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

Aritoshi Hattori, Kenji Suzuki*, Takeshi Matsunaga, Yoshikazu Miyasaka, Kazuya Takamochi and Shiaki Oh

Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan

* Corresponding author. Division of General Thoracic Surgery, Juntendo University School of Medicine, 1-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113-8431, Japan. Tel: +81-3-38133111; fax: +81-3-58000281; e-mail: kjsuzuki@juntendo.ac.jp (K. Suzuki).

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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-grass 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

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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 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

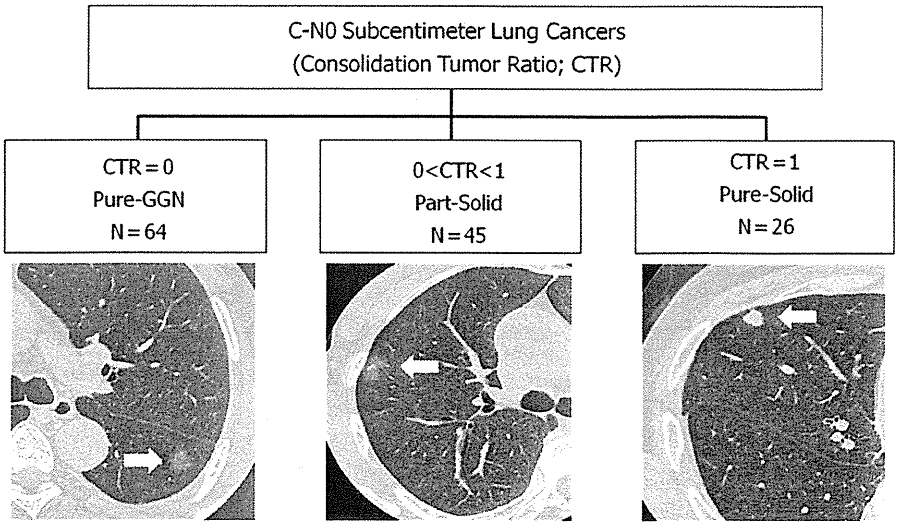

Figure 1: Scheme for the study population. Pure ground-glass nodule (GGN) was excluded from this study, and ultimately 71 patients with radiologically 'solid' subcentimetre lung cancers were considered in this analysis.

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

Factors	Number or mean ± 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 ± 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 ± 1.82 (0.50–13.5)
CEA ≤ 3/3 < CEA	46/15
SUVmax on PET	
SUVmax ≤ 2.5/2.5 < SUVmax	59/12

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

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 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)			
≥70	10	2 (20.0)	0.4017
<70	39	4 (10.2)	
Pack-year smoking			
≥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)			
≤3	41	4 (9.8)	0.2289
>3	8	2 (25.0)	
SUVmax on PET			
≤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

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.

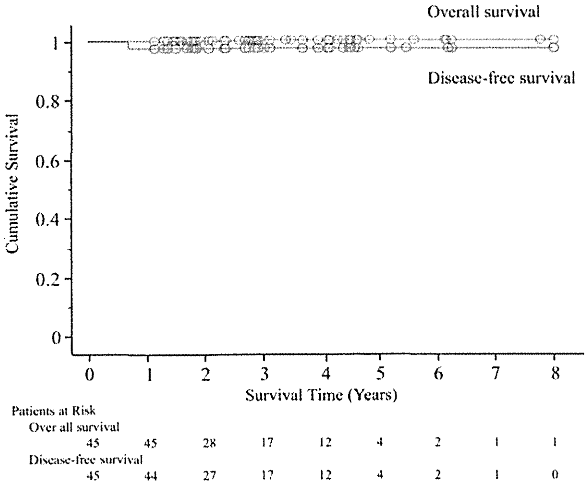

Figure 2: Survival curve for 45 patients with surgically resected subcentimetre lung cancer that showed a part-solid appearance on thin-section CT. For c-N0 status, the overall 5-year survival rate was 100% and the disease-free survival rate was 97.8%. c-N0: clinical-N0.

patients with pure-solid tumours. Wedge resection with or 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.

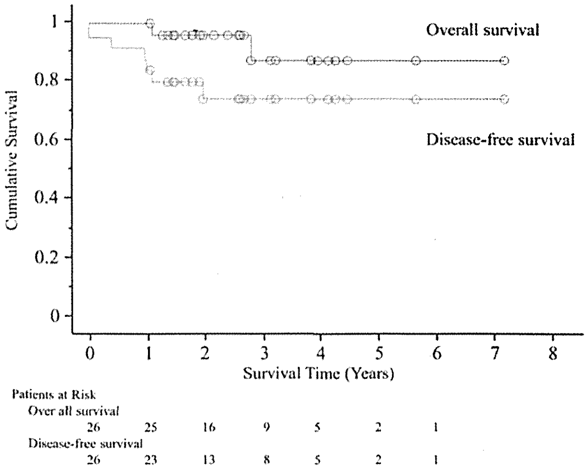

Figure 3: Survival curve for 26 patients with surgically resected subcentimetre lung cancer that showed a pure-solid appearance on thin-section CT. For c-N0 status, the overall 5-year survival rate was 87.3% and the disease-free survival rate was 74.8%.

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.

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]. 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].

