Original Article

Prognostic impact of micropapillary component in patients with node-negative subcentimeter lung adenocarcinoma: A Chinese cohort study

Jie Yao1*, Erjia Zhu2*, Ming Li3*, Jinshi Liu4, Lei Zhang5, Honggang Ke6, Hang Su2, Huikang Xie7, Guanxin Xu1, Ling Zhu1, Junqiang Fan1†, Chang Chen2† & Surgical Thoracic Alliance of Rising Star Collaborative Group

1 Department of Thoracic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China
2 Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
3 Department of Thoracic Surgery, Jiangsu Cancer Hospital, Nanjing Medical University, Nanjing, China
4 Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, China
5 Department of Thoracic Surgery, The First People’s Hospital of Changzhou, Changzhou, China
6 Department of Thoracic Surgery, Affiliated Hospital of Nantong University, Nantong, China
7 Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

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Correspondence
Chang Chen, Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 200433, China. Email: chenthoracic@163.com

*Dr. Yao J, Zhu E and Li M contributed equally to this work
†Drs. Fan J and Chen C were senior coauthors
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Abstract

Background: In this study, we investigated the prognostic significance of a micropapillary (MP) component in patients with subcentimeter lung adenocarcinoma.

Methods: A total of 311 patients with subcentimeter lung adenocarcinoma who underwent surgical resection between January 2009 to December 2012 from seven medical centers were included. Recurrence-free survival (RFS) and overall survival (OS) were analyzed.

Results: The five-year RFS was 79.8% in 97 (97/311, 31%) cases of adenocarcinoma with a MP component and 93.5% in the 214 (214/311, 69%) cases without. In multivariate analysis, MP was an independent risk factor for worse RFS (hazard ratio [HR], 3.73; 95% confidence interval [CI]: 1.87–7.42; P < 0.001) and OS (HR, 5.84; 95% CI: 2.20–15.49; P < 0.001). There was no significant difference among wedge resection, segmentectomy and lobectomy on RFS (P = 0.256) and OS (P = 0.103) in patients without MP. Regarding patients with a MP component, lobectomy achieved equivalent prognosis than segmentectomy, and both were better than wedge resection (P = 0.001).

Conclusions: A MP component still suggest a poor prognosis in subcentimeter lung adenocarcinoma. Patients with subcentimeter lung adenocarcinoma with a MP component of 5% or greater treated with wedge resection were at higher risk of recurrence than patients treated with anatomical resection.

Introduction

Lung cancer is now the leading cause of cancer-related death in the world and lung adenocarcinoma has become the most common histological type.1 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 and recommended that lung adenocarcinoma should be classified into five subtypes according to their predominant histological component.2 The prognostic impact of micropapillary (MP) and/or solid predominant subtype on survival outcomes in lung adenocarcinoma has been demonstrated to be associated with worse prognosis.3–6 However, the clinicopathological characteristics and long-term survival in patients with adenocarcinoma harboring a minor proportion of MP component (nonpredominant) remains unclear.
With the development of radiological techniques in high-resolution computed tomography (HRCT) scanning, the detection rate of small-sized nodules, especially subcentimeter nodules (tumor size ≤1 cm), has gradually increased. Several studies have reported that subcentimeter lung adenocarcinoma is associated with lower rate of nodal metastasis and recurrence, with a better long-term patient survival. Sublobar resection in these patients including segmentectomy and wedge resection has been reported to have an equivalent prognosis compared with lobectomy. However, the National Comprehensive Cancer Network (NCCN) guidelines propose lobectomy and systematic lymph node dissection as the standard procedure for early-stage lung adenocarcinoma. In addition, it has been recommended that lobectomy is the optimal choice to provide a potential cure in patients with small-sized lung adenocarcinoma MP predominant subtype. However, lung adenocarcinoma often harbors multiple histological subtypes. To date, whether patients with MP component (predominant or nonpredominant) in subcentimeter lung adenocarcinoma may benefit from less intensive resection has not been investigated.

