International Association for the Study of Lung Cancer classification and analyzed clinical, immunohistochemical and molecular data. Immunohistochemistry (IHC) for CDX2, CK20, CK7 and TTF1 were performed and EGFR, RAS and ALK status was determined as standard procedures.

Results: The series included 18 patients diagnosed and treated at our Institution between 2012 and 2015. Gastrointestinal primitive lesions were excluded using ^{18}FDG-CT-PET and endoscopic examination. Median age was 60.5 years, patients were predominantly males (M:F 12:6). More than a half of patients (56%) were never or former smokers. IHC characterization identified 14 cases expressing at least one intestinal differentiation marker (CDX2 and/or CK20), while TTF1 was expressed in five cases. At time of diagnosis, 15 cases (83%) were stage IV, while 3 patients were stage II and underwent systemic progression within one year from radical surgery. Most frequent metastatic sites were bone (44%), adrenal gland (32%) and pleura (28%). Exon 18-19-20-21 EGFR mutations were assessed in 15 patients, resulting in 3 (20%) rare mutations (exon 19 I745insKIPVAI; exon 18 G719A; exon 20 S768R) and no common sensitizing EGFR mutations. No RAS or ALK alterations were found. For metastatic disease, 15 patients were able to receive first-line treatment: 12 patients received platinum-based doublet (with the addition of bevacizumab in two cases), one capecitabine (n: 1), two patients received EGFR inhibitors. Eight patients were able to receive second-line systemic treatment and one patient was treated with fluoruracil, oxaliplatin and bevacixumab. Three patients obtained radiological response following chemotherapy and two of them received fluoropyrimidine. Median overall survival from metastatic diagnosis was 10 (95% CI: 8-NA) months and median progression-free survival was 6 (95% CI: 2-NA) months, but great heterogeneity in outcome was noticed and three EGFR, RAS wild-type patients live more than 30 months from diagnosis of metastatic disease. The presence of rare EGFR mutations was associated with no smoking history and worse outcome; best radiological response to EGFR inhibitors was progression.

Conclusion: Primary lung enteric adenocarcinoma has heterogeneous clinical behavior and is mainly refractory to standard chemotherapy. It presents specific epidemiological features and deeper genetic characterization is ongoing to define different subgroups and try to improve therapeutic approach.

Keywords: Pathology, EGFR rare mutations, rare histology, intestinal-like adenocarcinoma

P3.01-018
Reproducibility in Classification of Small Lung Adenocarcinomas: An International Interobserver Study

Topic: Morphology

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Background: The 2015 WHO classification for lung adenocarcinoma (ACA) provides criteria for diagnosis of adenocarcinoma in-situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (INV). Differentiating these entities can be difficult, and as understanding of prognostic significance increases, inconsistent classification is problematic.

Methods: Sixty cases of lung ACAs ($\leq$2cm) were reviewed by an international panel of 6 lung pathologists. One slide reflecting overall morphology of each case was digitally scanned to an internet browser-based viewer. In round one, the panel independently reviewed each case to assess predominant pattern, invasive component size, and final diagnosis (AIS, MIA or INV). After a consensus conference among participants, a second round of independent review of the cases was performed. Additionally, a discussion on interpretation of elastic stain for evaluation of invasion will precede a third round of review with assessment of a concomitant elastic stain for each case. Statistical analysis was performed for each round.

Results: In round one, the overall kappa value for AIS versus MIA and INV was 0.34 (fair agreement), and that for AIS and MIA versus INV was 0.44 (moderate agreement). The raters had 100% agreement on final diagnosis in 10 cases (AIS, n=2; MIA, n=2; INV, n=6). In 28 cases

with poor agreement on final diagnosis and invasive measurement, inconsistent measurement of multifocal invasion led to wide variance in 5 cases, and subjectivity in pattern recognition led to variance in 23 cases. Misinterpretation of the WHO criteria for MIA resulted in 18 instances of misclassification across all raters. A case with a predominant mucinous lepidic pattern had a range of diagnoses (AIS, n=1; MIA, n=1; INV, n=4). In round two, the overall kappa value for AIS versus MIA and INV is 0.40 (fair agreement), and that for AIS and MIA versus INV is 0.36 (moderate agreement). The raters had 100% agreement on final diagnosis in 12 cases (AIS, n=3; MIA n=4; INV, n=5). Misinterpretation of the WHO criteria for MIA was seen in 6 instances. The intraobserver kappa coefficient ranged widely from 0.259 to 0.859.

