case (2.5%) due to satellite lesion in other lobes). Other 34 patients underwent surgery. Surgical resection was performed successfully in 31 cases (77.5%), but in 3 cases (7.5%) due to adhesion to hillum of the lung tumor was not resectable. According to the above results, VATS diagnosing accuracy was 92.5%. CONCLUSION: VATS can help to determine TNM staging and prevent unnecessary thoracotomy in some patients and we recommend this method for accurate staging of NSCLC.

[905]

**Título / Title:** - Proteomic biomarkers in lung cancer.
**Resumen / Summary:** - Enlace al Resumen / Link to its Summary
**Revista / Journal:** - Clin Transl Oncol. 2013 Apr 20.

684
El correcto entendimiento del desarrollo tumoral depende del estudio integral de los proteínas. Son los principales orchestradores de procesos vitales, tales como las vías de señalización, que empujan el proceso carcinógeno. Las tecnologías proteómicas pueden ser aplicadas al estudio en el cáncer para detectar diferencias en la expresión proteica y evaluar diferentes respuestas a la terapia.

El cáncer de pulmón es la causa número uno de muerte por cáncer en el mundo. Generalmente se diagnostica en etapas avanzadas del enfermedad, lo que tiene una de las tasas de supervivencia a cinco años más bajas del 15%. El uso de diferentes técnicas proteómicas, como la electroforesis en gel de dos dimensiones (2D-PAGE), isótopos (ICAT, SILAC, iTRAQ) y espectrometría de masas, puede proporcionar nuevas comprensiones sobre la biología subyacente del cáncer de pulmón y también permitir el desarrollo de pruebas de detección tempranas y la identificación de cambios en la red proteica del cáncer que se asocian con la progresión y la resistencia al tratamiento.

[906]

TÍTULO / TITLE: - Evidence for tankyrases as antineoplastic targets in lung cancer.

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


AUTORES / AUTHORS: - Busch AM; Johnson KC; Stan RV; Sanglikar A; Ahmed Y; Dmitrovsky E; Freemantle SJ

INSTITUCIÓN / INSTITUTION: - From the Department of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, Hanover, NH, 03755, USA. Sarah.J.Freemantle@Dartmouth.edu.

RESUMEN / SUMMARY: - BACKGROUND: New pharmacologic targets are urgently needed to treat or prevent lung cancer, the most common cause of cancer death for men and women. This study identified one such target. This is the canonical Wnt signaling pathway, which is deregulated in cancers, including those lacking adenomatous polyposis coli or beta-catenin mutations. Two poly-ADP-ribose polymerase (PARP) enzymes regulate canonical Wnt activity: tankyrase (TNKS) 1 and TNKS2. These enzymes poly-ADP-riboseylate (PARsylate) and destabilize axin, a key component of the beta-catenin phosphorylation complex. METHODS: This study used comprehensive gene profiles to uncover deregulation of the Wnt pathway in murine transgenic and
human lung cancers, relative to normal lung. Antineoplastic consequences of genetic and pharmacologic targeting of TNKS in murine and human lung cancer cell lines were explored, and validated in vivo in mice by implantation of murine transgenic lung cancer cells engineered with reduced TNKS expression relative to controls. RESULTS: Microarray analyses comparing Wnt pathway members in malignant versus normal tissues of a murine transgenic cyclin E lung cancer model revealed deregulation of Wnt pathway components, including TNKS1 and TNKS2. Real-time PCR assays independently confirmed these results in paired normal-malignant murine and human lung tissues. Individual treatments of a panel of human and murine lung cancer cell lines with the TNKS inhibitors XAV939 and IWR-1 dose-dependently repressed cell growth and increased cellular axin 1 and tankyrase levels. These inhibitors also repressed expression of a Wnt-responsive luciferase construct, implicating the Wnt pathway in conferring these antineoplastic effects. Individual or combined knockdown of TNKS1 and TNKS2 with siRNAs or shRNAs reduced lung cancer cell growth, stabilized axin, and repressed tumor formation in murine xenograft and syngeneic lung cancer models. CONCLUSIONS: Findings reported here uncovered deregulation of specific components of the Wnt pathway in both human and murine lung cancer models. Repressing TNKS activity through either genetic or pharmacological approaches antagonized canonical Wnt signaling, reduced murine and human lung cancer cell line growth, and decreased tumor formation in mouse models. Taken together, these findings implicate the use of TNKS inhibitors to target the Wnt pathway to combat lung cancer.
fibroblasts and lung cancer cells co-cultured in 3D matrix and 2D mode to induce fibroblasts to become myofibroblasts with the supplement of the medium continuously. With this device, we verified that the cytokines secreted by lung cancer cells could effectively transform the fibroblasts into myofibroblasts. Moreover, compared to fibroblasts, the myofibroblasts showed higher resistance to anticancer drug VP-16. We also demonstrated that this kind of acquired resistance in myofibroblasts was associated with the expression of Glucose-regulated protein 78 (GP78). We concluded that this device allows for the assay to characterize various cellular events in a single device sequentially, facilitating a better understanding of the interactions among heterotypic cells in a sophisticated microenvironment.
expression of CSC-representative markers and alteration of EMT-associated markers were found at the invasive fronts and in MPEs compared with the expression in primary pulmonary tumor tissues. The expression of OCT-4 in MPEs significantly related to distant metastasis and stage, as well as inversely correlated with patient survival. Primary cultures confirmed the CSC properties in MPE. Five of eight cases of MPE yielded adequate cell clusters, which also showed variable expressions of CSC markers in addition to sphere formation and the ability for differentiation and metastasis. CONCLUSION: This pilot study offers a better understanding of the metastatic cascade. Establishing a model of MPE will provide further insight into the role of CSCs in metastasis and may explain the high therapeutic failure rates for patients with MPE.