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Factors associated with lymph node metastasis upstage after resection for patients with micropapillary lung adenocarcinoma

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Abstract

Background: Micropapillary adenocarcinoma has a poor prognostic histological pattern. Additionally, preoperative detection of lymph node metastases by preoperative examination is difficult in some patients with micropapillary adenocarcinoma, and postoperative upstage may occur. However, clinicopathological features of patients with micropapillary adenocarcinoma with nodal upstage have not been established, therefore this study aimed to identify the factors associated with potential lymph node metastases during preoperative examination to ensure effective surgical procedures.

Methods: Between January 2011 and December 2020, 1029 patients received complete resection for primary non-small-cell lung cancer by lobectomy or more extensive resection with systematic lymph node dissection at this institution. One hundred and thirty-one patients diagnosed with adenocarcinoma with micropapillary component were included in this study. The clinicopathological features of patients with nodal upstage whose postoperative N stage was more advanced than the preoperative N stage were examined.

Results: Forty patients had nodal upstage after resection. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) revealed that a maximum standardized uptake value (SUVmax) ≥5 for the primary lesion was significantly associated with postoperative nodal upstage. There were no significant differences in terms of sex, age, smoking history, surgical procedure, and diabetes. Among 38 patients with nodal upstage, 23 patients had no significant preoperative lymphadenopathy and showed no abnormal FDG uptake in the lymph nodes on ^{18}F-FDG-PET-CT, respectively.

Conclusions: Lymph node metastases were suspected in patients preoperatively diagnosed with micropapillary adenocarcinoma with FDG SUVmax ≥5 for the primary tumor. Therefore, standard surgical resection and careful lymph node dissection should be performed for such patients.

KEYWORDS

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, lung cancer, micropapillary component, nodal upstage, standardized uptake value

INTRODUCTION

The World Health Organization (WHO) classification of lung cancer was revised in 2015, and micropapillary adenocarcinoma (MPA) was added as a subtype of lung adenocarcinoma.[1] Since then, MPA has been increasingly reported, and its presence has been associated with a poor prognosis.[2,3]

The micropapillary histological pattern does not have a good prognosis, even during the early stage of lung adenocarcinoma,[4] because the presence of micropapillary structure in lung cancers is often associated with lymph

node metastases, lymphatic invasion, vascular invasion, and positive pleural lavage cytology.[5–7] Particularly for clinical stage I lung cancer patients, a significant number of patients have upstage after resection due to lymph node metastases.[4,8,9]

This study aimed to investigate the factors involved in the potential lymph node metastases in patients with MPA with nodal upstage because of new lymph node metastases after resection.

METHODS

Patient selection

Between January 2011 and December 2020, 1029 consecutive patients with non-small-cell lung cancer (NSCLC) who underwent complete resection using lobectomy or more extensive resection and systematic lymph node dissection at Kitasato University Hospital in Kanagawa, Japan, were included in this study. Surgical resection was performed using open thoracotomy or video-assisted thoracoscopic surgery (VATS). VATS was performed via three or four ports and was defined as complete endoscopic surgery using a monitor. Open thoracotomy was performed with direct vision, even when the thoracoscope was used as a supplementary instrument. Based on the medical records, MPA was observed in 135 patients; however, detailed preoperative data were unavailable for four patients. Therefore, 131 patients were finally enrolled in this study. The characteristics of the enrolled patients are shown in Figure 1.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kitasato University Hospital in Kanagawa, Japan (approval No. B20-343). The requirement to obtain written informed consent from each patient was waived because of the retrospective nature of the study and anonymity of the subjects.

