**AP19-PP-0001** Free Paper (Poster)

**PULMONARY PATHOLOGY**

**Overexpression of ID4 Protein May Promote Lymph Node Metastasis in Pulmonary Squamous Cell Carcinoma**

Mee Sook Roh 1 · Jeano Yun 1 · Phil Jo Choi 2 · Choonhee Son 1

Departments of Pathology, 1 Biochemistry, 2 Thoracic and Cardiovascular Surgery, and 3 Internal Medicine, Dong-A University College of Medicine, Busan, Korea

**Background:** Inhibitor of DNA binding (ID) family proteins are negative regulators of basic helix-loop-helix transcription factors. As key regulators of cell cycle and differentiation, their involvement in cell cycle control, cancer development, angiogenesis, and apoptosis has been implicated. ID4, a member of the ID family proteins, has been shown recently to have tumor suppressor properties in some cancers, whereas some other studies have related this protein to tumor metastasis. However, the expression and significance of ID4 in pulmonary squamous cell carcinomas (SCC) has not been fully addressed. **Methods:** We performed immunohistochemical detection of ID4 protein in 94 tissue samples from pulmonary SCC patients by using a tissue microarray. More than 10% of the cells with moderately to strongly intense nuclear and/or cytoplasmic staining were interpreted as positive for ID4. **Results:** ID4 immunoreactivity was observed in 58 (61.7%) of the 94 SCC cases. The tumors with positive ID4 expression more frequently showed lymph node metastasis (p = 0.014) than the tumors with negative ID4 expression. Although the relationship did not reach the statistical significance, the tumors with positive ID4 expression tended to be larger in size (p = 0.069). There were no significant associations between ID4 expression and other clinicopathologic features. **Conclusions:** We demonstrated that expression of ID4 may promote lymph node metastasis in pulmonary SCC. Further investigations are needed to study the mechanisms involved, an understanding of which may provide the basis for a rational approach to the prognostic or therapeutic role of ID4 expression in pulmonary SCC.

**Key Words:** Lung; Carcinoma, squamous cell; ID4 protein, human; Lymph node metastasis; Immunohistochemistry

**AP19-PP-0002**

**Loss of ARID1A Expression Is Associated with Poor Prognosis in Non-small Cell Lung Cancer**

Mee-Hye Oh · Hyun-Deuk Cho · Ji-Hye Lee · Hyun Ju Lee · Si-Hyong Jang

Department of Pathology, Soon Chun Hyang University Cheonan Hospital, Soon Chun Hyang University College of Medicine, Cheonan, Korea

**Background:** Adenine-thymine (AT)-rich inactive domain-containing protein 1A (ARID1A) is a large subunit of the SWI-SNF complex and is considered to perform a tumor suppressor function in various cancer types. In this study, we investigated the clinicopathologic significance including prognosis of ARID1A expression in non-small cell lung cancers (NSCLCs). **Methods:** Expression of ARID1A was studied by immunohistochemical analysis of 171 surgically resected NSCLC specimens including adenocarcinomas and squamous cell carcinomas on tissue microarray. **Results:** The ARID1A-negative group revealed significantly higher correlation with male (p = 0.020), larger tumor size (p = 0.006), squamous cell carcinoma than adenocarcinoma (p = 0.018) and smoker (p = 0.001). Univariate survival analysis showed that ARID1A-negative group had a significantly shorter cancer specific survival than ARID1A-positive group (p = 0.005). Meanwhile, male (p = 0.031), higher nodal status (p = 0.007), late pathologic stage (p = 0.024), and smoker (p = 0.008) significantly correlated with shorter survival. Multivariate survival analysis showed that ARID1A negativity (p = 0.024) and late pathologic stage (p = 0.025) were independent prognostic factors related with shorter cancer specific survival for NSCLC. **Conclusions:** Loss of ARID1A expression might be a molecular marker to predict poor prognosis of NSCLC.

**Key Words:** ARID1A; Carcinoma, non-small cell lung; Prognosis

**AP19-PP-0003**

**A Case of Combined Large Cell Neuroendocrine Carcinoma of Lung with a High-Grade Fetal Adenocarcinoma Component**

Masaki Suzuki 1,2, Junichi Morimoto 1,2, Yuko Yonemori 1,2, Takekazu Iwata 4, Ichiro Yoshino 1,2, Satoshi Ota 3, Yuko Nakatani 1,2

1 Department of Diagnostic Pathology, Chiba University Graduate School of Medicine; 2 Department of Pathology, Chiba University Hospital; 3 Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

A 67-year-old man was referred to our hospital because of a tiny nodule in the apical portion of the right lung on a computed tomography scan. During 8 months of watchful follow-up, size of the nodule increased from 6 to 16 mm. Large cell neuroendocrine carcinoma (LCNEC) was suspected on an endobronchial ultrasound-guided transbronchial needle aspiration biopsy, then a right upper lobectomy was performed. In macroscopic finding of the resected specimen, the peripheral lung parenchyma showed a well-demarcated, grayish-white and solid tumor, measuring 30 mm in size. Microscopically, the tumor consisted of four different histological components: high-grade fetal adenocarcinoma (H-FLAC), LCNEC, acinar adenocarcinoma and large cell carcinoma-like area. Approximately 10% of the tumor was H-FLAC composed of complex glandular structures resembling fetal lung. The tumor cells were columnar in shape with clear, glycogen-rich cytoplasm, and were frequently immunopositive for alpha-fetoprotein. Another 10% was LCNEC arranged in an organoid pattern, the tumor cells were columnar in shape with clear, glycogen-rich cytoplasm, and were frequently immunopositive for alpha-fetoprotein. Beta-human chorionic gonadotropin-immunopositive syncytiotrophoblast-like multinucleated cells intermingled with this component. We diagnosed the present case as combined LCNEC with acinar adenocarcinoma, H-FLAC, and syncytiotrophoblast-like cells. Pathological stage was defined as stage IIIA because of mediastinal nodal metastasis. Using our data base, we will demonstrate H-FLAC is a high-grade signature and not infrequently coexists with other high-grade histological subtypes including neuroendocrine and primitive elements.

