

What is the appropriate operative strategy for radiologically solid tumours in subcentimetre lung cancer patients?[†]

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Abstract

OBJECTIVES: Solid lung cancers, even subcentimetre lesions, are considered to be invasive pathologically. However, the clinicopathological features and appropriate operative strategies in patients with these small lesions are still controversial, especially for those with a radiologically solid appearance.

METHODS: Between 2004 and 2011, 135 patients underwent pulmonary resection for subcentimetre lung cancer with clinical-N0 (c-N0) status. The findings of preoperative thin-section computed tomography (CT) were reviewed, and subcentimetre lung cancer was divided into three groups: pure ground-glass nodule, part-solid and pure-solid lesions.

RESULTS: Among the 135 subcentimetre lung cancer patients with c-N0 status, 71 showed a solid appearance on thin-section CT scan. Furthermore, pathological nodal examinations were performed in 49 patients, and nodal involvement was found pathologically in 6 (12.2%) patients. All of them had pure-solid tumours ($P = 0.0010$). Among the patients with solid subcentimetre lung cancers, the maximum standardized uptake value (SUVmax) was the only significant predictor of nodal involvement by a multivariate analysis ($P = 0.0205$). With regard to the surgical outcomes, the overall 5-year survival and disease-free survival rates were 100 and 97.8% for part-solid lesions, and 87.3 and 74.8% for pure-solid lesions, respectively. Moreover, there was a significant difference in disease-free survival between a high SUVmax group (60.0%) and a low SUVmax group (94.9%) ($P = 0.0013$).

CONCLUSIONS: There might be a possibility of lymph node metastasis despite subcentimetre lung cancer, especially for radiological pure-solid nodules that show a high SUVmax. If limited surgery is indicated for solid subcentimetre lung cancer, a thorough intraoperative evaluation of lymph nodes is needed to prevent loco-regional failure.

Keywords: Sub centimetre • Solid appearance • Prognosis • Lymph node metastasis

INTRODUCTION

The recent development of computed tomography (CT) for the screening of lung cancer has made it possible to detect small lung nodules [1, 2]. While limited surgical resection has gradually become a standard treatment for small-sized lung cancers with a wide area of ground-glass nodule (GGN) on CT scan because they are pathologically less invasive [3–8], some reports have described poor survival for subcentimetre lung cancers, especially those with a solid appearance on thin-section CT scan [9, 10]. These observations have clearly indicated that 'tumour size less than 1 cm' does not mean the absence of tumour spread if the tumour has a solid component.

While important phase III prospective trials are now underway in Japan [11] and the USA [12] regarding the feasibility of limited resection for clinical-T1a non-small-cell lung cancer with a radiologically 'part-solid' or 'pure-solid' appearance, how should we

treat more localized lung cancers, such as those that are less than a centimetre in diameter, and especially those with a solid appearance on thin-section CT scan? To date, there has been no definitive answer on this point. In the current retrospective study, we focused on the features of nodal metastasis and appropriate operative strategies in patients with subcentimetre lung cancer, especially for solid lesions, with respect to survival and recurrence for these small nodules.

PATIENTS AND METHODS

This protocol was approved by the ethics committee at our institute and this retrospective study was performed under a waiver of authorization approved by the institutional review board of the Juntendo University School of Medicine.

Between January 2004 and December 2011, 135 patients underwent pulmonary resection for clinical-N0 (c-N0) subcentimetre lung cancer. For all 135 patients, the findings of preoperative thin-section CT were reviewed by three authors (Aritoshi Hattori, Takeshi Matsunaga and Kenji Suzuki). A thin-section CT scan was

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performed to evaluate the entire lung for preoperative staging. The size and features of subcentimetre tumours were determined preoperatively based on the findings of thin-section CT scan. In addition, all tumours were subsequently evaluated to estimate the extent of GGN on thin-section CT scan with 2 mm collimation. The lung was photographed with a window level of -500 to -700 H and a window depth of 1000 – 2000 H as a 'lung window'. The solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGN was defined as an area of a slight, homogeneous increase in density that did not obscure the underlying vascular markings.