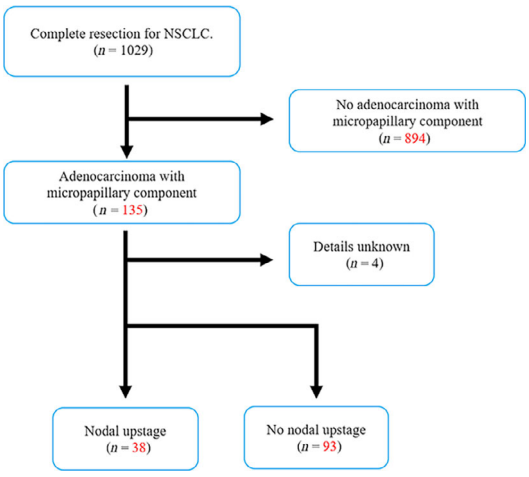

FIGURE 1 Flowchart of the identification of included patients

Staging and treatment

The clinical and pathological stages were reassessed according to the 7th Tumor-Node-Metastasis Classification of the Union for International Cancer Control.[9] The clinical stage was determined using computed tomography (CT), ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET)-CT, and contrast-enhanced brain magnetic resonance imaging. Chest CT was performed with a 1.25-mm slice thickness and contrast agent. However, it was not performed for patients with low renal function and contrast agent allergy. ^{18}F-FDG-PET-CT was performed 60 min after the injection of ^{18}F-FDG and interpreted by two or more experienced radiologists.

The clinical stage was determined by the in-hospital tumor board, which included thoracic surgeons, respiratory physicians, and radiologists. The pathological diagnosis was established by two experienced pathologists based on the 4th edition of the WHO Classification of Lung Tumors.[1]

All cases that included the micropapillary component over 5% were defined as MPA. Surgical resection was indicated up to clinical stage IIB. For stage IIIA, surgical resection was indicated for N2 cases with a single lymph node metastasis. Nodal upstage was defined when the postoperative N stage was more advanced than the preoperative N stage. The lesion located in the mantle one-third of the pulmonary field on chest CT was defined as a peripheral lesion, and the other lesions were defined as the central lesions. Abnormal FDG uptake on ^{18}F-FDG-PET-CT was defined as the maximum standardized uptake value (SUVmax) ≥2.5.

Statistical analyses

Categorical data were compared using Pearson's chi-squared test. Continuous data were compared using Student's *t*-test. Univariate and multivariate analyses were performed to identify factors associated with nodal upstaging. The candidate baseline factors included sex, age at the time of surgery, smoking history, clinical stage, and forced expiratory volume in 1 s. We examined the cutoff value of the SUVmax using the receiver operating characteristic (ROC) curves, which yielded the highest combined sensitivity and specificity for distinguishing metastatic lymph nodes. All statistical analyses were performed using JMP version 15.0 statistical software package for Windows (Statistical Analysis System Institute).

RESULTS

Clinicopathological features of patients with micropapillary adenocarcinoma

Among the 131 patients with MPA we investigated, the median age was 69 (range 38–87) years. A total of 72 patients were men (55.0%). The majority of patients (83 [63.4%])

TABLE 1 Clinicopathological characteristics of the study patients

	Nodal upstage group ($n = 38$)	No nodal upstage group ($n = 93$)	p value[a]
Sex			
Male	20 (52.6%)	52 (55.9%)	0.732
Female	18 (47.4%)	41 (44.1%)	
Age at surgery, years			
Median (range)	70.5(38-84)	69 (43-87)	0.231
Smoking history			
Yes	24 (63.2%)	59 (63.4%)	0.976
No	14 (36.8%)	34 (36.6%)	
FEV1.0			
<70%	11(28.9%)	32 (34.4%)	0.546
≥70%	27(71.1%)	61 (65.6%)	
Surgical procedure			
VATS	8 (21.1%)	23 (24.7%)	0.631
Open	30 (78.9%)	70 (75.3%)	
Diabetes			
Yes	3 (7.9%)	13 (14.0%)	0.335
No	35 (92.1%)	80 (86.0%)	
Tumor size, mm			
Median (range)	28.5 (11-74)	25 (9-65)	0.071
SUVmax of the tumor			
<5	8 (21.1%)	51 (45.2%)	**0.001**
≥5	30 (78.9%)	42 (54.8%)	
Tumor side			
Left	15 (39.5%)	33 (35.5%)	0.613
Right	23 (60.5%)	60 (64.5%)	
Lesion localization			
Central	16 (42.1%)	32 (34.4%)	0.407
Peripheral	22 (57.9%)	61 (65.6%)	

Note: Values in bold indicate statistically significant.
Abbreviations: FEV1.0, forced expiratory volume during 1 s; SUVmax, maximum standard uptake value; VATS, video-assisted thoracic surgery.
[a]Student's *t*-test.

had a history of smoking. Sixteen (12.2%) patients had diabetes and 114 (87.0%) patients had clinical N0. The tumor size ranged from 9 to 74 (median 25) mm. Nodal upstaging was observed in 38 patients (29.0%). A comparison between the nodal upstage group and the no nodal upstage group is shown in Table 1.