**Key Words:** High-grade fetal adenocarcinoma; Large cell neuroendo-
**Pulmonary Squamous Cell Carcinoma with Anaplastic Lymphoma Kinase Gene Translocation: A Case Report**

Hee Sung Park · Hyo Sup Shim

Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Anaplastic lymphoma kinase (ALK) gene rearrangements had been discovered in a minor subset of non-small cell lung cancer, preferentially adenocarcinoma. We report the first case of squamous cell carcinoma with ALK translocation. Forty three aged woman who denied smoking habit, visited out-patient hospital because of cough and chest pain. Positron emission tomography computed tomography scan of her whole body revealed 6 cm-sized hypermetabolic mass in the right lower lobe and left iliac bone lesion with strong fluoro-deoxyglucose uptake suggesting metastasis. Bronchoscopic examination showed endobronchial mass with total luminal obstruction in right lower lobar bronchus and biopsy for the endobronchial lesion was done. On light microscopy, moderately differentiated squamous cell carcinoma was observed and the tumor was diffusely immunoreactive for cytokeratin 5/6 and p63 without thyroid transcription factor-1 expression. Immunohistochemistry for ALK (5A4, Novocastra) of tumor presented strong cytoplasmic staining. Molecular studies were performed using paraffin embedded, formalin-fixed specimen of bronchoscopic biopsy. The tumor was epidermal growth factor receptor (EGFR) and K-RAS gene wild type. ALK fluorescence in situ hybridization (FISH) using dual-color break-apart probes (Vysis) demonstrated break apart of red and green signals and one or two single red signals were observed in 40 out of 50 non-overlapping nuclei. On 5’-RACE reaction, exon 21 of HIP1 fused to the exon 20 of ALK, leading to generate t(2;7)(p23;q11.23).

**Conclusions:** This is the first report of an HIP1-ALK fusion gene in NSCLC. Although the response to ALK inhibitors in this case is unknown yet, response to ALK tyrosine kinase inhibitor may be promising.

**Key Words:** HIP1-ALK; ALK fusion gene; 5’-RACE

---

**Differential Expression of Transforming Growth Factor β1 Protein in Pulmonary Adenocarcinoma: In Relation to Tumor Progression**

Jinyoung Yoo

Department of Pathology, St. Vincent’s Hospital, The Catholic University College of Medicine, Suwon, Korea

**Background:** This study was designed to investigate the significance of transforming growth factor β1 (TGFβ1) expression in tumor progression of lung adenocarcinoma. **Methods:** Sixty-five pulmonary adenocarcinomas were reclassified according to the newly proposed classification by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. Tumor samples from 20 adenocarcinomas in situ (AIS, formerly bronchioalveolar carcinoma [BAC]), 9 minimally invasive adenocarcinomas (MIA, formerly BAC with \( \leq 5 \) mm invasion), 17 lepistic predominant adenocarcinomas (LPA, formerly mixed adenocarcinoma showing nonmucinous BAC feature with >5 mm invasion), and 19 invasive adenocarcinomas without BAC feature were analyzed by immunohistochemistry for the expression of TGFβ1 protein. **Results:** TGFβ1 was more frequently expressed in invasive foci than in BAC components (87% vs 46%, \( p = 0.001 \)). Of invasive foci, TGFβ1 expression was demonstrated in 100% of MIA (9/9), 88% of LPA (15/17), and 79% of adenocarcinomas without BAC feature (15/19); no significant correlations were identified between the groups. However, the frequency of TGFβ1 expression was significantly higher in noninvasive components of LPA (82%, 14/17) than in either AIS (25%, 5/20) or in those of MIA (22%, 2/9), and the differences were statistically significant. In MIA, TGFβ1 was observed in all the invasive elements while it was expressed in 2 of 9 noninvasive elements (\( p = 0.002 \)). **Conclusions:** Our data indicate that TGFβ1 up-regulation is an early event in the invasive process,
Survivin Expression Is an Independent Poor Prognostic Marker in Lung Adenocarcinoma But Not in Squamous Cell Carcinoma

Ping-Li Sun1,2, Yan Jin1,2, Hojin Kim1,2, Sanghoon Jheon1,2, Choon-Taek Lee1,2, Jin-Haeng Chung1,2

