9018 POSTER

Improved staging using intraoperative ultrasound for mediastinal lymphadenectomy in NSCLC surgery

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Objectives: The extend of lymph node involvement in patients with non-small cell lung cancer (NSCLC) is the cornerstone of staging and influences both multimodality treatment and final outcome. We studied safety, accuracy and characteristics of intraoperative ultrasound (US) guided systematic mediastinal nodal dissection in patients with resected NSCLC.
Methods: Intraoperative hand held ultrasound probe was used in systematic mediastinal nodal dissection in 84 patients after radical surgery for NSCLC. Mapping of the lymph nodes by their number and station followed by histopathologic evaluation was performed. Data were compared with 86 patients who underwent lung resections and standard systematic mediastinal nodal dissection for NSCLC within the same time period at our institution. Statistical analysis was carried out.
Results: The surgical procedure used depended on the extent of the disease, as well as the cardiopulmonary reserve of the patients and was comparable in both groups of patients. Operating time was prolonged for 12 (6−20) minutes in patients with US guided mediastinal nodal dissection, but number and stations of evaluated lymph nodes was significantly higher ($p>0.001$) at the same group of patients. Skip nodal metastases were found in 24% of patients without N1 nodal involvement. We upstaged 12 (10%) patients using US guided mediastinal lymphadenectomy. Standard staging system seemed to be improved in US guided mediastinal lymphadenectomy patients. Complications rate showed no difference between analyzed groups of patients.
Conclusion: Higher number and location of analyzed mediastinal nodal stations in patients with resected NSCLC using hand held ultrasound probe suggested to be of great oncology significance. Procedure showed absolute safety and high accuracy. Our results indicate that intraoperative US may have important staging implication. Further clinical studies should be carried out in order to improve intraoperative staging in NSCLC patients.

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The benefits of PCR-Invader method for analysis of EGFR gene mutation in the primary non-small-cell lung cancer

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Background: In late years, reports about Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibitors (TKIs) in the non-small cell lung cancer (NSCLC) and the EGFR-mutation have increased. The theory that existence of somaticmutations in the EGFR kinase domain is corresponded with therapeutic sensitivity of TKIs in patients with NSCLC, has been recognized widespread, andEGFR mutation becomes one of the effect-prediction-factors of EGFR-TKIs. TheDirect Sequencing method is used commonly for analysis of their EGFR gene, there are few reports about PCR-Invader method for analysis of the EGFR gene.
Material and Methods: We intended 100 cases of lung specimen in the NSCLC, which were stored both as fresh-frozen tissues at −80°C and formalin-fixedparaffin-embedding tissues for this study. We analyzed retrospectively whether EGFR mutations could be detected by both the PCR-Invader and the DirectSequence method in each case.
Results: The EGFR mutations were found in 38% of cases by PCR-Invader method, and found in 32% by Direct Sequencing method. These mutations were recognized 18% in Exon21, 19% in Exon19 and 3% in Exon20. EGFR mutations were detected in the following characteristics: histological types were 37 adenocarcinomaand one adenosquamous carcinoma, the genders were 10 male and 28 female, and 31 cases were never smoker. By the PCR-Invader method using fresh-frozentissues, the mutation of Exon19 or Exon21 could be detected in 37 cases, although their mutations could be measured by Direct Sequence method in 32cases. Four cases of L858R in Exon21 and one case of E746-A750 deletion in Exon19 were detectable only by PCR-Invader method. In the formalin-fixedparaffin-embedding tissues, 22 cases of the EGFR mutations were found in Exon19 or Exon21 by PCR-Invader method and 20 cases of the mutations were detected by Direct Sequence method. Two cases of E746-A750 deletion in Exon19 were only detected by PCR-Invader method.
Conclusions: The PCR-Invader method for analysis of the EGFR mutation in the NSCLCmight be superior to the Direct Sequence method, as the ability of detection of Exon21 and Exon19-mutations was higher. Besides, the EGFR mutation measurement by the PCR- Invader method was reliable even if the formalin-fixedparaffin-embedding tissues were used.

9020 POSTER

Utilization of traditional chinese medicine for lung cancer in Taiwan: a population-based study