We plotted the ROC curve and analyzed the cutoff value of the SUVmax for the primary lesion. The area under the curve for an SUVmax of 4.84 was 0.369, which was the largest. Therefore, an SUVmax of 5.0 was considered the cutoff for the primary lesions (Figure 2). An SUVmax ≥5 for the primary tumor was observed significantly more frequently in the nodal upstage group than in the no nodal upstage group. There were no significant differences between the groups in terms of sex, age at surgery, clinical stage, diabetes, tumor location, and presence or absence of obstructive ventilatory impairment.

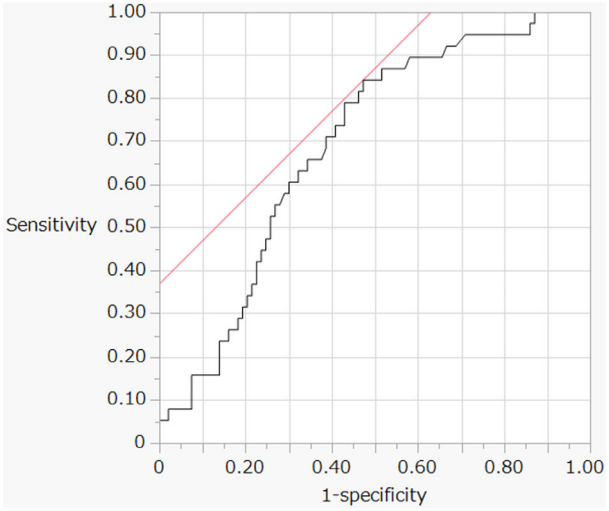

FIGURE 2 Receiver operating characteristic curves of the standardized uptake value of the primary tumor and nodal upstage

Clinical factors involved in nodal upstage

The univariate and multivariate analyses of the factors affecting nodal upstage are shown in Table 2. The multivariate analysis using 18F-FDG-PET-CT showed that an FDG SUVmax ≥5 for the primary tumor was a significant nodal upstaging factor. There were no significant differences in other clinical factors. Epidermal growth factor receptor mutational status was examined in only 59.5% (78/131) of the patients enrolled in this study. Therefore, gene mutation status was not included as a study variable.

Characteristics of lymph node in patients with nodal upstage

Regarding patients with nodal upstage, only one of 38 had lymph nodes larger than 10 mm in diameter on CT. That patient was preoperatively diagnosed as negative for malignancy because of interstitial pneumonia in the background and suspected reactive swelling.

Among the patients with nodal upstage, 23 (60.5%) had no lymph nodes with abnormal FDG uptake on ^{18}F-FDG-PET-CT. Patients with abnormal FDG uptake in the lymph nodes according to ^{18}F-FDG-PET-CT and with no lymph node metastasis were suspected to have physiological or inflammatory uptake.

DISCUSSION

During this study, patients with an FDG SUVmax ≥5 according to ^{18}F-FDG-PET-CT for the primary tumor were

TABLE 2 Factors associated with nodal upstage in patients with lung adenocarcinoma and micropapillary component

	Univariate		Multivariate	
	HR (95% CI)	***p* value[a]**	**HR (95% CI)**	***p* value[a]**
Age at resection, years				
<70	1	0.375	1	0.155
≥70	1.40 (0.66-3.00)		1.84 (0.79-4.29)	
Sex				
Male	1	0.732	1	0.828
Female	1.14 (0.54-2.43)		1.12 (0.40-3.13)	
Smoking history				
No	1	0.976	1	0.863
Yes	0.99 (0.45-2.16)		1.09 (0.38-3.16)	
FEV1.0				
≤70%	1	0.546	1	0.290
>70%	1.29 (0.57-2.93)		0.60 (0.23-1.54)	
Clinical stage				
I	1	0.272	1	0.511
II-III	1.58 (0.70-3.59)		1.34 (0.56-3.23)	
SUVmax of the main tumor				
<5	1	**0.001**	1	**0.001**
≥5	4.55 (1.89-11.0)		4.90 (1.96-12.2)	