Departments of Pathology, 1Thoracic and Cardiovascular Surgery, and 2Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Background: Survivin is a member of the inhibitors of apoptosis and frequently overexpressed in various cancer cells. Data from the previous studies on the clinicopathologic implication of survivin in non-small-cell lung carcinoma (NSCLC) are inconsistent. Methods: We investigated the expression of survivin in 373 cases of surgically resected NSCLC. Correlations between the expression of survivin and clinicopathologic, molecular features and prognostic significance were analyzed. Results: In adenocarcinoma, the increased expression of survivin was associated with the presence of vascular invasion, lymph node metastasis and tumor recurrences, but we didn’t find any correlation with survivin expression and clinicopathological parameters in squamous cell carcinoma. Patients with high survivin expression had significantly shorter disease-free survival (DFS: 42.2 months vs 58.8 months; \( p = 0.001 \)) and shorter overall survival (OS: 60.8 months vs 71.5 months; \( p = 0.009 \)) than those with low survivin expression group in adenocarcinoma. In squamous cell carcinoma, the expression of survivin was not associated with prognosis of the patients (DFS: 48.9 months vs 48.7 months; \( p = 0.837 \) and OS: 61.0 months vs 62.4 months; \( p = 0.771 \)). Multivariate analysis confirmed that survivin was an independent poor prognostic factor in adenocarcinoma (DFS: hazard ratio [HR], 1.687; 95% confidence interval [CI], 1.123 to 2.532; \( p = 0.012 \) and OS: HR, 1.965; 95% CI, 1.108 to 3.486; \( p = 0.021 \)). Conclusions: Our results suggest that survivin is an independent negative prognostic factor in adenocarcinoma, but not in squamous cell carcinoma. The role of survivin should be investigated separately based on histologic subtypes.

Key Words: Carcinoma, non-small cell lung; Prognosis; Apoptosis; Survivin

Increased Expression of Cell-Cycle and Inhibitor of Apoptosis Pathway Markers Is Associated with Solid Predominant Subtype of Lung Adenocarcinoma

Soo Young Chung, Joo Yeon Song, Min Suk Kim

Department of Pathology, Dongnam Institute of Radiological and Medical Sciences, Busan, Korea

Background: The 2011 International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) Lung Invasive Adenocarcinoma Classification included five growth patterns: lepidic, acinar, papillary, micropapillary, and solid predominant type. Clinically, solid predominant type of adenocarcinoma exhibits more malignant behavior and has a poorer prognosis. But, solid predominant type of adenocarcinoma in biopsy specimens can be very difficult to diagnosis. The purpose of this study was to evaluate immunohistochemistry panel for a distinction between solid predominant type and other type in surgically resected and matched biopsy specimens. Methods: We studied 87 consecutive cases of surgically resected and matched biopsy specimens. Primary antibodies used for immunostaining were cell-cycle pathway marker (Ki-67), inhibitor of apoptosis pathway markers (XIAP, survivin) and epithelial-mesenchymal transition marker (E-cadherin). Results: Solid predominant type of adenocarcinoma was significantly correlated with high expression of Ki-67 (100% vs 14% for solid type/other type), XIAP (91% vs 13% for solid type/other type), and survivin (80% vs 15% for solid type/other type). Solid predominant type of adenocarcinoma was not associated with epithelial-mesenchymal transitional marker. However, solid predominant type of adenocarcinoma tended to show more frequent lymph node metastasis regardless of T stage. Conclusions: The concordance rate of cell-cycle and inhibitor of apoptosis pathway markers between surgical samples and biopsy samples was strong.

Key Words: Adenocarcinoma, bronchiolo-alveolar; X-linked inhibitor of apoptosis protein; Ki-67 antigen; Epithelial-mesenchymal transition

An Unusual Case of Bronchial Mucous Gland Adenoma with Fibromyxoid Stroma and Cartilage Islands in a 68-Year-Old Aged Woman

Boram Lee, In Ho Choi, Jungho Han, Kyung Soo Lee, Young Mog Shim

Departments of Pathology, Radiology, and Thoracic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Pulmonary mucous gland adenoma is very rare neoplasm arising from the bronchial mucus glands, which is composed of unique seromucinous glands and it arise bland looking, basally located nuclei. The cartilage and hamartoma-like stroma in mucous gland adenoma is not reported in English literature, to our best knowledge. We, herein, report a case of bronchial mucous gland adenoma with fibromyxoid stroma and cartilage islands in a 68-year-old aged woman. The patient visited due to incidental pulmonary mass. Radiologically, it is located at the peripheral area of right upper lobe, measuring about 3 cm. Microscopic finding of wedge resected mass reveals multiple mucus glands that were surrounded by myxoid stroma with several lobules of cartilage. The glands had single layer of seromucinous epithelial cells without cellular atypia or identifiable foci of invasion. The stroma had scattered small spindle cells and well circumscribed lobule of cartilages on myxoid background. No mitotic figure was observed. The patient is alive and well after 5 months since operation.

Key Words: Lung neoplasms; Adenoma; Adenoma, pleomorphic; Cartilage
A Comprehensive Comparative Analysis of the Histomorphological Features of Anaplastic Lymphoma Kinase-Rearranged Lung Adenocarcinoma Based on Driver Oncogene Mutations

Hye Jin Kim1;2 ∙ Se Jin Jang2 ∙ Doo Hyun Chung1;2 ∙ Seol Bong Yoo2 ∙ Pingli Sun1
Yan Jin1;2 ∙ Jin-Haeng Chung1;2

1Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam; 2Department of Pathology, Seoul National University College of Medicine; 3Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; 4Department of Pathology, Presbyterian Medical Center, Jooenju, Korea

