also positive for desmin and h-caldesmon, suggesting that a fraction of these cells have a smooth muscle-like phenotype. In mixed adenocarcinoma with a BAC component, subepithelial myofibroblasts were present in the BAC componenet, but there seemed to be a gradual loss of a typical subepithelial pattern of myofibroblasts in invasive areas; they either disappeared partially or formed concentric layers of myofibroblasts around cancer cell nests. In most cases of frankly invasive adenocarcinoma, subepithelial myofibroblasts were absent and bundles of myofibroblasts emerged in cancer stroma. To further characterize the relationship to stromal invasion, we immmunostained adjacent sections for laminin-1 and collagen type 4 to highlight basement membranes, and then compared the results with smooth muscle α-actin staining. As expected, stromal invasion was associated with disruption of basement membranes and loss of a typical subepithelial pattern of myofibroblasts. Interestingly, however, a subset of invasive adenocarcinomas partially retained subepithelial myofibroblast, and survival analysis showed that invasive tumors with partial retention of subepithelial myofibroblasts were associated with low rates of lymphatic and vascular invasion, lymph node involvement, and better patient survival.

Conclusions: The results of this study suggest that subepithelial myofibroblasts occur in bronchiolo-alveolar carcinomas, but they were gradually replaced by typical stromal myofibroblasts during progression into invasive cancer. A subset of invasive adenocarcinomas retains subepithelial myofibroblasts. Analysis of subepithelial myofibroblasts may be helpful in defining a subset of lung adenocarcinoma with good prognosis.

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Low risk subgroup identification in stage IB lung adenocarcinoma patients

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Background: Several researchers have reported the efficacy of adjuvant chemotherapy in resected stage IB non-small cell lung cancer (NSCLC) patients. Due to the considerable variation in histological findings and outcomes of stage IB lung adenocarcinoma, it appeared there were unidentified subgroup factors. These factors affect treatment recommendations and choices. Identifying patients who do not need adjuvant chemotherapy saves patient stress and medical resources. This study's aim was to investigate resected stage IB adenocarcinoma patient prognostic factors and identify a subgroup with a better outcome, where adjuvant chemotherapy might not be beneficial and needed.

Methods: We reviewed records of 413 consecutive stage I lung adenocarcinoma patients who underwent complete surgical resection and systematic lymph node dissection at the National Cancer Center Hospital East from July 1992 through March 2000, to find 106 stage IB patients for prognostic factor investigation. We evaluated four clinical factors: gender, age (<70 vs. ≥70 years), smoking history (positive vs. negative), and serum carcinoembryonic antigen (CEA) level (<5 vs. ≥5 ng/ml). Seven pathological factors were also evaluated: maximum tumor diameter (<5 vs. ≥5 cm), differentiation grade (well vs. moderately or poorly differentiated), lymphatic permeation (positive vs. negative), vascular invasion (positive vs. negative), pleural invasion (positive vs. negative), and bronchioloalveolar carcinoma (BAC) component dominance (positive vs. negative). BAC component dominance was considered positive if the histological evaluation found half or more of the tumor consisted of a BAC component. A subgroup with better outcomes was identified and their survival compared with that of all stage IA patients who underwent surgical resection during the same period.

Results: The 5-year survival rate of all the stage IB lung adenocarcinoma patients was 81.7%. Univariate analyses found lymphatic permeation ($p<0.001$), vascular invasion ($p=0.003$), pleural invasion ($p=0.001$) and BAC-dominant histology ($p=0.003$) were significant unfavorable prognostic factors. A multivariate analysis demonstrated positive pleural invasion ($p=0.02$) was an independent unfavorable prognostic factor. The stage IB lung adenocarcinoma patients 5-year survival rate with and without pleural invasion of 63% and 89%, respectively shows the invasion factor impact. Additionally, stage IB adenocarcinoma patients without pleural invasion overall survival rate was very similar to that of stage IA patients (92.7%; $p=0.78$).

Conclusions: Pleural invasion is a factor that should be considered before recommending adjuvant chemotherapy to stage IB lung adenocarcinoma patients. The outcome for stage IB lung adenocarcinoma patients without pleural invasion is almost identical to stage IA patients where adjuvant chemotherapy has not shown an advantage. Adjuvant chemotherapy probably is not necessary or beneficial for stage IB patients without pleural invasion.

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Correlation between morphology and epidermal growth factor receptor mutations in lung adenocarcinomas; significance of hobnail cell type and micropapillary pattern

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The presence of epidermal growth factor receptor (EGFR) tyrosine kinase (TK) mutations significantly correlates with tumor sensitivity to tyrosine kinase inhibitor. Importantly, this mutation underlies responsiveness of the most predominant histologic subtype, adenocarcinoma. To clarify the correlation with EGFR mutations and pathological findings of adenocarcinomas of Japanese patients, detailed pathological features of the tumor were examined. Total of 107 surgically resected adenocarcinomas were investigated. Seventeen cases treated with gefitinib for relapse were included. We reviewed medical records, pathology slides and examined EGFR mutations in exon 18-21. EGFR mutations were found in sixty five (60.7%) patients and detected in all four exons. EGFR mutations were significantly associated with female gender ($P<0.01$), non-smoker status ($P<0.05$), hobnail cell type dominancy ($P<0.0001$), and papillary subtype (<0.0001). In addition, detailed pathological examination represented that the existence of bronchioloalveolar carcinoma (BAC) and micropapillary pattern (MPP) component was significantly associated with EGFR mutations ($P<0.05$ and <0.05, respectively). In seventeen patients with gefitinib treatment,