In this study, we aimed to evaluate the prognostic value and appropriate surgical procedure of MP subtype in subcentimeter lung adenocarcinoma from a multicenter study group.

**Methods**

**Patient population**

This retrospective study was approved by the Institutional Review Board of The Second Affiliated Hospital of Zhejiang University, Shanghai Pulmonary Hospital, Zhejiang Cancer Hospital, Jiangsu Cancer Hospital, Affiliated Hospital of Nantong University and The First People’s Hospital of Changzhou, on behalf of the Surgical Thoracic Alliance of Rising star group (STAR). Patients with surgically resected c-N0 subcentimeter lung cancer who underwent curative resection from seven medical centers between January 2009 and December 2012 were included in the study. The inclusion criteria were (i) tumor size ≤1 cm; (ii) nonenlarged lymph nodes on CT scan; and (iii) pathologically diagnosed lung adenocarcinoma. The exclusion criteria were as follows: (i) previous neoadjuvant chemotherapy; (ii) presence of multiple primary cancer; (iii) incomplete follow-up information; and (iv) positive surgical margin. Ultimately, a total of 311 patients with subcentimeter lung adenocarcinoma were included in our study. Patients’ demographic and clinical data, disease extent, treatment and follow-up information were collected.

**Preoperative evaluation**

Preoperative staging was performed with chest CT scan, brain MRI, and bone scintigraphy. Hilar or mediastinal lymph nodes larger than 1 cm in the short axis on CT images were defined as clinical N factor positive. Preoperative positron-emission tomography (PET) scan was performed at the discretion of the individual clinician, especially in patients with suspicion of lymph node metastasis. Mediastinoscopy was not performed unless suspicious lymphadenopathy was indicated on CT or PET scan. Surgical resection was indicated for patients without pathological evidence of mediastinal lymph node involvement including those with hilar nodal disease on CT or PET scan.

**Surgical indication and tumor margin**

Lobectomy with systematic hilar and mediastinal lymph node dissection was the primary procedure. The indication for limited resection was decided on the basis of a combination of the performance status of patients and CT findings. Sublobar resections, including anatomical segmentectomy and wedge resection, were indicated for patients with peripheral lesions located at the outer one-half of lung parenchyma, or patients with shadows composed mainly of ground-glass nodules on CT. In contrast, we performed compromised limited resection for high-risk patients with any contraindications for standard radical surgery, regardless of the tumor size or presence of a solid component on CT. The surgical technique was aimed at securing sufficient margins of at least 2.0 cm. The tumor margin was defined as the distance from the primary tumor to the closest staple lines. The tumor margin distance was measured by pathologists, and the tumor margin distances recorded the pathological reports were used for the analyses.

**Histopathological evaluation**

All patients’ pathological slices were reviewed and reclassified by two clinical pathologists in each center who were blinded to patient characteristics and clinical information. When disagreement occurred, a third senior pathologist was enlisted in order to reach an agreement. According to the 2015 WHO classification of lung adenocarcinoma, invasive lung adenocarcinoma was divided into lepidic, acinar, papillary, solid, and MP subtypes based on the predominant histological pattern presenting in the tumor. The percentage of each histological subtype was recorded in 5% increments, and a subtype was considered present if ≥5% in the tumor. The pattern with largest percentage was defined as predominant pattern of histological
subtype. The micropapillary pattern was defined as (i) a floret pattern with tumor cells growing in papillary tufts forming florets that lack fibrovascular cores; and a (ii) stromal pattern with tumor cells invading stromal spaces encased by connective tissues. Representative images were added to the results section (Fig 1). Adenocarcinomas with a proportion of MP component >0% were defined as MP positive adenocarcinomas. Adenocarcinomas without any MP component were defined as MP negative adenocarcinomas.

We also retrospectively investigated the diagnostic accuracy of presence of micropapillary component by frozen section. In our cohort, all specimens were intraoperatively diagnosed by frozen section results. Two senior pathologists reported the presence of a micropapillary component using a multihead microscope and discussed the results until a consensus was achieved.