Background: Molecular classification of lung cancer correlates well with histomorphological features. However, specific histomorphological features that differentiate anaplastic lymphoma kinase (ALK)-rearranged tumors from ALK-negative tumors have not been fully evaluated. Methods: Eighty ALK-rearranged and 213 ALK-negative (91 epidermal growth factor receptor-mutated; 29 K-ras-mutated; 93 triple-negative) resected lung adenocarcinomas were analyzed for several histomorphological parameters and histological subtype. Results: ALK-rearranged tumors were associated with younger age at presentation, frequent nodal metastasis, and higher stage of disease at diagnosis. ALK-rearranged tumors were more likely to show a solid predominant pattern than ALK-negative tumors (p<0.001). Unlike ALK-negative tumors, a lepidic predominant pattern was not observed in ALK-rearranged tumors (p=0.001). In multivariate analysis, the most significant morphological features that distinguished ALK-rearranged tumors from ALK-negative tumors were cribiform formation (odds ratio [OR], 3.253; p=0.028), presence of mucin-containing cells (OR, 4.899; p=0.008), close relationship to adjacent bronchioles (OR, 5.361; p=0.001), presence of psammoma bodies (OR, 4.026; p=0.002), and a solid predominant pattern (OR, 13.685; p=0.023). Conclusions: ALK-rearranged tumors exhibited distinct clinicopathological and morphological features. These clinicopathological and morphological features may serve as clinical enrichment factors to help oncologists and pathologists detect ALK rearrangement in lung adenocarcinoma patients.

Key Words: Anaplastic lymphoma kinase; Histology; Lung neoplasms; Adenocarcinoma

Serum MicroRNAs Associated with Lung Adenocarcinoma with Bone Metastasis

Chang Hun Lee1 ∙ Dong Hoon Shin1 ∙ Mi Hyun Kim2 ∙ Min Ki Lee1 ∙ Shine Young Kim2

1Departments of Pathology, Internal Medicine, and Laboratory Medicine, Pusan National University School of Medicine, Busan, Korea

Background: Lung cancer metastases to the bones lesions may be overlooked and often are not diagnosed until they manifest as bone pain or skeletal-related events. Serum microRNAs (miRNAs) as a non-invasive blood-based biomarker for cancer patients play a role in regulating a variety of targets which make them a powerful tool for early diagnosis of disease, risk assessment, and prognosis. Methods: We investigated serum miRNAs that may serve as biomarkers to differentiate between lung adenocarcinoma patients with and without bone metastasis. Five miRNAs associated with metastasis (miR-21, miR-146a, miR-148a, miR-328, and miR-378) were selected through literature review. We examined these serum miRNAs concentrations by quantitative real-time reverse transcription-polymerase chain reaction from clinically matched 19 patients with bone metastasis and 13 without bone metastasis. Results: The initial analysis showed that miRNAs were stable and detectable in all serum samples. The serum concentrations of miR-21, miR-146a, and miR-378 were significantly higher in bone metastasis than no bone metastasis (p=0.037, p=0.041, and p=0.037, respectively). The values of the area under the receiver-operating characteristic curve were 0.721 for the miR-21 assay (p=0.023), 0.717 for the miR-146a assay (p=0.027) and 0.721 for the miR-378 (p=0.032). There were no significant differences in the concentrations of miRNAs according to the status of other metastatic site. Conclusions: The present study suggests that circulating serum miRNAs may be a specific indicator of bone metastasis detection in advanced lung adenocarcinoma. Further large-sampled studies will be required to validate the definite role of serum miRNAs and related metastatic sites.

Key Words: Lung adenocarcinoma; Bone metastasis; Serum microRNAs

Four Rare Cases Showing Ground Glass Opacities on Chest Computed Tomography

Hye In Ahn1, Hyun Sung Kim1, Ju Yeon Pyo2, Yong Wook Park2, Young-Ha Oh2

1Department of Pathology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

Ground glass opacities (GGO) on chest computed tomography (CT) can be detected in variable lung diseases. We have experienced 4 rare cases presenting as GGO, which were very tough to make an accurate diagnosis. A 31-year-old woman presented with exertional dyspnea. A CT scan showed numerous small nodules in both lungs with mediastinal lymphadenopathies. Biopsy showed multifocal small, non-casing granulomas engulfling refractile foreign bodies, which can be considered early stage of occupational pneumonia. A 54-year-old non-smoking male patient showed multiple lung nodules increasing in size for 2 years on chest X-ray. She had a history of a resection of the desmoid tumor in abdominal wall 15 years ago. Biopsy from lung nodules showed bland spindle cells in the fibromyxoid stroma, consistent with fibromatosis. A 46-year-old non-smoking woman was diagnosed with asthma 1 year ago and had been treated with inhaled corticosteroid. She admitted our hospital for aggravating dyspnea under the impression of pneumonia. Biopsy showed accumulation of intra-alveolar cosinophils and eosinophilic vasculitis, which can be diagnosed with Churg-Strauss syndrome, based on clinicopathologic findings. A 73-year-old female patient has been suffered from mild fever and cough. Her CT showed multiple nodular consolidations in right lung. Biopsy revealed tiny interstitial aggregates of meningothelial-like cell lesions, positive for vimentin and epithelial membrane antigen. In conclusion, histologic examination is still the golden standard for the diagnosis of many forms of lung lesions, leading clinicians to treat the patients accurately.