According to the radiological findings on thin-section CT scan, we defined the ratio of the maximum diameter of consolidation to the maximum tumour diameter as the consolidation/tumour ratio (CTR). In a current study, pure GGN was defined as a tumour with CTR equal to 0. A part-solid nodule was defined as a tumour with focal nodular opacity that contained both solid and GGN components ($0 < \text{CTR} < 1.0$), and a pure-solid nodule was defined as a tumour that only showed consolidation without GGN ($\text{CTR} = 1.0$). A flow chart of patients with subcentimetre lung cancer is shown in Fig. 1. In this study, 'solid' subcentimetre lung cancers were composed of part- and pure-solid nodules. The evaluation of pure-GGN lesions were excluded from this study.

With regard to the technique used for ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scanning, 71 patients underwent a PET/CT scan at the Yotsuya Medical Cube (Tokyo, Japan). The technique used for ^{18}F -FDG-PET/CT scanning at the Yotsuya Medical Cube was as follows. All patients were asked to fast for at least 6 h before FDG injection to minimize their blood insulin level and normal tissue glucose uptake. The subjects were injected intravenously with 3.5 MBq/kg of ^{18}F -FDG, and static emission images were obtained 60 min after injection. Image acquisition was performed using a Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). After CT image acquisition, emission scanning was performed from the head to the mid-thighs in six bed positions. The acquired PET data were reconstructed to volumetric images with a 2-dimensional ordered subset expectation maximization algorithm (2 iterations/15 subsets) incorporating a CT-based attenuation correction.

All PET/CT images were interpreted by one or two experienced nuclear medicine radiologists. A workstation (Xeleris; Elegems, Haifa, Israel) was used for image display and analysis, and the maximum standardized uptake value (SUVmax) of the primary tumour was obtained.

As for the operations, if tumours showed part-solid subcentimetre appearance, some would be considered as radiological non-invasive lung adenocarcinomas, and candidates for limited surgical resection based on the CTR on thin-section CT scan [8]. The indications for lobectomy for part-solid subcentimetre lung cancer were based on the Japan Clinical Oncology Group (JCOG 0802 [11]). In contrast, a pure-solid subcentimetre lung cancer warranted a major lung dissection with systemic lymph node dissection or sampling in our report. Non-anatomical wedge resection with lymph node sampling was performed for a few elderly, or cardiopulmonary high risk patients.

With regard to nodal assessment, patients who underwent segmentectomy or lobectomy were evaluated for hilar or mediastinal lymph node status. Non-invasive modalities for mediastinal lymph node staging, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS), were used preoperatively in any of these patients at our institute. In patients at high risk for lymph node dissection or who underwent

wedge resection, the intraoperative pathological node assessment was performed by lymph node sampling only when a positive node was strongly suggested by a thorough check of intraoperative nodal findings.

The medical records of each subcentimetre lung cancer patient were reviewed to determine gender, age, pack-year smoking, maximum tumour dimension on thin-section CT scan, consolidation status, pleural involvement, air bronchogram in the tumour, serum carcinoembryonic antigen (CEA) level (ng/ml) and SUVmax on PET. The relationships between these factors and postoperative nodal status were investigated to identify significant predictors among solid subcentimetre lung cancers. Clinical follow-up was performed at least every 6 months for 2 years and at least yearly thereafter. Thin-section CT scan or PET/CT scan was performed every year. Evidence of death and or recurrence was obtained from the medical records. A univariate analysis was performed using Fisher's exact test or χ^2 test to compare two factors. A multivariate analysis was used to identify the clinical factors that predicted nodal involvement, which was performed by logistic regression analysis using SPSS Statistics 21 (SPSS, Inc.). Forward and backward stepwise procedures were used to identify the significant factors that were essential for predicting the prognosis. Survival was calculated by the Kaplan–Meier method, starting from the date of surgery for subcentimetre lung cancer. Statistical analysis was considered to be significant when the probability value was less than 0.05.