Follow-up policy

All patients received a physical examination, blood examination including tumor markers and chest HRCT scan every 6 to 12 months during the first two years after operation and yearly thereafter. The last follow-up date was October 2018, the postoperative local recurrence or distant metastasis was diagnosed using chest HRCT, brain magnetic resonance imaging (MRI), and bone scanning as well as ultrasound and/or abdominal CT. The postoperative recurrence pattern was divided into locoregional, and distant recurrence. Locoregional recurrence was defined as any recurrent disease within the ipsilateral hemithorax, lung metastasis, and/or hilar or mediastinal lymph node metastasis. Distant recurrence was considered distant metastases. Recurrence was confirmed by radiological findings, including CT and/or positron emission tomography findings.

Statistical analysis

Categorical variables were compared using the $\chi^2$ test and Fisher’s exact test as appropriate, and continuous variables were compared using independent $t$-test. Overall survival (OS) and recurrence-free survival (RFS) were analyzed by the Kaplan-Meier method. In addition, univariate and multivariate Cox proportional regression analysis were used to evaluate the prognostic impact of various factors. Univariate and multivariate logistic regression model was performed to determine the relationship of micropapillary component and other clinicopathological factors. The input variables in the multivariate model were those with $P$-values less than 0.1 in the univariate analysis. A two-sided $P$-value of less than 0.05 indicated statistical significance. All statistical analysis was performed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

The overall characteristics of the patients were compared according to the positive or negative MP adenocarcinomas (Table 1). In patients with subcentimeter lung adenocarcinoma, there were 97 cases (31%) identified with a MP component, Average value of micropapillary proportion was 18.1%. Median value of micropapillary proportion was 15.0%. Micropapillary proportion ranged from 5.0% to 70.0%, and 214 cases (69%) were identified without MP component. Gender, age, smoking history, tumor location,

Figure 1  Micropapillary adenocarcinoma consists of small papillary clusters of glandular cells growing within the airspace which lack fibrovascular cores (a, x100; b x 200).
total size, visceral pleural invasion (VPI) and surgical procedure were not related to the presence of MP subtype, while predominant subtype had a remarkable correlation with MP presence \((P < 0.001)\). Additionally, patients with lepidic-predominant tumors had a lower probability of harboring a MP component \((P < 0.001)\). The relationship between the MP positive adenocarcinomas and patient characteristics is shown in Table 2. A multivariate logistic analysis demonstrated that the presence of lepidic subtype was a significant lower risk factor in the presence of MP subtype (odds ratio [OR], 0.21; 95% confidence interval [CI]: 0.11–0.39), while gender, age, smoking history, tumor location, total size, VPI were not related to the presence of MP subtype.

Patients were subclassified into MP positive and MP negative groups. The MP positive group had a significant worse OS \((P < 0.001)\) and RFS \((P < 0.001)\) than the MP negative group (Fig 2). In the multivariate analysis, the.

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### Table 1: Patient characteristics according to the presence of a micropapillary component