Note: Values in bold indicate statistically significant.
Abbreviations: CI, confidence interval; FEV1.0, forced expiratory volume during 1 s; HR, hazard ratio; SUVmax, maximum standard uptake value.
[a]Cox regression models for comparison of upstage lymph node metastasis.

more likely to have lymph node metastasis after resection. For patients with suspected MPA preoperatively and with an FDG SUVmax ≥5 according to ^{18}F-FDG-PET-CT for the primary tumor, the possibility of lymph node metastasis should be considered even in the absence of evident lymphadenopathy or abnormal FDG uptake according to ^{18}F-FDG-PET-CT in the lymph nodes.

MPA was first reported in 1993 by Siriaunkul et al., who observed it in patients with breast cancer.[10] In 2002, Amin et al. were the first to report cases of primary lung adenocarcinoma with a micropapillary component.[11] Makimoto et al.[12] examined 122 patients with Noguchi type C lung adenocarcinoma 20 mm or smaller in diameter; of their 67 patients with a micropapillary component, lymph node metastasis was observed in 74%, and the 5-year survival rate was 54%. They reported that the presence of a micropapillary component was a poor prognostic factor for lung cancer.[13] Therefore, MPA has been added to the lung adenocarcinoma subtype in the 4th edition of the WHO classification.[1]

In addition to the poor prognosis, it should be noted that it is difficult to perform accurate stage evaluation before resection. MPA tends to metastasize to regional lymph nodes; however, preoperative CT and ^{18}F-FDG-PET-CT often fail to detect lymph node metastases.[13]

Bao et al. reported that patients with clinical T1aN0M0 NSCLC who had undergone surgical resection with systematic mediastinal node dissection or sampling had significantly more N1 and N2 disease with the micropapillary component.[9] Miyoshi et al. reported that 53% of patients with MPA had upstage after resection, and that upstage was caused by lymph node metastases in 25 patients, intrapulmonary metastases in 16 patients, and both in 19 patients.[6] Moon et al. reported that the presence of a micropapillary component was significantly more likely to be nodal upstage in 350 patients with clinical N0 lung adenocarcinoma.[14] Therefore, MPA has been reported as a factor associated with nodal upstage. Nodal upstage was observed in 29.0% of patients with MPA. Therefore, for patients who were predicted to have MPA preoperatively, there is an urgent need to investigate the predictors of nodal upstage.

Dales et al. performed a meta-analysis of preoperative CT staging for NSCLC and reported that lymph node with minor diameter larger than 1.0 cm on CT suggested lymph node metastases (sensitivity 79%, specificity 78%), and that this size criterion was useful for preoperative diagnosis.[15]

Additionally, ^{18}F-FDG-PET-CT can be used for more accurate staging than CT alone.[16] The sensitivity and specificity estimates for the SUVmax ≥2.5 positivity criterion were 81.3% and 79.4%, respectively.[17] In contrast, abnormal FDG uptake on ^{18}F-FDG-PET-CT is likely attributable to inflammation and sarcoid-like reactions, and it may be difficult to interpret.[18]

In this study, of the 38 patients with nodal upstage, only one had lymph nodes larger than 1.0 cm in minor diameter and 23 (60.5%) showed no abnormal FDG uptake in the lymph nodes on ^{18}F-FDG-PET-CT. The possibility of lymph node metastasis must be considered seriously in the absence of lymphadenopathy and abnormal FDG uptake in the lymph nodes on ^{18}F-FDG-PET-CT for patients with MPA.