RESULTS

Among the 135 resected c-N0 subcentimetre lung cancer patients, 71 (52.6%) showed a solid appearance on thin-section CT scan. Among patients with a solid subcentimetre lung cancer, 29 were men and 42 were women. Patients ranged in age from 24 to 84 years, with an average of 65 years. With regard to the GGN status, 45 patients had a part-solid tumour, and 26 had a pure-solid tumour. The overall characteristics of solid subcentimetre lung cancer are given in Table 1.

Among 71 solid subcentimetre lung cancer patients, intraoperative nodal assessment, i.e. lymph node dissection or sampling, was performed in 49 (69.0%) patients. Among them, nodal involvement was found pathologically in 6 (12.2%) patients with c-N0 solid subcentimetre lung cancer. According to a univariate analysis, our results revealed that a pure-solid appearance ($P = 0.0010$) and the SUVmax on PET ($P < 0.0001$) were significant predictors of postoperative lymph node metastasis in patients with solid subcentimetre lung cancer with pathological nodal examinations (Table 2). Moreover, a multivariate analysis showed that SUVmax on PET was the only significant predictor of pathological nodal involvement (hazard ratio; 8.579, 95% confidence interval; 1.392–52.889, $P = 0.0205$) in this cohort (Table 3).

Interestingly, all the patients with pathological nodal metastasis had a pure-solid appearance ($\text{CTR} = 1.0$) based on the findings of thin-section CT scan. Moreover, the frequency of lymph node metastasis was 41.2% for patients with c-N0 solid subcentimetre lung cancer if the tumour showed SUVmax ≥ 2.5 and a pure-solid appearance on thin-section CT scan.

The median follow-up period was 36 months. Although pure-GGN lesions were excluded from this study, the overall 5-year survival rate and disease-free survival rate of pure-GGN were each 100%. For 45 patients with part-solid subcentimetre lesions, the overall 5-year survival rate was 100% and disease-free survival rate

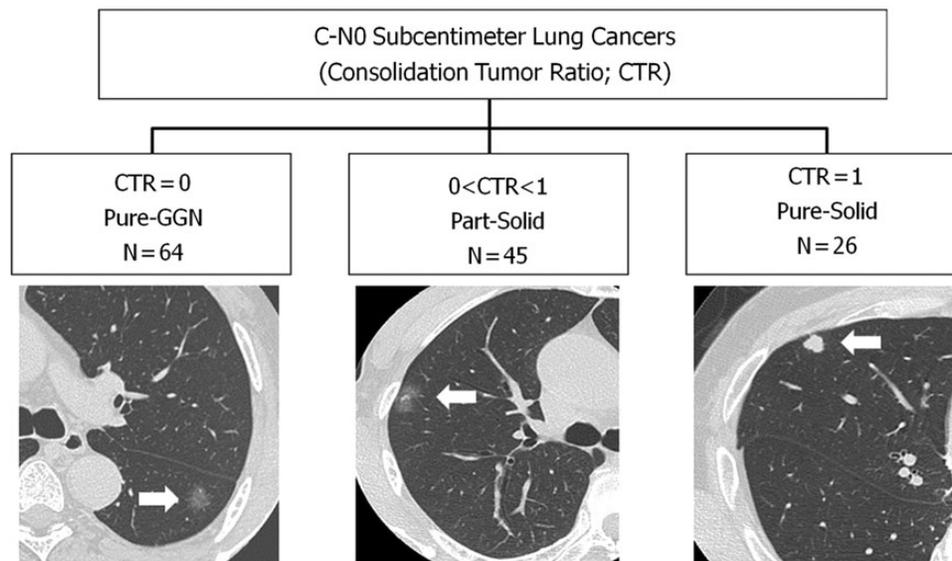


Figure 1: Scheme for the study population. Pure ground-glass nodule (GGN) was excluded from this study, and ultimately 71 patients with radiologically 'solid' subcentimetre lung cancers were considered in this analysis.