| Characteristics                  | Micropapillary (−) N = 214 | Micropapillary (+) N = 97 | P-value |
|----------------------------------|-----------------------------|---------------------------|---------|
| **Age**                          |                             |                           |         |
| ≤65                              | 168 (79)                    | 71 (73)                   | 0.313   |
| >65                              | 46 (21)                     | 26 (27)                   |         |
| **Sex**                          |                             |                           |         |
| Male                             | 80 (37)                     | 44 (45)                   | 0.212   |
| Female                           | 134 (63)                    | 53 (55)                   |         |
| **Smoking**                      |                             |                           |         |
| Yes                              | 44 (21)                     | 21 (22)                   | 0.881   |
| No                               | 170 (79)                    | 76 (78)                   |         |
| **Tumor location**               |                             |                           |         |
| Upper and middle                 | 139 (65)                    | 57 (59)                   | 0.312   |
| Lower                            | 75 (35)                     | 40 (41)                   |         |
| **Total size (cm)**              |                             |                           |         |
| ≤0.5                             | 15 (7)                      | 7 (7)                     | 0.999   |
| >0.5                             | 199 (93)                    | 90 (93)                   |         |
| **Predominant component**        |                             |                           |         |
| Lepidic                          | 106 (50)                    | 17 (18)                   | <0.001  |
| Acinar                           | 68 (32)                     | 45 (46)                   |         |
| Papillary                        | 30 (14)                     | 26 (27)                   |         |
| Micropapillary                   | 0 (0)                       | 4 (4)                     |         |
| Solid                            | 10 (5)                      | 5 (5)                     |         |
| **Lepidic pattern**              |                             |                           |         |
| Present                          | 168 (79)                    | 37 (38)                   | <0.001  |
| Absent                           | 46 (21)                     | 60 (62)                   |         |
| **Acinar pattern**               |                             |                           |         |
| Present                          | 141 (66)                    | 73 (75)                   | 0.113   |
| Absent                           | 73 (34)                     | 24 (25)                   |         |
| **Papillary pattern**            |                             |                           | 0.999   |
| Present                          | 139 (65)                    | 63 (65)                   |         |
| Absent                           | 75 (35)                     | 34 (35)                   |         |
| **Solid pattern**                |                             |                           | 0.032   |
| Present                          | 14 (7)                      | 14 (14)                   |         |
| Absent                           | 200 (93)                    | 83 (86)                   |         |
| **VPI**                          |                             |                           | 0.361   |
| Present                          | 40 (19)                     | 23 (24)                   |         |
| Absent                           | 174 (81)                    | 74 (76)                   |         |
| **Nodal involvement**            |                             |                           | 0.186   |
| N0                               | 212 (98)                    | 94 (97)                   |         |
| N1                               | 1 (1)                       | 2 (2)                     |         |
| N2                               | 1 (1)                       | 1 (1)                     |         |
| **Surgery**                      |                             |                           | 0.714   |
| Lobectomy                        | 161 (75)                    | 71 (73)                   |         |
| Segmentectomy                    | 24 (11)                     | 14 (14)                   |         |
| Wedge resection                  | 29 (14)                     | 12 (12)                   |         |
Cox regression model was used to adjust for gender, age, smoking history, tumor location, and total size. The five-year OS and RFS were significantly worse for patients with MP presence (OS: HR, 5.84; 95% CI: 2.20–15.49, \( P < 0.001 \); RFS: HR, 3.73; 95% CI: 1.87–7.42, \( P < 0.001 \)) (Table 3).

For all 79 patients who underwent limited resection, no patients had a margin distance <10 mm, 47 (60%) patients had a margin distance of 11–20 mm, and 22 (40%) patients had a margin distance >20 mm. The margin distance of patients in the segmentectomy group was comparable to the wedge resection group (17 ± 3.1 mm vs. 16 ± 4.2 mm; \( P = 0.235 \)). In addition, we evaluated the oncological outcomes on the basis of operative procedure in patients in the MP positive and MP negative groups, and there was no difference in the MP negative group among wedge resection, segmentectomy or lobectomy on OS (\( P = 0.103 \)) and RFS (\( P = 0.256 \)) (Fig 3). However, in the MP positive groups, patients who underwent anatomic lobectomy or segmentectomy had a superior five-year OS (\( P = 0.001 \)) and RFS (\( P = 0.033 \)) than those who underwent wedge resection. We also found that the sensitivity and specificity of frozen section diagnosis of presence of micropapillary

