Editorial

Micropapillary lung adenocarcinoma and micrometastasis

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Lung adenocarcinoma (ADC) is the most common type of lung cancer, and it has been subtyped by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) histologic classification. Invasive ADC has been classified into five predominant subtypes—lepidic, acinar, papillary, micropapillary (MIP), and solid (1). Semiquantitative assessment and reporting of each subtype in 5% increments is recommended to represent all subtype patterns. Several independent retrospective studies have already demonstrated the prognostic value of the new classification (2,3). Of patients with high-grade pattern tumors, the MIP and solid subtypes behave more aggressively and have a worse prognosis compared with low-grade pattern tumors with the lepidic subtype.

The MIP subtype is defined as tumor cells that grow in papillary tufts forming florets that lack fibrovascular cores (4). Several large studies with cohorts >300 patients have validated the negative prognostic significance of MIP-predominant tumors (2,3). Our group has demonstrated that the presence (≥5%) and increasing percentage of the MIP pattern is associated independently with an increased risk of local recurrence in patients who were treated with limited resection (e.g., wedge resection or segmentectomy) for small (≤2 cm) lung ADC (5). Additionally, Tsao *et al.* (6) suggested that patients with stage I–III ADC who have a MIP subtype may benefit from adjuvant chemotherapy and have exhibited improved disease-free survival (DFS) rates.

Lymph node (LN) metastasis is an important factor when determining treatment for non-small cell lung cancer (NSCLC), and a strong correlation between the MIP pattern and LN metastasis has been reported (*Figure 1*) (3,7). The MIP-predominant subtype, as well as a MIP component (≥5%), are both significantly associated with LN metastasis. The term "occult LN metastasis" is used to describe metastases that are not diagnosed by standard clinical and pathologic methods in node-negative LNs. LN micrometastasis, as a type of occult LN metastasis, is defined as isolated tumor cells or cellular clusters ≤0.2 mm in greatest dimension identified within LNs (4). Preoperative LN staging by computed tomography or ^{18}F-fluorodeoxyglucose positron emission tomography fails to detect occult LN metastases and often exhibits a high false-negative rate (8). Even during histologic evaluation, it is difficult to identify this small focus of metastatic tumor cells on routine hematoxylin and eosin (H&E) slides. However, increasing evidence has shown that LN micrometastasis is predictive of poor prognosis in many malignancies including breast, colon, bladder, and lung cancer (9,10). Retrospective studies have reported that LN micrometastasis correlates with decreased overall survival (OS) and worse DFS in early-stage NSCLC (11-13). The MIP pattern is one of the most important factors reported to be related to a high risk of LN micrometastasis in early-

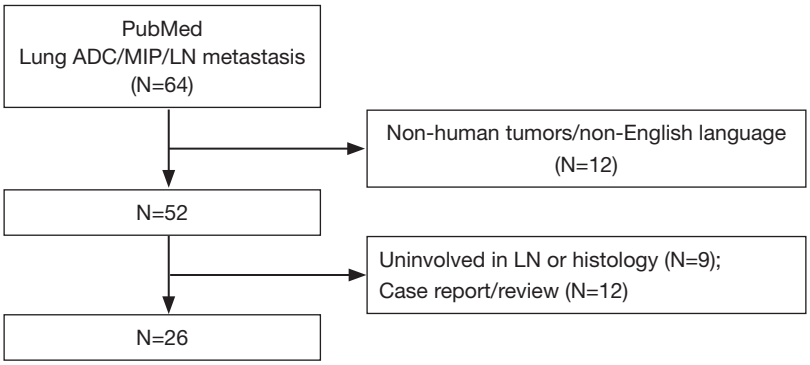

Figure 1 Criteria for inclusion and exclusion of literature. ADC, adenocarcinoma; MIP, micropapillary; LN, lymph node.

Table 1 The relationship between the MIP pattern and LN micrometastasis

Author/year	Stage	No. of patients	LN micrometastases (%)*	MIP-positive (%)**	MIP-negative (%)**	P value
Yeh/2015	I–II	297	11	29	12	<0.001
Wang/2015	IA	292	10	43	7	0.001
Hung/2016	I–II	471	18	54	46	0.001
Moon/2016	cN0	350	13	34	5	<0.001
Tsubokawa/2016	IA	347	6	15	5	<0.001
Dai/2017	I	235	15	37	7	<0.001

*, percentage of the cases with LN micrometastasis; **, percentage of MIP-positive or MIP-negative cases in the cases with LN micrometastasis. These studies demonstrate a significant correlation between MIP and LN micrometastasis. MIP, micropapillary; LN, lymph node.

stage lung cancer (*Table 1*).

