O13. Subtype-specific KRAS mutations in advanced lung adenocarcinoma

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Background: So far there is no strong evidence for the predictive effects of KRAS mutations on the clinical outcome of platinum-based chemotherapy in advanced lung adenocarcinoma. However, most of the studies did not take into account the subtype-specific mutations in the KRAS gene.

Methods: For this very reason we studied a cohort of 505 unresectable stage III-IV lung adenocarcinoma patients with known KRAS mutational status. Formalin fixed paraffin embedded histological samples were subjected to restriction fragment length-based KRAS codon 12 and 13 mutation screen. All mutant cases then were analyzed by direct sequencing. Next, the correlation of various subtype-specific mutations with the clinicopathological characteristics including smoking status, progression-free survival (PFS), overall survival (OS) and response rate (RR) to platinum-based treatment was analyzed.

Results: In our cohort, 338 non-KRAS mutant (67%), 147 codon 12 mutant (29%) and 20 codon 13 mutant (4%) patients had been identified. We found no significant differences among the different KRAS mutation groups in PFS or in OS. Importantly, we found that the G12V subtype of KRAS codon 12 mutation was significantly more frequent in never-smoker than in ever-smoker patients (26% vs. 6%, P=0.023). Furthermore, patients with G12V mutations had a non-significantly higher RR when compared to other patients presenting with other codon 12 mutation subtypes (G12x) (66% vs. 47%, respectively; P=0.072). There was also a non-significant increase in the median PFS in the G12V mutant cohort (7.8 vs. 5.8 months in the G12x group, P=0.145).

Conclusions: KRAS mutation status per se is neither prognostic nor predictive in advanced lung adenocarcinoma. However, subtype-specific analysis may reveal clinically relevant subgroups.

Keywords: Non-small cell lung cancer (NSCLC); adenocarcinoma; KRAS; mutation
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P1. Molecular subclassification of NSCLC based on hsa-mir-205 and hsa-mir-21 expression using real time PCR

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Background: Routine histopathology is the current standard of lung cancer classification, but this time-honored method is unreliable. Nowadays, the new methods of treatment based on molecular targets emerge, and these approaches require using high precision in non-small cell lung cancer (NSCLCs) sub-classifications. MicroRNAs (miRNAs) are small, non-coding RNA molecules regulating gene expression by inducing mRNA degradation or by blocking translation. Recently, hsa-mir-205 was identified as a highly specific marker of stratified squamous epithelium with expression in squamous cell lung carcinoma. The
objectives of our study were as follows: evaluation of expression levels of hsa-mir-205 and hsa-mir-21 on large group well-characterized, completely resected fresh frozen lung tumors, by LNA qRT- polymerase chain reaction (PCR), in order to predict histo-pathological subtype of NSCLC; an attempt to develop a molecular assay, based on the expression levels of hsa-mir-205 and hsa-mir-21 in tumor tissues, for precise discrimination of squamous cell carcinoma and adenocarcinoma of the lung.

Methods: Freshly frozen specimens of tumor tissues were obtained from resected 57 squamous and 41 adenocarcinoma of NSCLC. Levels of miRNA expression (hsa-mir-205, hsa-mir-21 and U6 snRNA as the endogenous control) were quantitated using the miRCURY LNA™ Universal RT microRNA PCR system (Exiqon). Sample score was then obtained using the formula Score according to Lebanony et al., which defines the normalized expression of hsa-mir-205 minus half the normalized expression of hsa-mir-21.

Results: We found a difference in the relative expression level of hsa-mir-205 (P<0.0001) and the “sample score” (P<0.0001) between the group of squamous and adenocarcinoma of NSCLC. The sensitivity and specificity of the developed molecular tests was 90.5% and 88.1% for the relative expression level of hsa-mir-205 and 87.5% and 89.3% for the “sample score”.

Conclusions: hsa-mir-205 is a highly useful marker for the differentiation of squamous cell carcinoma and adenocarcinoma of the lung. Molecular assay, based on the level of expression of hsa-mir-205 and the “sample score” can be used as potential tool in subclassification of NSCLC patients.

Keywords: Non-small cell lung cancer (NSCLC); tumor marker; tumor classification


P2. VATS sentinel node biopsy reduces the need for systematic mediastinal lymphadenectomy in early stage NSCLC

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Objective: Systematic mediastinal lymphadenectomy is still essential for an adequate postoperative staging of non-small cell lung cancer (NSCLC). We tried to investigate the controversial role of sentinel node biopsy (SNB) in early stage NSCLC surgery using videothoracoscopic approach (VATS).

Methods: A total of 52 patients with clinical T1N0MO NSCLC underwent SN navigation VATS lobectomy using Tc-99 labeled tin colloid followed by systematic mediastinal lymphadenectomy (SML) in 2 years time period (2010-2012). Mapping of the mediastinal lymph nodes by their number and station followed by histopathological evaluation was performed. Patients data were statistically analyzed.

Results: Intraoperative SN was identified in 45 (87%) of these patients with 92% of accuracy. We found lobe specific skip nodal metastases in 5 (10%) patients resulting in upstaging. The incidence of ML metastases seemed to be more often in adenocarcinoma patients (P<0.05), but skip nodal metastases showed higher rate in squamous cell carcinoma patients. Intraoperative frozen section was not confirmed accurate for detecting micrometastases in two (4%) patients. Operative time was prolonged for 10 [8-25] minutes showing no difference in complication rate.

Conclusions: Minimally invasive VATS procedure showed absolute safety and high accuracy. Our results indicated that SN identification could reduce mediastinal lymph node dissection in early stage NSCLC. Further clinical studies should be carried out in order to prove that minimally invasive surgical procedures could be curative for T1N0MO NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); mediastinal lymphadenectomy; sentinel node