### Table 2 Relationship between the presence of a micropapillary component and patient characteristics

| Variables | Univariate | Multivariate |
|-----------|------------|--------------|
|           | OR (95% CI) | \( P \)-value | OR (95% CI) | \( P \)-value |
| Sex (female) | 0.72 (0.44–1.17) | 0.184 | 0.17 (0.10–0.29) | <0.001 |
| Age (>65) | 1.34 (0.77–2.33) | 0.305 | 1.58 (0.92–2.71) | 0.100 |
| Smoking (yes) | 1.07 (0.59–1.92) | 0.827 | 1.00 (0.61–1.65) | 0.999 |
| Tumor location (lower) | 1.27 (0.73–2.22) | 0.392 | 2.41 (1.10–5.27) | 0.028 |
| Total size (cm) | 1.18 (0.42–3.35) | 0.752 | 1.35 (0.76–2.42) | 0.309 |
| Predominant component | | | 3.38 (0.56–20.58) | 0.186 |
| Lepidic (reference) | | | | |
| Acinar | 4.13 (2.19–7.79) | <0.001 | 1.60 (0.99–2.61) | \( P < 0.001 \) |
| Papillary | 5.40 (2.60–11.25) | <0.001 | 1.81 (0.93–3.53) | \( P = 0.083 \) |
| Solid | 3.12 (0.95–10.24) | 0.061 | 1.17 (0.56–2.45) | 0.675 |
| Lepidic (present) | 0.17 (0.10–0.29) | <0.001 | 0.16 (0.09–0.28) | <0.001 |
| Acinar (present) | 1.58 (0.92–2.71) | 0.100 | | |
| Papillary (present) | 1.00 (0.61–1.65) | 0.999 | | |
| Solid (present) | 2.41 (1.10–5.27) | 0.028 | 0.81 (0.34–1.93) | 0.634 |
| VR (present) | 1.35 (0.76–2.42) | 0.309 | | |
| Nodal involvement (present) | 3.38 (0.56–20.58) | 0.186 | | |

**Note:** Predominant component was not included in multivariate analysis because of the association with presence of each components in adenocarcinoma. CI, confidence interval; OR, odds ratio.

![Figure 2](image-url) Prognostic impact on (a) RFS; (---) MP (--), and (---) MP (+) and (b) OS between patients with positive or negative MP component (---) MP (--), and (---) MP (+). (OS: overall survival; RFS: recurrence-free survival; MP: micropapillary).
component was 59.9% and 90.6%. The data of recurrence pattern of subcentimeter lung cancer with micropapillary component according to the surgical procedure is shown in Table 4. All recurrence (100%) in patients who underwent wedge resection was locoregional. Three quarters of recurrence (75%) in the anatomical resection group was locoregional. Locoregional recurrence was higher in patients who underwent wedge resection (Table 4).