Conclusion: Interobserver agreement on diagnosis of small lung ACAs between raters was fair to moderate, with minimal improvement after a consensus conference. Inconsistent measurement of multifocal invasion, subjectivity in pattern recognition, misinterpretation of the WHO criteria, and subjective interpretation of mucinous ACA have contributed to interobserver discordance. A third round of evaluation is currently ongoing to assess for improvement and the utility of elastic stains.

Keywords: minimally invasive adenocarcinoma, small lung adenocarcinoma, adenocarcinoma in situ

P3.01-019
Desmoplasia is Associated with Poor Prognosis and Carcinoma-Associated Fibroblast Heterogeneity in Non-Small Cell Lung Cancer

Topic: Morphology

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Background: Cancer-associated fibroblasts (CAFs) are known to influence tumor development, progression and metastasis. Their characteristics and prognostic role in non-small cell lung cancer (NSCLC) patients have been recognized. However, the functional heterogeneity of CAFs between patients and its genetic basis is less understood.

Methods: Two pathologists scored for desmoplasia on Hematoxylin-Eosin stained sections of resected lung tumors from two patient cohorts: one consisting of 171 NSCLC patients (128 adenocarcinoma, 43 squamous carcinoma) and the second of 24 primary cultures of CAFs. Percent area of desmoplasia among total tumor stroma was used to define high desmoplasia (HD) *versus* low desmoplasia (LD). The desmoplasia and survival analysis were assessed for 171 NSCLC patients. Gene expression data on RNA extracted from CAFs in contracted gels following 24 hours incubation was obtained using Illumina Human HT-12v4 Bead Chips array and was preprocessed and normalized using RMA and values were log2 transformed. Significant genes whose expression is strongly correlated (Spearman correlation coefficient and p value) with percent of desmoplasia were identified in both cohorts. The gene set enrichment analysis (GSEA) was applied to test for the enrichment of CAF cohort significant genes in 171 NSCLC cohort. Additionally, CAF significant genes were subjected to pathway enrichment analysis using Pathway Data Integration Portal ver. 2.5 (http://ophid.utoronto.ca/pahtDIP).

Results: The prognosis of adenocarcinoma patients with HD had poorer outcome in comparison to the patients with LD (disease free survival at 3 years 34% vs. 75% p=0.00045 and relapse rate 41% vs. 14%, p=0.0051). In the CAF cohort, the number of genes that are significantly associated with desmoplasia for enrichment are 356. Using GSEA, these genes were enriched in 171 NSCLC cohort (with a p value of 0.045). Protein-protein interaction (PPI) partners of these 356 genes were acquired using Integrated Interaction Database — IID (version 2016-03, http://dcv.uhnres.utoronto.ca/iid/). Obtained genes were then ranked according to their degree, i.e., number of PPIs. Top 44 (top 1%) of the genes were then selected to pathway enrichment analysis using pathDIP version 2.5. 245 pathways that significantly enriched by these 44 genes (FDR < 0.01) were obtained. Many of these pathways are known to be involved in lung cancer.

Conclusion: We demonstrated that the prognosis of lung adenocarcinoma patients with HD had poorer outcome in comparison to the patients with LD. Furthermore, PPI analysis of CAF genes associated with HD reveals enrichment of many cancer-related pathways, suggesting their high relevance to lung cancer.

Keywords: non-small cell lung cancer, Heterogeneity, Prognosis, cancer-associated fibroblasts

P3.01-020
Evolving Trends in Lung Cancer Pathology

Topic: Morphology

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