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Background: Complementary/alternative medicine (CAM) used in lung cancer has increased. Traditional Chinese medicine (TCM) is an important category of CAM and is popular in Taiwan. The National Health Insurance covered 99% of the inhabitants and 91% of the medical institutes in Taiwan, including TCM and Western medicine. Basing on the National Health Insurance Research Database (NHIRD), a nationwide survey was conducted. This study aimed to investigate the utilization of TCM for lung cancer in Taiwan.
Material and Methods: Only TCM outpatient service was covered by National Health Insurance. TCM outpatient reimbursement claims from NHIRD of 2007 were analyzed. The data of registry for catastrophic illness patients was used to analyze the prevelance of lung cancer. Patients with lung cancer were identified by ICD-9 Code of 162, and 162.0−162.9.
Results: In 2007, a total 1202 (6.3%) lung cancer patients used 7990 TCM outpatient visits. Female patients (50.3%) were a little more than male ones (49.7%). Median age was 62. Hospitals provided more TCM service (67.5%) than TCM clinic (32.5%). The most frequently used therapies were traditional Chinese herbs/medicine (97.1%), following by acupuncture and traumatology manipulative therapies (2.9%). For TCM users of lung cancer, 27.3% patients had one visit, 39.7% had 2−6 visits, and 33.0% had more than 6 visits of TCM outpatient service in 2007. The cost of per visit was NTD 626.57(USD 18.51/ EUD 14.27).
Conclusions: Our results revealed that a small portion of lung cancer patients use TCM in Taiwan. The cost of TCM is low. Further research is needed to investigate the efficiency of TCM and interaction of TCM and Western medicine.

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Preliminary results of MAGE-A3 expression and baseline demographic data from MAGRIT, a large phase III trial of MAGE-A3 ASCI (Antigen-Specific Cancer Immunotherapeutic) in adjuvant NSCLC

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Background: The MAGE-A3 gene is a tumor-specific gene expressed in Non-Small Cell Lung Cancer. The MAGRIT Phase III trial evaluates the potential efficacy of the MAGE-A3 ASCI in resected stage IB, II and IIIA MAGE-A3(+) NSCLC patients. We report here the frequency of MAGE-A3 gene expression according to stage, histology and tumor size. Demographics of the first randomized patients are reported.
Methods: MAGE-A3 expression was tested by quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR) on Formalin Fixed Paraffin-Embedded (FFPE) tumor tissue from surgical samples. Baseline patient and tumor characteristics were collected and associated with the expression of MAGE-A3.
Results: Tumor samples from 2690 operable NSCLC patients were screened for MAGE-A3 expression between Oct 4, 2007 and April 14, 2009 and 32.9% found positive. The number of invalid samples is low (2.3%). The expression of the MAGE-A3 gene is 34% in stage IB, 34.9% in stage II, 31.3% in stage IIIA. It is 47.2% in squamous cell carcinoma and 24.3% in adenocarcinoma. Irrespective from stage and histopathology, expression increased with primary tumor size: 23.7% for tumors <2cm to

up to 42.6% for tumors >5 cm. The mean age of the first 424 MAGE-A3-positive patients randomized was 63 years. Gender: 24.1% females. 84.1% of the patients had received (bi-)lobectomy/sleeve lobectomy and 15.7% pneumonectomy. Radical mediastinal lymphadenectomy had been performed in 57%. Pathological stage: 52.4% stage IB, 34.2% stage II and 13.0% stage IIIA. Histopathological type: 50.7% squamous cell carcinoma and 33.3% adenocarcinoma. Adjuvant platinum-based chemotherapy was given to 46.8% of patients (25.7% Stage IB, 68.1% Stage II, 78.8% Stage IIIA).
Conclusions: The expression rate reported here confirms previously reported expression rate from a Phase II trial of MAGE-A3 in resected NSCLC[1] and from smaller cohorts in comparable stages of NSCLC[2,3]. Although the MAGE-A3 expression appears constant throughout disease stages, it differs according to the histological type, with a more frequent expression in squamous cell tumors, and also according to the tumor size, with increased expression in large tumors. Radical mediastinal lymphadenectomy is performed in more than half of the patients and about half of patients randomized do receive adjuvant chemotherapy.

References

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9022 POSTER

The nicotinic acetylcholine receptor (nAChR) subunit α3 (CHRNA3) polymorphism in advanced non-small-cell lung cancer (NSCLC) patients (p) with EGFR mutations treated with erlotinib

