

# Histologic subtype component predicts lymph node micrometastasis and prognosis in patients with stage I lung adenocarcinoma

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Lung cancer is the major cancer-related death in the world. Complete resection is the gold standard for management of early-stage non-small cell lung cancer (1). For extent of pulmonary resection in patients with lung cancer, lobectomy is the standard procedure (2). However, more sublobar resection was done recently due to more small-sized peripheral ground glass nodules were found by chest computed tomography screening. The application of sublobar resection in lung cancer of small size needs more investigation (3). Furthermore, whether radical mediastinal lymph node dissection should be performed in these patients is a controversial issue (3).

The International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a histologic subtyping system for lung adenocarcinoma (4). The invasive adenocarcinomas were mainly classified into five subtypes: lepidic, acinar, papillary, micropapillary or solid (4). The poor prognostic value of micropapillary and solid predominant subtypes in patients undergoing operation for lung adenocarcinomas has been well demonstrated in the literature (5-10). Several studies have reported that a minor micropapillary component in adenocarcinoma, even not the predominant subtype, closely correlates with disease recurrence (11,12).

For lung adenocarcinoma, radical lymph node dissection

could be considered in patients with high risk of occult lymph node metastasis. Recently, Dai *et al.* (13) have conducted a retrospective study to investigate the relationship between histologic subtype component and lymph node micrometastasis in patients with stage I lung adenocarcinoma. Lymph node micrometastasis was observed in 35 (15%) of the 235 patients in their study. Patients with micrometastasis had significantly worse recurrence-free survival and overall survival compared with those without micrometastasis. Micropapillary component was an independent predictor of increased frequency of micrometastasis. They also found that patients with resected stage I lung adenocarcinoma with a micropapillary component and lymph node micrometastasis had significantly worse outcomes. Furthermore, the presence of micrometastasis correlated with a higher risk of locoregional recurrence rather than distant recurrence in micropapillary-positive patients.

The prognostic value of histologic subtypes of lung adenocarcinoma has been reported in the literature (5-10). For patients with early-stage lung adenocarcinoma, micropapillary or solid predominant subtype is significantly related to worse disease-free survival (8,10). Presence of a minor histologic subtype, even not the predominant subtype, may also have significant prognostic value in lung adenocarcinoma. Presence of micropapillary or solid

subtype in lung adenocarcinoma correlated with disease recurrence and death (11,12). In our recent study (14), patients of node-negative lung adenocarcinoma of 3 cm or smaller with micropapillary/solid predominant pattern had significantly worse disease-free survival than those with other subtypes. For patients with tumors of 2 cm or smaller, presence of solid pattern was a prognostic factor for higher possibility of recurrence (14). Dai *et al.* (13) further demonstrated that lymph node micrometastasis could provide helpful prognostic information in resected stage I lung adenocarcinoma with a micropapillary component. All the above results are useful for patient stratification for adjuvant therapy in patients with resected early-stage lung adenocarcinoma.

Several studies have demonstrated the association between predominant histologic subtype and lymph node metastasis in patients with lung cancer (6,15-19). Patients with micropapillary or solid predominant pattern had higher possibilities having lymph node metastasis (6,17,18). We have also demonstrated that micropapillary or solid predominant pattern was correlated with higher frequencies of N1 or N2 metastasis (9). Zhang *et al.* (19) reported that lepidic predominant adenocarcinoma was significantly related to freedom from lymph node metastasis. Presence of a minor histologic component in adenocarcinoma has also been reported to closely correlate with lymph node metastasis. Tumors with presence of the micropapillary component were significantly related to presence of lymph node metastasis (15,16).

Some studies have reported the relationship between presence of histologic pattern and occult lymph node metastasis (7,13,20). For lung adenocarcinoma of 5 cm or smaller, the presence of the micropapillary pattern was significantly associated with occult mediastinal lymph node metastasis (7). Dai *et al.* (13) have shown that lymph node micrometastasis was observed in 35 (15%) of the 235 patients with stage I lung adenocarcinoma in their study. Presence of micropapillary component was an independent predictor of higher possibility of micrometastasis. In our previous study (20), we have also shown that micropapillary or solid pattern component was a predictor of occult mediastinal lymph node metastasis in tumors  $\leq 3$  cm. The solid subtype component was also a predictor of occult mediastinal lymph node metastasis in tumors of 2 cm or smaller. All these studies demonstrated that micropapillary or solid subtype component was a significant predictor of occult lymph node metastasis or micrometastasis.

Radical lymph node dissection improves staging accuracy

for patients undergoing resection for lung cancer (3). The micropapillary or solid component may be identified by pre-operative biopsy or frozen section during operation. In the situation when micropapillary or solid component was identified in a lung adenocarcinoma, radical lymph node dissection should be considered to discover occult lymph node metastasis and thus lead to accurate staging.

In conclusion, micropapillary or solid subtype is a significantly poor prognostic factor for patients with lung adenocarcinoma. Presence of the micropapillary or solid subtype component is also a predictor of occult lymph node metastasis or micrometastasis. Radical mediastinal lymph node dissection should be considered to identify occult lymph node metastasis or micrometastasis for accurate lung cancer staging.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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