Recently, some studies have reported that MPA can be diagnosed preoperatively. Ding et al. have constructed diagnostic models using artificial intelligence and successfully estimated the presence of micropapillary components from CT images with 92% accuracy.[19] Additionally, the usefulness of bronchoscopy for the detection of micropapillary components has been reported. Gao et al. investigated the factors affecting the diagnostic yield of bronchoscopy for patients with adenocarcinoma and reported that micropapillary type predominance was noted in 17 patients, with an endoscopic diagnostic yield of 94.1%.[20] Hoshi et al. reviewed cytologic specimens obtained by bronchoscopy performed preoperatively and reported that cytologic specimens may be better able to reflect micropapillary features than histologic specimens.[21] Furthermore, the development of instruments for bronchoscopy and the diagnostic techniques for pathology, cytology, and transbronchial cryocytology have been reported to result in better diagnostic accuracy than conventional methods of freezing and collecting tissue because they result in less crushing (and therefore less damage) and the collection of larger specimens.[22] Therefore, it is anticipated that more patients will be diagnosed with MPA before resection.

MPA has been reported as a risk factor for local recurrence after limited resection.[23,24] Nitadori et al. reported that the recurrence rate was significantly lower in the lobectomy group than in the limited resection group of patients with adenocarcinoma with a micropapillary component of 5% or more.[23] Satoh et al. revealed that lymph node metastases and vascular infiltration rates were significantly higher in patients with stage I adenocarcinoma in whom MPA clusters were found by preoperative bronchoscopic cytology than in those in whom MPA clusters were not found.[4] Therefore, patients with a preoperative diagnosis of MPA should undergo lobectomy with lymph node dissection as standard treatment.

During this study, patients with an FDG SUVmax ≥5 for the primary tumor had significant nodal upstage. Therefore, patients with an FDG SUVmax ≥5 for the primary tumor and MPA before resection require strict lymph node dissection, even when clear lymph node metastases are not detected. For patients with predicted MPA preoperatively, it may be possible to determine the exact staging and the appropriate extent of resection and surgical procedures by considering ^{18}F-FDG-PET-CT findings.

This study has several limitations. First, this was a retrospective study conducted at a single institution, and the imaging modality was different among patients. Second, there were no clear criteria for assessing metastases on ^{18}F-FDG-PET-CT scans performed preoperatively, and the results were mainly based on the radiologists' subjective findings. Third, the sample size and statistical power were small. Therefore, further large clinicopathological studies are required to overcome these limitations, so we plan to continue the study to increase the number of patients.

CONCLUSIONS

In patient with MPA, we revealed that an FDG SUVmax ≥5 for the primary tumor was a significant nodal upstaging factor. For patients with lung MPA diagnosed preoperatively and FDG SUVmax ≥5 for the primary tumor, the possibility of lymph node metastases should be considered, and standard surgical resection with radical lymph node dissection instead of limited resection should be performed for these patients.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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REFERENCES

1. Travis WD, Brambilla E, Burke AP. WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon: World Health Organization; 2015.
2. Wang W, Hu Z, Zhao J, Huang Y, Rao S, Yang J, et al. Both the presence of a micropapillary component and the micropapillary predominant subtype predict poor prognosis after lung adenocarcinoma resection: a meta-analysis. J Cardiothorac Surg. 2020; 15:154.
3. Nakashima H, Jiang SX, Sato Y, Hoshi K, Matsumoto T, Nagashio R, et al. Prevalent and up-regulated vimentin expression in micropapillary components of lung adenocarcinomas and its adverse prognostic significance. Pathol Int. 2015;65:183–92.
4. Satoh Y, Hoshi R, Horai T, Okumura S, Nakagawa K, Ishikawa Y, et al. Association of cytologic micropapillary clusters in cytology samples with lymphatic spread in clinical stage I lung adenocarcinomas. Lung Cancer. 2009;64:277–81.
5. Yoshida Y, Nitadori JI, Shinozaki-Ushiku A, Sato J, Miyaji T, Yamaguchi T, et al. Micropapillary histological subtype in lung adenocarcinoma of 2 cm or less: impact on recurrence and clinical predictors. Gen Thorac Cardiovasc Surg. 2017;65:273–9.
6. Miyoshi T, Satoh Y, Okumura S, Nakagawa K, Shirakusa T, Tsuchiya E, et al. Early-stage lung adenocarcinomas with a micropapillary pattern, a distinct pathologic marker for a significantly poor prognosis. Am J Surg Pathol. 2003;27:101–9.
7. Mikubo M, Naito M, Matsui Y, Shiomi K, Ichinoe M, Yoshida T, et al. Relevance of intraoperative pleural lavage cytology and