Key Words: Lung; Multiple pulmonary nodules; Biopsy
Transcription Factors Associated with Epithelial-Mesenchymal Transition in the Microenvironment of the Primary Lung Adenocarcinoma

Young-In Maeng · Min-Kyung Kim · Sun-Jae Lee · Woo-Jung Sung · Hoon-Kyu Oh Kwan-Kyu Park

Department of Pathology, Catholic University of Daegu School of Medicine, Daegu, Korea

Background: The tumor microenvironment has many roles involving tumor progression, invasion and metastasis. The tumor cells at the tumor border lose epithelial properties and acquire mesenchymal features. This, epithelial-to-mesenchymal transition (EMT) has been suggested to be an important process for tissue and lymphovascular invasion. Methods: Pulmonary tissue samples from 23 patients with primary adenocarcinoma were evaluated with using immunohistochemical and immunofluorescence multi-staining the EMT-associated markers and transcription factors. The data were analyzed in specific area; such as tumor center, tumor border, and uninvolved lung parenchyma. Results: In this study we show that transcription factors associated with EMT markers Snail, Slug, Twist, and Zeb1 are differentially expressed between normal and invasive cancer. The invasive adenocarcinoma expressed less Slug and Twist and more Zeb1 and it was associated with the loss of epithelial marker (E-cad) and gaining of mesenchymal marker (smooth muscle actin) at the invasive border of lung carcinoma. The process of EMT has been suggested to be of prime importance for tissue and lymphovascular invasion. Conclusions: The process of EMT may be activated in the tumor border of lung adenocarcinoma. Related transcription factors, such as snail and zeb-1, might be induced by paracrine effects of surrounded inflammatory cells and fibroblasts. Furthermore, our data show that transcription factors might be induced by inflammation, increasing metastatic potential of lung cancer cells. As our understanding of the underlying molecular processes in primary lung adenocarcinoma develops, elucidation of these interactions will be central to development of novel therapeutic strategies.

Key Words: Lung neoplasms; Tumor border; Tumor microenvironment; Epithelial-mesenchymal transition; Adenocarcinoma

Immunohistochemistry of Epidermal Growth Factor Receptor (EGFR) Mutation-Specific Antibodies for Detection of EGFR Mutation Status in Lung Adenocarcinoma: A Comparison with Direct Sequencing Analysis

Mi Jin Kim · Eun Wha Lee · Kyeong Cheol Shin · Gwan Ho Lee

Departments of Pathology and Internal Medicine, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu, Korea

Background: Mutation analysis of epidermal growth factor receptor (EGFR) has become the best predictor of the response to tyrosine kinase inhibitors therapy in primary lung adenocarcinoma. Direct sequencing has been usually assessed for the detection of EGFR mutations. Recently, monoclonal antibodies specific to EGFR mutations were introduced. This study is performed using two major forms of mutation-specific antibodies for exon 19 and exon 21 to compare with direct sequencing. Methods: Tissue microarrays were constructed for 116 resected lung adenocarcinoma samples. We performed an immunohistochemical (IHC) analyses using two EGFR mutation-specific antibodies, E746-A750 deletion (anti-EGFR E746-750del [sp111]) and L858R mutation (anti-EGFR L858R [sp125]). EGFR stains were scored as negative (0), 1+ (weak and focal), 2+ (moderate and focal), and 3+ (strong and diffuse), with reference of EGFR PharmDx guideline. EGFR mutation was detected by direct DNA sequencing method. Results: Of total 116 samples of lung adenocarcinoma, direct sequencing identified EGFR mutations in 45 cases (39%). IHC staining with exon 19 and exon 21-specific antibody was seen in 8 out of 19 cases (42%) with E746-A750del and 11 of 23 cases (48%) of L858R mutation, based on sequencing results. Sensitivity, specificity, positive predictive value, and negative predictive value of these two antibodies were 76%/79%, 90%/87%, 85%/80%, and 84%/86%, respectively. Conclusions: The mutation-specific immunohistochemical assay showed good correlation with direct sequencing in this study. The cases with of score 3+ in both antibodies were 100% mutated. Immunohistochemistry for specific mutated EGFR antibodies demonstrated promising results for a reliable screening of patients in lung adenocarcinoma.

Key Words: Lung; Adenocarcinoma; EGFR antibody; EGFR sequencing

Basaloid Squamous Cell Carcinoma of the Lung with Low-Grade Features Presenting as an Endobronchial Tumor

Aiko Ishii1 · Satoshi Ota2 · Yoko Yonemori1 · Junji Morimoto3,4 · Ichiro Yoshino3
Mari-Mino Kenudson · Eugene Jerome Mark1 · Yukio Nakatani1,2

Departments of 1 Diagnostic Pathology and 2 Pathology, Chiba University Hospital; 3 Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan; 4 Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Basaloid squamous cell carcinoma is a high-grade neoplasm and no low-grade counterpart has been reported to the best of our knowledge. A 56-year-old male presented with bloody sputum. The chest X-ray revealed an abnormal shadow in the left upper lung field. The tumor showed fluorescence uptake activity on a positron emission tomography scan. A transbronchial biopsy from the tumor mass filling the B1+2a bronchus revealed a monotonous and uniform basaloid cell proliferation with pseudopapillary and peripheral palisading growth patterns. The patient underwent left upper lobectomy and is currently free of disease 7 months postoperatively. Macroscopically, the resected specimen showed a 2.7 cm whitish solid tumor fully occupying the bronchi al lumen, further extending from B1+2a to its peripheral bronchi, bronchioles and some alveolar walls. Microscopically, the tumor cells were small to medium-sized with high nuclear/cytoplasmic ratios, and had round to oval nuclei with a condensed chromatin pattern, resembling basal cells. The cells were arranged in a pseudopapillary pattern with well-developed vasculature and a lobular pattern with prominent peripheral palisading. Some areas showed tumor cells with eosinophilic cytoplasm and intercellular bridges. The basic histologic appearance resembled ameloblastoma. No keratin pearls were observed. Mitotic activity was low and tumor necrosis was not seen. Immunohistochemi-
peripheral low-grade mucoepidermoid carcinoma of the lung.