Table 1: Overall characteristics of 71 patients with solid subcentimetre lung cancer with clinical-N0 status

Factors	Number or mean \pm SD (range)
Total	71
Age (years)	65.0 (24–84)
Gender (male/female)	29/42
Pack-year smoking (30 or less/more than 30)	48/23
Maximum tumour dimension (mm)	7.8 \pm 2.16 (2.0–10.0)
1–5/6–10 (mm)	13/58
GGN status	
Pure-GGN/part-solid nodule/pure-solid nodule	64/45/26
CEA (ng/ml)	2.06 \pm 1.82 (0.50–13.5)
CEA \leq 3/3 < CEA	46/15
SUVmax on PET	
SUVmax \leq 2.5/2.5 < SUVmax	59/12

GGN: ground-glass nodule; CEA: carcinoembryonic antigen; SUV: standardized uptake value; PET: positron emission tomography.

was 97.8% (Fig. 2). On the other hand, 26 patients with pure-solid lesions showed a poor outcome, as reflected by both the overall 5-year survival (87.3%) and disease-free survival (74.8%) (Fig. 3).

The relationships between the consolidation status, the mode of surgical resection and pathological aspects are given in Table 4. With regard to part-solid subcentimetre lung cancer, wedge resection was performed in 15 (33%) patients, segmentectomy was performed in 16 (36%) and lobectomy was performed in 14 (31%). The operative procedures for patients with part-solid subcentimetre lung cancer were selected based on the findings of thin-section CT scan, tumour location or other perioperative factors including SUVmax on PET. Regarding the indications for lobectomy for part-solid subcentimetre lung cancer, 4 patients were in clinical trials for part-solid lung cancers according to the Japan Clinical Oncology Group (JCOG 0802 [11]), and the other patients had centrally located or right middle lobe tumours.

Table 2: Results of a univariate analysis for predictors of nodal involvement among 49 solid subcentimetre lung cancer patients with pathological nodal examination

Clinicopathological factors	Number of patients	Number of patients with nodal involvement (%)	P-value*
Total	49	6 (12.2)	
Gender			
Male	20	4 (20.0)	0.1690
Female	29	2 (6.9)	
Age (years)			
\geq 70	10	2 (20.0)	0.4017
<70	39	4 (10.2)	
Pack-year smoking			
\geq 30	17	3 (17.6)	0.4005
<30	32	3 (9.4)	
Maximum tumour dimension (mm)			
1–5	9	2 (22.2)	0.3122
6–10	40	4 (10.0)	
GGN status			
Part-solid nodule	30	0 (0)	0.0010
Pure-solid nodule	19	6 (31.6)	
CEA (ng/ml)			
\leq 3	41	4 (9.8)	0.2289
>3	8	2 (25.0)	
SUVmax on PET			
\leq 2.5	39	1 (2.6)	<0.0001
>2.5	10	5 (50.0)	

GGN: ground-glass nodule; CEA: carcinoembryonic antigen; SUV: standardized uptake value; PET: positron emission tomography.

*P-value in χ^2 test or Fisher's exact test.

On the other hand, standard lobectomy was performed in 13 (52%) patients for pure-solid subcentimetre lung cancer with high risk, regardless of the results of intraoperative frozen section diagnosis for nodal dissection. Furthermore, hilar or mediastinal lymph node dissection or sampling was performed in 73% of patients with pure-solid tumours. Wedge resection with or

Table 3: Results of a multivariate analysis for predictors of nodal involvement among 49 solid subcentimetre lung cancer patients with pathological nodal examination

Variable	Hazard ratio	95% Confidence interval	P-value*
Age (>70 years)	5.552	0.247-125.43	0.2796
Gender (male)	2.726	0.154-48.398	0.4944
Pack-year smoking (<30)	0.017	0.001-1.420	0.0711
Maximum tumour dimension (mm)	1.623	0.737-3.356	0.1881
CEA (ng/ml)	2.445	0.920-6.570	0.0759
SUVmax on PET	8.579	1.392-52.889	0.0205

CEA: carcinoembryonic antigen; SUV: standardized uptake value; PET: positron emission tomography.
*P-value in logistic regression analysis.

