Editorial

Prognostic contribution of non-predominant solid and micropapillary components in lung adenocarcinomas

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Lung cancer is the leading cause of cancer-related mortality worldwide, and adenocarcinoma is the most common histological type of lung cancer. Most cases of lung adenocarcinomas have mixed histological patterns, which were histopathologically diagnosed as "adenocarcinoma, mixed subtype" in the World Health Organization (WHO) classification of 2004 (1). However, in 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) proposed a new classification in which major histological patterns (lepidic, acinar, papillary, solid, and micropapillary) and variants (mucinous, colloid, enteric, and fetal adenocarcinoma) were defined, and recommended that lung adenocarcinomas should be classified according to their predominant subtypes, after identification and quantification of all histological patterns in the tumor in 5% increments (2). This classification of lung adenocarcinoma was adopted in the new WHO classification in 2015 (3).

Several issues still need to be resolved in the classification, including the prognosis of major histological patterns and variants. The relationship between prognosis and rare variants has been less examined (4,5), and past studies (6-9) have focused primarily on the relationship between prognosis and major histological patterns. These studies examined the relationship between prognosis and classification, and indicated that patients with lepidic predominant adenocarcinomas had the most favorable outcome of all subtypes of invasive lung adenocarcinoma. In contrast, lung adenocarcinoma with solid and micropapillary predominant subtypes was reported to have a poor prognosis. The results obtained in these studies support the significance of the novel classification according to predominant subtypes. However, the evaluation of patients with lung adenocarcinoma that contains non-predominant solid and/or micropapillary patterns has not been clearly described.

Yanagawa *et al.* (10) investigated the proportion of solid and micropapillary patterns in resected lung adenocarcinomas and validated the relationship between the proportion and the clinicopathological backgrounds, including prognosis. They examined a total of 531 resected lung adenocarcinomas and classified the cases into the following five subgroups according to the proportion of solid and/or micropapillary patterns: (I) both patterns absent (S–/MP–); (II) solid predominant (S pre); (III) micropapillary predominant (MP pre); (IV) solid pattern present (≥5%) but not predominant and micropapillary absent (S+ not pre/MP–); and (V) MP pattern present (≥5%) but not predominant (MP+ not pre). Among patients with all stages of disease, the univariate analysis of Yanagawa's study revealed that the S–/MP– subgroup had a better recurrence-free survival (RFS) and overall survival (OS) than the others. In contrast, the MP pre-subgroup had a worse RFS and OS than the others. The multivariate analysis of the study indicated that the S–/MP– subgroup had a

significantly higher RFS rate, and the MP pre-subgroup had a lower RFS rate, than the other subgroups. There were no significant differences in RFS among the remaining three subgroups (S pre, S+ not pre/MP–, and MP+ not pre). These data demonstrated that lung adenocarcinomas with solid and micropapillary patterns, regardless of predominance, were associated with a worse prognosis than those without these patterns. Kamiya *et al.* (11) also reported that survival rates tended to worsen as the extent of the micropapillary pattern progressed, and that the disease-free survival and OS for patients with micropapillary pattern were worse than for patients without the pattern. Zhao *et al.* (12) determined that presence of a minor component (>5% of the tumor) of the solid and/or micropapillary pattern was correlated with lymph node metastasis and poor prognosis.

In Yanagawa's study (10), the multivariate analysis was performed only for patients with stage I disease, and showed that the S–/MP– subgroup tended to have higher RFS and OS rates than the other groups. Other studies have also investigated lung adenocarcinomas with solid and/or micropapillary patterns in patients with early-stage disease. Miyoshi *et al.* (13) focused on 154 patients with p-stage I disease and determined that the 5-year survival of patients with micropapillary pattern was 79%, which was significantly lower than that of those without the pattern (93%). In addition, lymph node metastasis, pleural invasion, intrapulmonary metastasis, and nonsmoking status were significantly more frequent in the subgroup with micropapillary pattern than in those without this pattern. Nitadori *et al.* (14) investigated surgically resected cases of small lung adenocarcinomas (≤2 cm) and indicated that a micropapillary component ≥5% was associated with an increased risk of recurrence, compared with a micropapillary component <5%. Tsubokawa *et al.* (15) found that in stage IA patients with papillary and acinar predominant tumors, a micropapillary component ≥5% of the entire tumor negatively influenced survival. However, there was no difference in the prognosis of patients with micropapillary-positive and negative tumors with lepidic or solid predominant patterns. In a recent study by Matsuoka *et al.* (16), the presence of a solid and/or micropapillary component ≥1% was associated with a worse prognosis in patients with acinar- and papillary-predominant lung adenocarcinoma. These studies of patients with early-stage adenocarcinoma suggest the significance of focusing not only on the solid and micropapillary predominant subtypes but also on minor components to predict a poor prognosis.

In most past studies, however, early-stage cases have included patients with adenocarcinoma in situ (AIS), which is a non-invasive lesion, and both the AIS and invasive subtypes have been analyzed as the same subgroup, stage I. In December 2016, the Union for International Cancer Control (UICC) published the 8th edition of the UICC TNM classification of malignant tumors. The new TNM classification categorizes AIS of the lung as stage 0 and distinguishes cases with AIS from those with invasive lesions. Additional study is needed to confirm whether the presence of a minor component of the solid and/or micropapillary subtype is a worse prognostic factor in stage I disease of the 8th TNM classification.

Although Yanagawa's study did not analyze cases based on the surgical procedure, other past studies have reported an association between surgical procedure and prognosis. Nitadori *et al.* (14) demonstrated that the presence of a micropapillary component (≥5%) was significantly associated with an increased risk of recurrence compared with a micropapillary component <5% in patients who underwent limited resection (wedge resection or segmentectomy). In particular, when the surgical margin was less than 1 cm, a micropapillary component of 5% or greater was strongly associated with the risk of local recurrence. In contrast, there was no significant difference in the risk of recurrence for patients who underwent lobectomy, irrespective of the presence of the micropapillary component. Additionally, Yeh *et al.* (17) determined that the presence or absence of micropapillary and solid patterns were correlated with disease recurrence in both permanent and frozen sections; the presence of the micropapillary pattern was associated with distant recurrence, whereas the presence of the solid pattern was associated with locoregional recurrence. In the study, frozen sections had a high specificity (94% and 96%), but a low sensitivity (37% and 69%) for micropapillary and solid patterns, respectively. Therefore, an intraoperative frozen section might help to predict the risk of recurrence and to select for the appropriate surgical procedure. If a patient treated with local resection has a tumor with a micropapillary or solid pattern, a larger anatomical resection such as lobectomy might be required.

In conclusion, Yanagawa's study (10) indicated that patients with micropapillary and/or solid patterns had a worse prognosis, regardless of the predominance of the patterns. A future study is necessary to confirm whether these histological patterns are worse prognostic factors in

the 8th TNM classification, similar to previous reports.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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