**Key Words:** Carcinoma, bronchogenic; Carcinoma, squamous cell; An-ebloblastoma like features

**AP19-PP-0022**

Detection of Epidermal Growth Factor Receptor (EGFR) Mutation in Lung Adenocarcinoma: Comparison of Immunohistochemistry Using Novel EGFR-Mutation Specific Antibodies and Direct Sequencing

Seog Yun Park · Geon Kook Lee · Jiun Choi

Department of Pathology, National Cancer Center of Korea, Goyang, Korea

**Background:** Mutations in epidermal growth factor receptor (EGFR) are the best predictors of response to tyrosine kinase inhibitor therapy in patients with lung adenocarcinoma and most pathologists have used DNA-based methods to assess EGFR status. Recently, the detection method of EGFR mutation using EGFR specific monoclonal antibodies have newly developed and reported. The aim of our study was to evaluate and compare the methods of immunohistochemistry using EGFR mutation-specific antibodies and DNA sequencing for determination of EGFR mutation status.

**Methods:** Eighty seven primary lung adenocarcinomas with formalin-fixed paraffin embedded tissue samples were analyzed for EGFR mutations in exon 18, 19, 20, and 21 by direct DNA sequencing and immunohistochemistry was performed with the rabbit monoclonal antibodies E746-A750del and L858R. Re-

**AP19-PP-0020**

Genomic Copy Number Signatures Uncovered Genetically Distinct Group Which Is Different from Adenocarcinoma and Squamous Cell Carcinoma of the Lung Cancer

Eunjung Lee · Ji-Yun Lee1 · Bong Kyung Shin · Han Kyeom Kim

Department of Pathology, Korea University Guro Hospital, 1Korea University College of Medicine, Seoul, Korea

**Background:** Adenocarcinoma (AC) and squamous cell carcinoma (SCC) have different clinical presentation, morphology, treatment and prognosis. Recent studies suggested that fundamental genetic alterations related to carcinogenesis of each tumor type may be different. In this study, we evaluate the difference of genetic alteration of ACs and SCCs that may can be applied for diagnosis of non-small cell lung carcinoma (NSCLC).

**Methods:** We have investigated genomic alterations of total 50 primary NSCLC samples (25 ACs and 25 SCCs) as well as paired normal tissue using whole genomic array comparative genomic hybridization. Common copy number alterations (CNAs) were evaluated in each subtypes and compared each other to establish CNA signatures.

**Results:** Total CNAs were more frequently identified in SCCs than ACs. The most common gain was gain of 3q in SCCs and 7q in ACs. Forty-four genes from SCCs and 28 genes from ACs were located in the commonly gained and lost region in more than 68% of cases. The results of non-supervised hierarchical clustering with combined AC and SCC revealed three clustered groups—AC group, SCC group and genetically distinct another group which overlapping AC and SCC.

**Conclusions:** The present study contributed to the molecular biological characterization of AC and SCC of lung which showed subtype of tumor has unique genetic CNA uncovered by high resolution comparative genomic hybridization. We identified genetically distinct three groups by clustering of AC and SCC. The further study about significance of these distinct three groups is necessary. Identified CNAs can be used as diagnostic or therapeutic markers in the future.

**Key Words:** Carcinoma, mucoepidermoid; Lung; Biopsy, fine-needle; Cytology

**AP19-PP-0021**

Peripheral Low-Grade Mucoepidermoid Carcinoma of the Lung Misinterpreted as Adenocarcinoma: A Case Report

Heae Sung Park · Soon Won Hong

Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Mucoepidermoid carcinoma of the lung is a rare tumor mostly arising centrally, and is not usually considered in the differential diagnosis of a peripheral lung mass. It is important to differentiate low-grade mucoepidermoid carcinoma of the lung from pulmonary adenocarcinoma, for the former can be cured by surgical resection alone. We report a case of peripheral low-grade mucoepidermoid carcinoma of the lung which was misinterpreted as adenocarcinoma in preoperative fine needle aspiration (FNA). A 58-year-old female was referred due to an incidentally found solitary pulmonary nodule. Percutaneous FNA of the lesion was performed. Cytological features showed moderate cellularity on the clean background. There were some clusters of polygonal cells with nuclear overlapping and papillary configuration. Tumor cells had moderate amount of eosinophilic cytoplasm and increased nucleocytoplasmic ratio. The tumor nuclei were round to oval, centrally located and showed finely granular and hyperchromatic chromatin with smooth nuclear membranes and small nucleoli. The patient underwent segmentectomy. The cut surface displayed a well-defined nodule. Histological examination showed a protruding mass within the subsegmental bronchus. Gland formation and intraluminal mucin production were observed. After immunohistochemical and special stains, the tumor was finally diagnosed as low-grade mucoepidermoid carcinoma. Diagnosis of mucoepidermoid carcinoma can be achieved with cytology specimens when epidermoid, intermediated, and mucus-secreting cells coexist. The presenting case was low-grade mucoepidermoid carcinoma with mainly intermediate cells. Correct diagnosis of such case by FNA can be challenging. However, lack of nuclear pleomorphism and mild atypia might suggest low-grade mucoepidermoid carcinoma rather than adenocarcinoma.