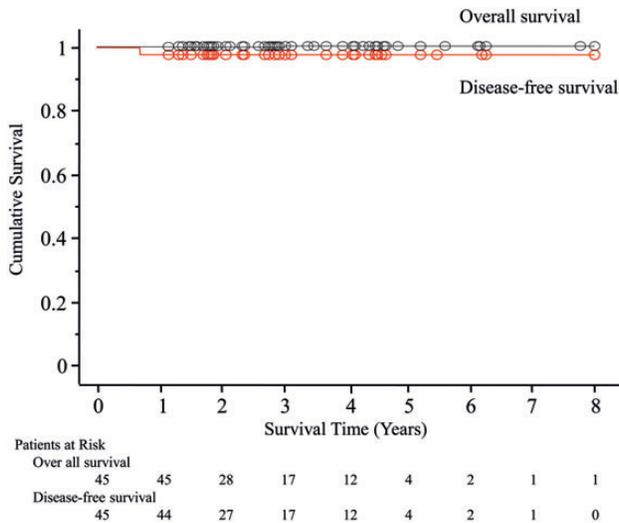


Figure 2: Survival curve for 45 patients with surgically resected subcentimetre lung cancer that showed a part-solid appearance on thin-section CT. For c-N0 status, the overall 5-year survival rate was 100% and the disease-free survival rate was 97.8%. c-N0: clinical-N0.

without lymph node sampling was performed in 9 patients with pure-solid tumours because of their poor condition, including reduced pulmonary function.

When we divided solid subcentimetre lung cancer patients into two groups based on an SUVmax cut-off value of 2.5, there was a significant difference in disease-free survival between the high SUVmax group (60.0%) and the low SUVmax group (94.9%) ($P=0.0013$) (Fig. 4). Moreover, postoperative recurrence developed in 4 (33%) of the 12 patients with both a pure-solid appearance and SUVmax ≥ 2.5 . Conversely, postoperative loco-regional failure has not been found with limited surgery in patients with a low SUVmax, even for pure-solid subcentimetre lung cancer.

DISCUSSION

Owing to the improved quality of CT images and increased opportunities for CT examinations in screening programs, smaller and fainter lung nodules are being detected on CT imaging [1, 2].

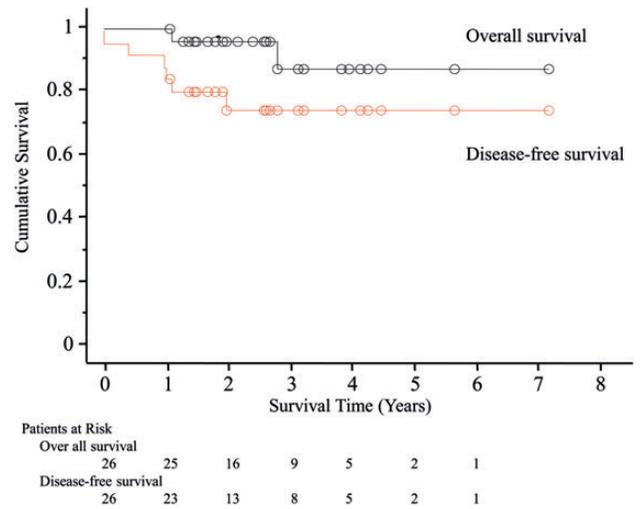


Figure 3: Survival curve for 26 patients with surgically resected subcentimetre lung cancer that showed a pure-solid appearance on thin-section CT. For c-N0 status, the overall 5-year survival rate was 87.3% and the disease-free survival rate was 74.8%.