histologic subtype in lung adenocarcinoma. Ann Thorac Surg. 2018;106:1654–60.
8. Chang C, Sun X, Zhao W, Wang R, Qian X, Lei B, et al. Minor components of micropapillary and solid subtypes in lung invasive adenocarcinoma (≤3 cm): PET/CT findings and correlations with lymph node metastasis. Radiol Med. 2020;125:257–64.
9. Bao F, Yuan P, Yuan X, Lv X, Wang Z, Hu J. Predictive risk factors for lymph node metastasis in patients with small size non-small cell lung cancer. J Thorac Dis. 2014;6:1697–703.
10. Siriaunkgul S, Tavassoli FA. Invasive micropapillary carcinoma of the breast. Mod Pathol. 1993;6:660–2.
11. Amin MB, Tamboli P, Merchant SH, Ordóñez NG, Ro J, Ayala AG, et al. Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. Am J Surg Pathol. 2002;26:358–64.
12. Makimoto Y, Nabeshima K, Iwasaki H, Miyoshi T, Enatsu S, Shiraishi T, et al. Micropapillary pattern: a distinct pathological marker to subclassify tumours with a significantly poor prognosis within small peripheral lung adenocarcinoma (≤20 mm) with mixed bronchioloalveolar and invasive subtypes (Noguchi's type C tumours). Histopathology. 2005;46:677–84.
13. Ohno Y, Koyama H, Yoshikawa T, Nishio M, Aoyama N, Onishi Y, et al. N stage disease in patients with non-small cell lung cancer: efficacy of quantitative and qualitative assessment with STIR turbo spin-echo imaging, diffusion-weighted MR imaging, and fluorodeoxyglucose PET/CT. Radiology. 2011;261:605–15.
14. Moon Y, Kim KS, Lee KY, Sung SW, Kim YK, Park JK. Clinicopathologic factors associated with occult lymph node metastasis in patients with clinically diagnosed N0 lung adenocarcinoma. Ann Thorac Surg. 2016;101:1928–35.
15. Dales RE, Stark RM, Raman S. Computed tomography to stage lung cancer. Approaching a controversy using meta-analysis. Am Rev Respir Dis. 1990;141:1096–101.
16. Shim SS, Lee KS, Kim BT, Chung MJ, Lee EJ, Han J, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. Radiology. 2005;236:1011–9.
17. Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roqué i Figuls M, et al. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev. 2014;2014:CD009519. https://doi.org/10.1002/14651858.CD009519.pub2
18. Halpern BS, Schiepers C, Weber WA, Crawford TL, Fueger BJ, Phelps ME, et al. Presurgical staging of non-small cell lung cancer: positron emission tomography, integrated positron emission tomography/CT, and software image fusion. Chest. 2005;128:2289–97.
19. Ding H, Xia W, Zhang L, Mao Q, Cao B, Zhao Y, et al. CT-based deep learning model for invasiveness classification and micropapillary pattern prediction within lung carcinoma. Front Oncol. 2020;10:1186. https://doi.org/10.3389/fonc.2020.01186
20. Gao W, Li C, Wang H, Han P, Nie Y. Multivariate analysis of the diagnostic yield of conventional bronchoscopy in peripheral lung adenocarcinoma. Cancer Manag Res. 2019;11:9883–9.
21. Hoshi R, Tsuzuku M, Horai T, Ishikawa Y, Satoh Y. Micropapillary clusters in early-stage lung adenocarcinomas. Cancer. 2004;122:81–6.
22. Hetzel J, Eberhardt R, Herth FJ, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicenter trial. Eur Respir J. 2012;39:685–90.
23. Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, et al. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. J Natl Cancer Inst. 2013;105:1212–20.
24. Lee MC, Buitrago DH, Kadota K, Jones DR, Adusumilli PS. Recent advances and clinical implications of the micropapillary histological subtype in lung adenocarcinomas. Lung Cancer Manag. 2014;3:245–53.

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