**Key Words:** Carcinoma, bronchogenic; Carcinoma, squamous cell; Mucosa-oid squamous tumors in the lung.
Key Words: EGFR mutations; Mutation-specific antibody; Immunohistochemistry; Lung; Adenocarcinoma

Lepidic Growth Pattern in Pulmonary Metastasis from Adenoid Cystic Carcinoma of the Trachea: A Rare Case Report
Yuko Endo1, Yuichi Saito1, Eisaku Miyachi2, Hironori Ninomiya2, Noriko Motoi3, Toshimasa Ohtani1, Masayuki Nakao1, Hirofumi Uehara4, Mingyong Mum5, Sakae Okumura1, Ken Nakagawa1, Yuichi Ishikawa1
Division of Pathology, The Cancer Institute, Tokyo; 1Thoracic Oncology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto, Japan

A lepidic growth pattern of the primary lung adenocarcinomas is a characteristic feature of adenocarcinoma in situ. The lepidic pattern is detected as ground-glass opacity (GGO) on chest computed tomography (CT). So, GGO is usually a marker of primary lung tumors. Rarely, however, tumors metastatic to the lung exhibit a lepidic pattern, which raises a problem of differential diagnosis by CT. We report here a case of pulmonary metastasis of adenoid cystic carcinoma (ACC) arising in the trachea. A 59-year-old Japanese woman suffered from a tracheal ACC and underwent total laryngectomy. Three years after the surgery, we found three pulmonary nodules in the right lower lobe of lung on chest CT, two of which had a GGO component and therefore were suspected to be primary while the other solid lesion was thought to be metastatic. Wedge resection was performed thorascopically. Tumor cells of the two nodules with a lepidic pattern were negative for thyroid transcription factor-1, so turned out to be metastatic. One year later, a new nodule, “a pure GGO” lesion, was detected in the left lower lobe of lung on CT and followed up for half a year. During the period, the pure GGO lesion changed to a “mixed GGO” lesion, i.e., with both a solid and a GGO area, radiologically. So, the lesion was suspected to be malignant and lobectomy was performed. Histologically, the tumor was again metastatic. We should keep in mind a possibility that metastatic ACCs might show a lepidic growth pattern histologically.

Key Words: Pulmonary metastasis; Lung neoplasms; Lepidic growth; Carcinoma, adenoid cystic

A Case of Pulmonary Epithelioid Hemangioendothelioma with a Histological and Clinical Progression That Lead to Poor Outcome
Asuka Kurosawa1, Satoshi Ota2, Kazusa Takekaki2, Michiyoh Kanbe1, Yoko Yonemori1, Ichiro Yoshino1, Yukio Nakatani2
Departments of 1Diagnostic Pathology, 2Pathology, and 3General Thoracic Surgery, Chiba University Hospital, University Graduate School of Medicine, Chiba, Japan

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare endothelial neoplasm that typically presents as multiple nodules with an indolent course but may occasionally show rapid growth and poor prognosis. Here we report a case of PEH with a rapid progression and poor outcome after a stable clinical course. Chest X-ray examination of a 70-year-old male who was diagnosed as having gastric cancer revealed multiple lung nodules, which were thought to be inflammatory in nature. After 30 months’ follow-up with no significant change, a 5 mm-nodule in the left S8 increased to 18 mm in size. The patient underwent...
excisional biopsy of a few nodules including the S8 lesion. Grossly, the smaller nodules were white and well-defined, whereas the S8 lesion was greyish white and somewhat poorly circumscribed. Microscopically, the smaller nodules displayed the typical histology of PEH with mildly atypical epithelioid cells embedded in the hyaline matrix, while the S8 lesion showed closely packed pleomorphic cells with prominent nucleoli and common mitotic figures (2/HPF). The Ki-67 labeling index was under 5% in the smaller nodules and over 40% in the S8 lesion. p53 protein was more strongly and diffusely expressed in the main lesion. These findings suggested the progression of malignant potential in one of the PEH nodules. Ten months after the biopsy, pleural effusion with positive cytology developed and the patient succumbed to death. The present case demonstrates the histological progression may reflect an increase of malignant potential in PEH and calls for further investigation in the underlying molecular mechanism.

**Key Words:** Lung; Hemangioendothelioma, epithelioid; Multiple pulmonary nodules; Pleural effusions, malignant

**AP19-PP-0027**

**ALK Fusion Gene in Small Cell Lung Cancer**

Kenichi Taguchi, Gouji Toyokawa, Mitsuhiro Takenoya, Ryo Toyozawa, Eiko Inamasu, Miyako Kojo, Yoshimasa Shiraihi, Yousuke Morodomi, Tomoyoshi Takenaka, Fumihiko Hirai, Masafumi Yamaguchi, Takashi Seto, Mototsugu Shimokawa, Yukito Ichinose

Cancer Pathology Laboratory, Institute for Clinical Research, National Kyushu Cancer Center; 2Department of Thoracic Oncology, National Kyushu Cancer Center; 3Cancer Information Research, Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan

**Background:** Anaplastic lymphoma kinase (ALK) fuses echinoderm microtubule-associated protein-like 4 (EML4) to acquire a transforming activity in lung adenocarcinomas. However, the presence of an EML4-ALK fusion gene in other lung cancer histological type is an extremely rare phenomenon. **Methods:** We analyzed 30 consecutive patients with small cell lung cancer (SCLC) for EML4-ALK by reverse transcription polymerase chain reaction and immunohistochemistry. **Results:** Our analysis of 30 consecutive patients with SCLC for EML4-ALK revealed that two patients, including a patient we previously reported, harbored the EML4-ALK fusion gene. **Conclusions:** Although the frequency and significance of the fusion gene in SCLC patients has not been determined, this phenomenon suggests that SCLC patients harboring the EML4-ALK fusion gene can be successfully treated with ALK inhibitors.