Table 4: Relationships between GGN status, surgical interventions and pathological aspects

	GGN status	
	Part-solid tumour (n = 45)	Pure-solid tumour (n = 26)
Operative mode		
Wedge resection	15	9
Segmentectomy	16	4
Lobectomy	14	13
Lymph node dissection or sampling		
None	15	7
Hilar only	16	1
Mediastinal/hilar	14	18
Nodal involvement		
Nx	15	7
N0	30	13
N1	0	2
N2	0	4
Pathology		
Adenocarcinoma (including BAC)	43	18
AAH	2	0
Squamous cell carcinoma	0	5
Others	0	3

GGN: ground-glass nodule; BAC: bronchioloalveolar carcinoma; AAH: atypical adenomatous hyperplasia.

With the recent increase in opportunities for discovering subcentimetre lung lesions, the clinicopathological features and proper management of tumours smaller than 1 cm have become of greater concern in thoracic surgery [9, 10, 13, 14]. Recently, the indication for limited surgery has been extended to very early lung cancers that are located peripherally and show a GGN appearance on thin-section CT scan; these are good candidates for limited surgery because of their minimally invasive nature according to the results of the prospective trial JCOG 0201 [8].

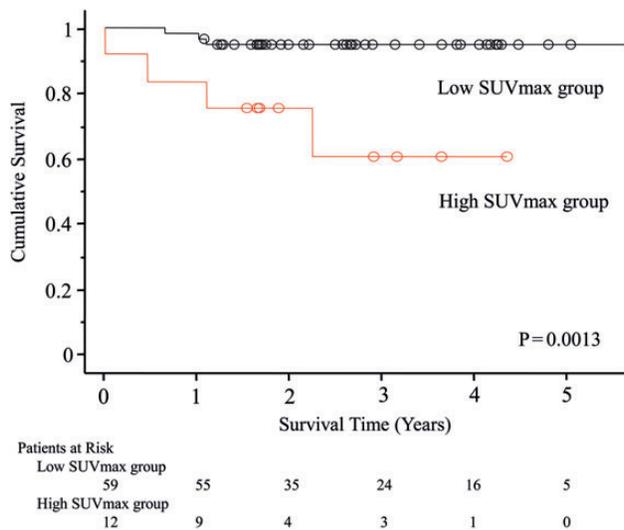


Figure 4: Comparison of the survival curves for patients with surgically resected solid subcentimetre lung cancers grouped according to the level of SUVmax on PET. A statistically significant difference was observed between the survival outcomes in the high SUVmax group (60.0%) and the low SUVmax group (94.9%) (log-rank test, $P = 0.0013$). SUVmax: maximum standardized uptake value; PET: positron emission tomography.

On the other hand, there has been considerable discussion regarding limited surgery for lung cancer with a solid appearance on thin-section CT scan, i.e. invasive lung cancer. Invasive lung cancer can be associated with occult lymph node metastasis, regardless of how small it is [15]. This could result in incomplete resection following limited surgical resection [16]. Pathological nodal metastasis was found in ~15% of subcentimetre lung cancer patients exclusively with a solid appearance on thin-section CT [9]. These observations clearly demonstrate that ‘tumour size less than 1 cm’ does not indicate the absence of tumour spread, and limited resection should not necessarily be indicated for solid subcentimetre lesions. Therefore, what is the proper management of subcentimetre lung cancer with a broad area of solid lesion? We tried to investigate the appropriate surgical strategy for subcentimetre lung cancer, especially for solid, i.e. invasive, lesions from the perspective of lymph node metastasis and postoperative outcomes.

According to the results in 71 solid subcentimetre lung cancer patients with c-N0 status, both postoperative nodal involvement and poor outcomes were found after lung resection, especially in patients with a high SUVmax and a radiological pure-solid appearance on thin-section CT. Thus, the findings on thin-section CT and the SUVmax value for solid subcentimetre lesions could reflect the pathological nature of lung cancer more accurately than the size. Furthermore, the accurate nodal assessment is crucial even in subcentimetre tumours, because the patients with more invasive lesions need a systemic therapy such as adjuvant chemotherapy.