### Table 3 Cox regression model to predict RFS and OS of c-N0 subcentimeter lung adenocarcinoma

| Variables                      | Univariate |          |          | Multivariate |          |          |
|-------------------------------|------------|----------|----------|--------------|----------|----------|
|                               | HR (95% CI)| P-value  | HR (95% CI)| P-value      |          |          |
| RFS                           |            |          |           |              |          |          |
| Sex (female)                  | 0.48 (0.25–0.94) | 0.031    | 0.53 (0.27–1.06) | 0.072          |          |          |
| Age (>65)                     | 1.04 (0.47–2.28) | 0.930    |          |              |          |          |
| Smoking (yes)                 | 1.37 (0.64–2.93) | 0.413    |          |              |          |          |
| Tumor location (lower)        | 0.61 (0.26–1.46) | 0.266    |          |              |          |          |
| Total size (cm)               | 1.46 (0.32–6.58) | 0.625    |          |              |          |          |
| Predominant component         |            |          |           |              |          |          |
| Lepidic                       |            |          |           |              |          |          |
| Acinar                        |            |          |           |              |          |          |
| Papillary                     |            |          |           |              |          |          |
| Solid                         |            |          |           |              |          |          |
| Micropapillary                | 9.52 (2.05–44.17) | 0.004    | 3.90 (1.93–7.87) | <0.001          |          |          |
| Lepidic (present)             | 0.65 (0.34–1.28) | 0.214    |          |              |          |          |
| Acinar (present)              | 1.36 (0.64–2.91) | 0.425    |          |              |          |          |
| Papillary (present)           | 0.60 (0.31–1.17) | 0.131    |          |              |          |          |
| Solid (present)               | 1.82 (0.71–4.70) | 0.214    |          |              |          |          |
| Micropapillary (present)      | 3.93 (1.98–7.82) | <0.001   | 5.42 (1.58–18.65) | 0.007          |          |          |
| VPI (present)                 | 0.69 (0.23–2.03) | 0.495    |          |              |          |          |
| Nodal involvement (present)   | 6.83 (2.09–22.33) | 0.001    |          |              |          |          |
| Surgery                       |            |          |           |              |          |          |
| Lobectomy (reference)         |            |          |           |              |          |          |
| Segmentectomy                 | 0.61 (0.14–2.57) | 0.496    | 0.45 (0.10–1.94) | 0.283          |          |          |
| Wedge resection               | 2.50 (1.11–5.60) | 0.026    | 3.13 (1.38–7.13) | 0.007          |          |          |
| OS                            |            |          |           |              |          |          |
| Sex (female)                  | 0.58 (0.27–1.28) | 0.179    |          |              |          |          |
| Age (>65)                     | 1.77 (0.76–4.12) | 0.184    |          |              |          |          |
| Smoking (yes)                 | 1.66 (0.69–4.01) | 0.257    |          |              |          |          |
| Tumor location (lower)        | 0.78 (0.30–2.06) | 0.616    |          |              |          |          |
| Total size (cm)               | 1.66 (0.26–10.39) | 0.590    |          |              |          |          |
| Predominant component         |            |          |           |              |          |          |
| Lepidic (reference)           |            |          |           |              |          |          |
| Acinar                        | 1.95 (0.71–5.38) | 0.195    |          |              |          |          |
| Papillary                     | 1.97 (0.60–6.45) | 0.264    |          |              |          |          |
| Solid                         | 1.43 (0.17–11.93) | 0.738    |          |              |          |          |
| Micropapillary                | 19.76 (4.85–80.42) | <0.001   | 19.76 (4.85–80.42) | <0.001          |          |          |
| Lepidic (present)             | 0.46 (0.21–1.00) | 0.050    | 0.91 (0.35–2.39) | 0.849          |          |          |
| Acinar (present)              | 1.24 (0.52–2.98) | 0.626    |          |              |          |          |
| Papillary (present)           | 0.58 (0.26–1.26) | 0.169    |          |              |          |          |
| Solid (present)               | 2.58 (0.97–6.88) | 0.059    | 1.49 (0.48–4.61) | 0.489          |          |          |
| Micropapillary (present)      | 5.73 (2.39–13.76) | <0.001   | 5.73 (2.39–13.76) | <0.001          |          |          |
| VPI (present)                 | 0.18 (0.02–1.35) | 0.095    | 0.19 (0.02–1.41) | 0.104          |          |          |
| Nodal involvement (present)   | 4.82 (1.11–20.93) | 0.036    | 4.50 (1.01–20.00) | 0.048          |          |          |
| Surgery                       |            |          |           |              |          |          |
| Lobectomy (reference)         |            |          |           |              |          |          |
| Segmentectomy                 | 0.62 (0.08–4.80) | 0.651    | 0.47 (0.06–3.69) | 0.470          |          |          |
| Wedge resection               | 4.61 (1.92–11.08) | 0.001    | 4.61 (1.86–11.46) | 0.001          |          |          |

*Predominant component was not included in multivariate analysis because of the association with presence of each components in adenocarcinoma. CI, confidence interval; HR, hazard ratio.
Discussion

The new eighth edition of the tumor, node, and metastases (TNM) classification of NSCLC suggests that T component, especially the maximum tumor size, is the most important predictor of prognosis. T1 disease is subclassified into T1a (≤ 1 cm), T1b (> 1 to ≤ 2 cm) and T1c (>2 to ≤ 3 cm) diseases according to different survival outcomes in various tumor sizes. Considering the distinct prognosis of subcentimeter lung adenocarcinoma, in our study we aimed to evaluate the postoperative outcomes of this group of adenocarcinomas. As far as we are aware, our study is currently the first multicenter study to evaluate the prognostic significance of MP present in subcentimeter lung adenocarcinoma. Our study revealed that subcentimeter lung adenocarcinoma had an excellent prognosis, while patients with MP subtype are associated with a poor prognosis.