Our group and Hung *et al.* (11,12) have investigated the relationship between primary tumor histologic patterns and occult LN metastasis in clinically N2-negative (cN0-1) lung ADC. Similar studies have been conducted by Wang *et al.* and Tsubokawa *et al.* in stage IA lung ADC and by Moon *et al.* in cN0 lung ADC (13-15). In these studies, the reported incidence rate of LN metastasis in early-stage lung cancer varied from 6% to 40%. While LN metastasis is present in 15% to 63% of patients with MIP-positive tumors, the metastatic rate of MIP-negative tumors is significantly lower. This suggests that the presence of the MIP pattern is significantly associated with occult LN metastasis.

Several methods have been used to detect LN micrometastasis including immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR) (16,17). IHC was the standard and reliable method to detect LN micrometastasis in lung cancer. Several antibodies, such as cytokeratins (CAM 5.2 and AE1), Ber-EP4, and TTF-1, have been used to detect LN micrometastasis, and the majority of this research has demonstrated that LN micrometastasis detected by IHC is significantly associated with worse survival. RT-PCR for tumor-specific mRNA has been used to detect the carcinoembryonic antigen (CEA) in regional LNs of lung cancer. Even though RT-PCR is a more sensitive detection method, CEA is not specific to NSCLC, and, therefore, its clinical impact is insignificant.

Recently, Dai *et al.* (17) investigated the relationship between LN micrometastasis and histologic patterns in a cohort of 235 patients with stage I lung ADC. Immunohistochemical staining for cytokeratin (AE1/AE3) and thyroid transcription factor-1 (TTF-1) were used to identify LN micrometastasis. In their study, 23 (37%) cases with a MIP component had confirmed LN micrometastasis compared with only 12 (7%) cases without a MIP component that had confirmed LN micrometastasis. These LN tumor cells were positive for both AE1/AE3 and TTF-1. Dai *et al.* further indicated that MIP-positive/micrometastasis-positive patients had significantly worse survival compared with MIP-positive/

micrometastasis-negative patients [recurrence-free survival (RFS), P=0.039; OS, P=0.002] and MIP-negative patients (RFS, P<0.001; OS, P<0.001). Moreover, in MIP-positive patients, the presence of LN micrometastasis correlated with a higher risk of locoregional recurrence (P=0.031) rather than distant recurrence (P=0.456). The strength of this study is the investigation of both LN micrometastasis and the MIP component on prognosis and recurrence pattern, which is a finding that has not been reported previously. This study, however, is limited by: (I) its retrospective nature carried out at a single center; (II) a small number of patients; and (III) a survival analysis that did not include lung cancer-specific survival, which is one of the most important survival parameters of lung cancer (18).

Although the MIP pattern has been shown to be related to poor prognosis, little is known about its biologic mechanism. Kamiya *et al.* (19) reported that the MIP component likely acquired anchorage-independent growth and a high potential for malignancy based on IHC for E-cadherin, beta-catenin, CD34, Ki-67, and laminin. Tsutsumida *et al.* (20) confirmed that high mucin 1 (MUC1) expression was present on the cell membranes of MIP pattern tumors. The expression of MUC1 is believed to be indicative of cell polarization inversion, which contributes to tumor invasion. Nagano *et al.* (21) discovered that expression of glucose transporter-1 (GLUT-1), a hypoxic marker, was higher in lung ADC tumors with a MIP component.

The most recently described method of invasion in NSCLC is spread through air spaces (STAS). Clinical research examining STAS has shown a positive association between this new pattern of invasion and presence of the MIP pattern and lymphatic invasion in the primary tumor (22,23). Jeong *et al.* (24) found no difference in endothelial cell proliferation in LN micrometastasis. This indicates that malignant cells may use the already present lymphatic vasculature to reach the LN. Vessel co-option of alveolar capillaries has been described as a method of survival implemented by isolated cancer cells in lung parenchyma (25). The MIP subtype, lymphatic invasion, and the possible co-option mechanism may provide some insight into the relationship between STAS around the primary tumor and LN metastasis.

In summary, the novel concept of the impact of the MIP component on LN micrometastasis and its consequent effect on prognosis need to be investigated in a large cohort of patients. Understanding the underlying biologic mechanisms may also yield clarification regarding the optimal surgical approach (lobectomy versus limited resection) and improve operative decision making for patients with lung ADC with a MIP component.

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Footnote

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