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Background: Polymorphisms in the 15q region, containing the genes for α3 and α5 subunits of heteromeric nAChRs, are associated with a predisposition to lung cancer even in a smoking-independent manner. Activation of the nAChR pathway leads to upregulation of the CREB (CMP response element-binding) protein, which transactivates the EGFR and induces the release of EGF and VEGF. CREB overexpression decreases survival in never-smokers with NSCLC. We hypothesized that CHRNA3 would influence outcome in NSCLC p with EGFR mutations treated with erlotinib.
Material and Methods: Stage IV NSCLC p with EGFR mutations were prospectively treated with erlotinib. Genomic DNA was derived from tumor tissue obtained by laser capture microdissection. Deletions in exon 19 (del 19) were determined by length analysis after PCR amplification with a FAM-labelled primer in an ABI Prism 3130 DNA Analyzer. Exon 21 point mutations L858R were detected with a TaqMan assay. DNA was extracted from lymphocytes and CHRNA3 (rs1051730) polymorphism was genotyped with the TaqMan allele discrimination assay.
Results: 185 NSCLC p with EGFR mutations were treated with erlotinib. Median age, 68; 136 females; 182 Caucasians, 3 Asians; 123 never-smokers, 44 ex-smokers, 10 current smokers; 145 adenocarcinomas, 21 BAC, 19 LCC; 179 stage IV, 6 stage IIIB with malignant pleural effusion; 99 first-line erlotinib, 86 second-line; 110 del 19, 75 L858R. 62 p had the homozygous (CC) CHRNA3 genotype; 94 were heterozygous (CT); 29 were homozygous for the variant (TT). No differences in p characteristics were found according to the CHRNA3 genotype. Overall response: CR, 19 p (11.6%); PR, 97 p (59.1%); ORR, 116 p (70.7%); SD, 33 p (20.1%); PD, 15 p (9.1%); 21 p had no measurable disease according to RECIST criteria. No differences in response were observed according to the CHRNA3 genotype. Median follow-up, 14 months (m) (range, 1−42 m). Median time to progression (TTP), 14 m (95% CI, 10.9−17.1). Median survival (MS), 28 m (95% CI, 24.9−31.1). Hazard ratios for shorter TTP were 3.7 for male gender (P = 0.05), 4.65 for PS 2 (P = 0.19), 0.18 for CT genotype (P = 0.03), 0.21 for CC genotype (P = 0.07), and 2.31 for L858R (P = 0.23).
Conclusions: p with EGFR mutations have an impressive response rate and TTP when treated with erlotinib. However, a subgroup of p with the variant CHRNA3 TT genotype have a significant risk of relapse, perhaps due to overexpression of EGF and VEGF through hyperactivation of the nAChR pathway. Assessment of the CHRNA3 polymorphism can help identify these patients and provide a useful guide for additional therapeutic decisions.

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Relationship between SNPs of glucose transporter related genes and 18F-deoxyglucose (FDG) uptake of PET-CT in non-small cell lung cancers (NSCLCs)

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Backgrounds: Lung cancer cell growth is an energy-related process using glucose metabolism. This uptake is mediated by glucose transporters (Gluts). Previous study revealed that increased expression of Gluts are related with increased uptake of FDG and clinically related with poor outcome. But there were no reports about the relationship between genetic phenotypes of Gluts and increased FDG uptake in NSCLCs. In this study, the authors checked the SNPs of Gluts and other related genes and its relationship with the uptake of FDG in NSCLCs.
Materials and Methods: From October, 2005 to February 2008, 122 blood samples were collected from NSCLCs patients. Male to female ratio was 2: 1 and mean age was 64.5 year. Of the 122 patients, adenocarcinomas were 75, squamous cell carcinomas were 47. SNPs of *Glut1, VEGFA, APEX2, HIF1A* were checked by using SNaPShot assay (ABI PRISM ANaPShot Multiplex kit, CA, USA) and analysed using Genemapper software. Also PET-CT were checked and SUVmax value were taken and compared with the SNPs of the each gene.
Results: In squamous cell lung cancers, the level of SUVmax was higher in GLUT1 TT type than in AA+AT type (11.6 8.9. Also in squamous cell lung cancers, GlUT1 type showed shorter survival time than AA+AT type.
Conclusions: Non-small cell lung cancers, especially in squamous cell type which have GLUT1 recessive type (TT) showed increased level of SUVmax and shortened survival time indicates that genotypic types of glucose transporters have clinical implication regarding to prognosis.

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LCK-positive tumor-infiltrating lymphocytes is associated with a better prognosis in stage I non-small cell lung cancer patients

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Objective: The correlation between tumor-infiltrating immune cells and the prognosis of lung cancer is controversial. For this reason, we have invistigated the expression in the tumor infiltrate of a T-cell activation marker, the "lymphocyte-specific protein tyrosin kinase" (LCK), to assess if it could be associated with a better prognostic outcome in early stage NSCLC patients.
Methods: This retrospective study included 25 patients undergoing lobectomy with standard hilo-mediastinal lymphadenectomy for pathological stage I NSCLC between 7−2003 and 6−2005. The presence of LCK was detected in the tumor infiltrate by immunohistochemistry on the specimen of all patients. No patient received adjuvant therapy.
Results: Resection was radical (R0) in all the patients. There was no post-operative mortality. Median follow-up time was 48 months (range 40−60). Twelve patients had a recurrence within 40 months from the operation while 13 patients had no recurrence. The presence of LCK in the tumor-infiltrate was found in 3 of 12 patients (25%) showing recurrence and in 9 of 13 patients (69%) without recurrence (Fisher's exact text p = 0.01). Relapse-free survival (RFS) and overall survival (OS) (Kaplan-Meier analysis) resulted significantly longer in the LCK-positive group (median-RFS: not reached Vs 25 months, Log-rank p < 0.001; median-OS: not reached Vs 30 months, Log-rank p = 0.02). The distribution of patients according to T-stage was similar between the LCK-positive group (6 T1, 6 T2) and the LCK-negative group (6 T1, 7 T2).
Conclusion: LCK-positive tumor-infiltrate is clearly associated with a longer RFS and OS and a lower relapse rate in patients with radically resected stage I NSCLC.