Previous studies have found that IASLC/ATS/ERS classification could predict prognosis for stage I lung adenocarcinoma. Yoshizawa et al. reported a five-year RFS rates of lepidic predominant, papillary predominant, and acinar predominant subtypes were 90.0%, 83.0%, and 67.0%, respectively. In our study, we found that patients with MP subtype had a significantly worse RFS compared to those with non-MP subtype. The five-year RFS rates of patients with MP subtype were 72.0% and 63.0% for node-negative and node-positive patients, respectively.

Figure 3 (a, b) Prognostic impact of surgical procedure on RFS and OS in patients with negative MP component; (a) Lobectomy, Segmentectomy, and Wedge resection; (b) Lobectomy, Segmentectomy, and Wedge resection or (c, d) positive MP component Lobectomy, Segmentectomy, and Wedge resection; Lobectomy, Segmentectomy, and Wedge resection. (OS: overall survival; RFS: recurrence-free survival; MP: micropapillary; Lob, lobectomy; Seg, segmentectomy; Wed, wedge resection).
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Established by the Lung Cancer Study Group about section as standard procedures of lung cancer surgery was cancer cases, but also those harboring scant MP components. Thus, we should not only focus on MP predominant lung subtypes. However, previous studies have focused mainly on the relationship between prognosis and predominant histological patterns. Lung adenocarcinoma usually contains complex mixtures of different histological subtypes. A few studies have revealed that minor components of solid and/or MP subtypes are associated with nodal metastasis and poor prognosis. In our study, there were only four MP predominant cases, but MP components were found in 97 cases. As reported in a previous study, we found patients with lung adenocarcinomas harboring MP components had shorter RFS and OS.

In conclusion, patients with subcentimeter lung adenocarcinoma have a favorable prognosis. However, MP subtype is still an independent risk factor of worse survival in patients with subcentimeter lung adenocarcinoma. Thus, lobectomy or segmentectomy should be performed in patients with MP subtype despite tumor diameter ≤ 1 cm and a prospective study focusing on the diagnostic accuracy of MP by frozen section is necessary in the future.

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Table 4 Patterns of recurrence in patients with subcentimeter lung adenocarcinoma with a micropapillary component based on surgical procedure

| Characteristics | Anatomical resection (N = 85) | Wedge resection (N = 12) |
|-----------------|-----------------------------|--------------------------|
| Locoregional recurrence | 13 (15) | 5 (42) |
| Only hilar node | 4 (5) | 2 (17) |
| Only mediastinal node | 4 (5) | 1 (8) |
| Hilar and mediastinal node | 1 (1) | 1 (8) |
| Malignant effusion | 2 (2) | 0 (0) |
| Ipsilateral nodule | 2 (2) | 1 (8) |
| Distant recurrence | 4 (5) | 0 (0) |
| Adrenal gland | 2 (2) | 0 (0) |
| Contralateral nodule | 2 (2) | 0 (0) |
| Total | 17 (20) | 5 (42) |

84.0% respectively, but only 70.0% and 67.0% in solid and MP predominant subtypes. However, previous studies have focused mainly on the relationship between prognosis and predominant histological patterns. Lung adenocarcinoma usually contains complex mixtures of different histological subtypes. A few studies have revealed that minor components of solid and/or MP subtypes are associated with nodal metastasis and poor prognosis. In our study, there were only four MP predominant cases, but MP components were found in 97 cases. As reported in a previous study, we found patients with lung adenocarcinomas harboring MP components had shorter RFS and OS.

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Disclosure
The authors have no conflicts of interest to declare.

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