With regard to the preoperative nodal assessment other than surgery, no other invasive modalities for mediastinal lymph node staging, such as mediastinoscopy or EBUS, were used preoperatively in any of these patients at our institute. This is because our study enrolled c-N0 subcentimetre lung cancer. Preoperatively suspicion lesions of lymph node metastasis were radiologically defined as those with more than 10 mm in diameter of a minor axis. In this study, there was no occurrence of such swollen lymphatic lesions. Therefore, we did not perform preoperative invasive

diagnostic methods. However, in order to improve the preoperative diagnostic accuracy of lymphatic involvement, our study may be beneficial to identify the candidates for undergoing preoperative invasive procedure like mediastinoscopy or EBUS.

With regard to the operative strategies for solid subcentimetre lung cancers, a thorough lymph node assessment is mandatory especially in patients with radiologically pure-solid tumours and a high SUVmax level, despite their subcentimetre size. This is due to the high probability of pathological nodal involvement and a high loco-regional recurrence rate even in these cohorts. In contrast, the appropriate operative modes are still controversial for these subcentimetre lesions. At our institute, a major lung resection was performed in subcentimetre lung cancer patients with a radiologically pure-solid appearance whenever operable due to the strong possibility of nodal involvement. Intraoperative frozen section diagnosis for the resected lymph node was performed in the case of lobectomy or segmentectomy in accordance with the oncological surgical procedure, but basically we adopt lobectomy for pure-solid lung cancer, especially in cases with a high SUVmax because of the possible presence of nodal involvement [16] and the desire to prevent probable occult lymph node metastasis [15]. Regarding the operative strategy for pure-solid subcentimetre lung cancers with a low SUVmax, intentional segmentectomy may be considered as a possibility because of the absence of nodal metastasis and postoperative loco-regional failure. On the other hand, limited resection can be used in the case of part-solid subcentimetre lung cancers because of the possible absence of nodal metastasis. But the appropriate operative modes are still unclear for these lesions. Further studies regarding the appropriate operative strategies for subcentimetre lung cancers are warranted.

The role of FDG-PET in the evaluation of subcentimetre lesions remains unclear [17–19]. Its main limitation is false-negative findings because of its low sensitivity for small adenocarcinoma with a predominant bronchioloalveolar carcinoma component, especially for those smaller than 5 mm [18–20]. On the other hand, FDG-PET is expected to be effective for the appropriate management of solid subcentimetre lung cancer, i.e. invasive lung cancer, because of the possibility that they are sensitive to FDG due to their invasive nature. Based on our study, the selective use of PET for solid subcentimetre lung cancers could be suitable for predicting postoperative lymph node involvement and loco-regional recurrence despite their small size. Thus, a high SUVmax, especially in a small lung cancer, provides important information and can aid therapeutic management. Therefore, if solid subcentimetre lung cancers are FDG avid, they may have high malignant potential, and may be associated with a high frequency of lymph node metastasis and a poor prognosis despite their small size. On the other hand, in our study, loco-regional failure was not found by limited surgery for pure-solid lesions with a low SUVmax. Thus, in practice, limited surgical resection such as segmentectomy might be considered as a possibility for patients with pure-solid subcentimetre lung cancers, for tumours with low FDG avidity despite a pure-solid appearance. In the future, further refinement of PET scanners may be needed for the accurate diagnosis of subcentimetre lung cancers.

This study was limited by a relatively short median follow-up period. Further investigations regarding definitive prognoses are warranted.

In conclusion, even in cases of subcentimetre lung cancer, lymph node metastasis is frequently observed for radiologically pure-solid nodules, especially for tumours that show a high SUVmax. If limited surgery is indicated for solid subcentimetre

lung cancer, a thorough intraoperative evaluation of lymph nodes is needed to prevent loco-regional failure.

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