**Key Words:** Small cell lung carcinoma; Oncogenic driver mutation; EML4-ALK fusion protein, human

**AP19-PP-0029**

**PBK/TOPK Expression in Non-small Cell Lung Cancer: Its Correlation and Prognostic Significance with Ki-67 and p53**

Hong Shen, Bin Lei

Department of Pathology, Nanfang Hospital, Southern Medical University, Nanjing, China

**Background:** This study is to evaluate the prevalence and prognostic significance of PDZ-binding kinase/T-LAK cell-originated protein kinase (PBK/TOPK) and its correlation with Ki-67 and p53 in non-small cell lung cancer (NSCLC). **Methods:** We detected the expression of PBK/TOPK in 30 normal lung tissues, 32 lymph-node metastases, and 279 primary tissues of non-small cell lung cancer, and investigated the correlation between PBK/TOPK and Ki-67/p53 in the primary tissues of NSCLC by immunohistochemistry. **Results:** The results showed that there were obvious differences (p<0.000) about PBK/TOPK expression in different tissues, with a higher expression in lymph-node metastases than those that in primary tumor and normal lung tissue. The expression of PBK/TOPK was associated with histological type, lymph node metastasis and TNM stage (p<0.05), also positively correlated with the expression of Ki-67/p53 (p<0.05) in NSCLC. The high expression of PBK/TOPK, Ki-67 or p53 was significantly associated with the poor prognosis (p<0.05), and all of them could be as independent predictive factors in NSCLC (p<0.05). Furthermore, the prognosis of patients with high expression for both PBK/TOPK and Ki-67 or both PBK/TOPK and p53 were significantly unfavorable (p<0.05). **Conclusions:** PBK/TOPK is an independent prognostic factor and positively correlates with Ki-67 and p53 in NSCLC.

**Key Words:** Carcinoma, non-small-cell lung; PDZ-binding kinase; Ki-67 antigen; Tumor suppressor protein p53; Correlation

**AP19-PP-0030**

**Retrospective Study of Clinicopathologic Features of 87 Cases of Lung Adenocarcinoma**

Thong Minh Tran, Duyen Hoa Le, Bich Na Thi Pham

Department of Pathology, Cho Ray Hospital, Ho Chi Minh City, Vietnam

**Background:** Lung cancer is the leading cause of cancer death for both men and women. It is among the most lethal, accounting for about 29% of all cancer deaths. Tobacco is the leading cause of lung cancer. **Methods:** This descriptive study was carried out in the Department of Pathology, Cho Ray Hospital, Ho Chi Minh City, Vietnam. 87 consecutive histopathologically confirmed cases of bronchogenic adenocarcinoma were included in the study. **Results:** Total of 150 consecutive new cases of primary cancer of the lung were diagnosed in Cho Ray Hospital. Of these, 87, 36, 13, and 14 patients were histologically classified as adenocarcinoma, squamous cell, large cell, non-small cell, and small cell lung cancer. Adenocarcinoma was the most common type. Our study group included 53 male and 34 female patients aged between 32 to 88 years with mean age of 60.06 years. Fifty-two point eight three percent of male patients were smokers. Although 4.6% of patients with bronchial carcinoma were identified while they were asymptomatic, usually as a result of a routine chest radiograph or through the use of screening computed tomographic scans, most patients presented with some signs or symptoms. The most frequent presenting symptoms were persistent cough and chest pain, 65.52% and 57.47%, respectively. **Conclusions:** Persistent cough and chest pain are the most important clinical symptoms of adenocarcinoma, especially in patients who have smoking habit and/or exposure to environmental risk factors. Our experience...
with this series of adenocarcinoma patients should help physicians have further insights into the clinical characteristics of those with adenocarcinoma of the lung.

**Key Words:** Lung neoplasms; Adenocarcinoma, squamous cell

---

**Retrospective Study of Histopathological Features and Epidermal Growth Factor Receptor Mutations of 116 Non-small Cell Lung Cancer Cases**

*Nghia Trong Doan · Thong Minh Tran · Van Hung Pham 1*

Department of Pathology, Cho Ray Hospital; 1Department of Biology, Nam Khoa Biotek Company, Ho Chi Minh City, Vietnam

**Background:** Lung cancer is the most frequently diagnosed cancer and the most common cause of death due to malignant tumors. There are two main types of lung cancer including non-small cell lung cancer (NSCLC) and small cell lung cancer. First-line treatment of the advanced NSCLC often involves platinum-based combination chemotherapy but this treatment continues to be restricted. However, in patients with NSCLC and activating mutation of the epidermal growth factor receptor (EGFR), targeted treatment has undergone a significant change. Testing for mutations in EGFR is therefore an important step in the treatment-decision pathway. **Methods:** To evaluate the histopathological features and EGFR mutations of 116 bronchial non-small cell carcinoma cases that were diagnosed at Cho Ray Hospital between June 2010 and February 2012. **Results:** Our study group included male and female with ratio 1.8/1, patients aged between 40 to 69 years with mean age of 55 years. Percentage of EGFR mutations is 54.3%. Mutations were more frequently found in women (66%) and in those with adenocarcinoma (54%). The most common mutations were deletions in exon 19 (38%) and L858R in exon 21 (27%). **Conclusions:** Testing for mutation in EGFR is crucial one and should be done routinely. **Key Words:** Primary bronchial carcinoma; Bronchial non-small cell carcinoma; EGFR mutations