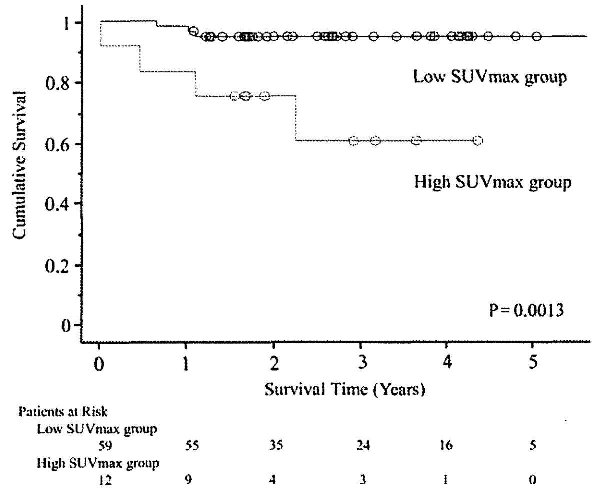

Figure 4: Comparison of the survival curves for patients with surgically resected solid subcentimetre lung cancers grouped according to the level of SUVmax on PET. A statistically significant difference was observed between the survival outcomes in the high SUVmax group (60.0%) and the low SUVmax group (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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ORIGINAL ARTICLE

Clinical features of multiple lung cancers based on thin-section computed tomography: What are the appropriate surgical strategies for second lung cancers?

Aritoshi Hattori · Kenji Suzuki · Kazuya Takamochi · Shiaki Oh

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Abstract

Purpose We investigated the proper surgical strategies for second lung cancers based on the findings of thin-section CT.

Methods We classified 59 patients with second lung cancers into two categories based on the thin-section CT findings. In the ground glass nodule (GGN) group ($n = 29$), the first and/or the second lung cancers showed a GGN on thin-section CT. In the Solid group ($n = 30$), both the first and second lung cancers showed a solid appearance.

Results The overall 5-year survival rate after second surgery was 71.7 %. The univariate analyses revealed that the presence of more than three lung tumors was significantly more common in the GGN group. Regarding the surgical strategies, all the patients in the GGN group underwent limited resection for at least one of the operations, whereas 36 % of those in the Solid group underwent bilateral lobectomy. The 5-year survival in the GGN group (89.1 %) was significantly better than that in the Solid group (40.8 %) ($p = 0.0305$).

Conclusions Limited resection should be performed for GGN patients as much as possible to preserve lung function, due to the possible presence of more than three lung cancers. Despite the higher likelihood of having more tumors, the GGN patients had a better survival. In contrast, lobectomy for second lesions should be aggressively considered for solid tumor patients whenever possible.

Keywords Second lung cancer · Surgery · Prognosis · Thin-section computed tomography

Introduction

Due to recent advances in treatment strategies and the long-term survival of lung cancer patients, there have been more opportunities to detect second lung cancers, and thoracic surgeons are frequently being asked to treat patients with second primary lung cancers. Survivors of lung cancer are at a higher risk for various second malignancies, including lung cancer [1]. The risk of second lung cancers after a prior lung surgery has been estimated to be 1–2 % per patient year [2]. Several authors have reported acceptable results with an aggressive surgical approach for patients with second lung cancers, and this has offered the greatest chance for long-term survival in patients with multiple lung cancers [3–16]. However, a consensus has not yet been reached regarding the appropriate surgical strategies for second lung cancer due to the presence of various preoperative patient factors, such as the extent and site of the new disease, the initial surgical procedure and the patient's pulmonary functional reserve [17].

In general, ground glass nodule (GGN) lesions are considered to have a tendency for multicentric expression. Clinically, however, we have experienced different patterns in the findings of multiple primary lung cancers (MPLCs), i.e., minimally invasive or invasive lesions. The

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A. Hattori · K. Suzuki (✉) · K. Takamochi · S. Oh
Department of General Thoracic Surgery, Juntendo University School of Medicine, 1-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113-8431, Japan
e-mail: kjsuzuki@juntendo.ac.jp

A. Hattori
e-mail: ahattori@juntendo.ac.jp

universal principles that underlie the combination or the sequence of the expression of MPLCs, which are important factors to consider when deciding on the proper surgical strategy, have not yet been clarified. For example, it is unknown whether MPLCs have unique clinical features based on the findings of thin-section CT scans, and what the most appropriate treatment strategies are for second lung cancers. If we had some knowledge regarding the tendencies of second malignancies and their predictive factors based on thin-section CT scans, thoracic surgeons would be better equipped to design follow-up plans and manage surgical strategies for second lung cancers.

The primary objective of this study was to investigate the clinical features of MPLCs based on the features of thin-section CT scans, and to identify proper treatment strategies for second primary lung cancers.

Patients and methods

Between January 2004 and May 2012, 1112 patients with primary lung cancer underwent pulmonary resection at our institute. Among them, 59 patients (5.6 %) with clinical-N0 (c-N0) status, who were detected during the follow-up period after the prior surgery and were pathologically diagnosed with a second primary lung cancer, were retrospectively investigated for this study using our institute's database. All patients underwent lung resections by staged surgery. For the clinicopathological definition of the second primary lung cancers, our criteria basically relied on the report published by Martini and Melamed [18]. In this study, second primary lung cancers were defined as lung lesions that were discovered during the follow-up period after surgery for prior lung cancer.

With regard to the histological studies, all resected specimens were formalin fixed and sliced at 5–10 mm intervals. Both the first and second lung cancers were evaluated microscopically by conventional hematoxylin and eosin staining. All histological materials included in the series were initially assessed by a pathologist at our institute. Basically, pulmonary metastasis (PM) was discriminated from MPLCs on the basis of the criteria described by Martini and Melamed [18]. PM was defined as an independent mass isolated from the primary malignancy with histopathological features identical to the primary tumor and lacking microscopic features suggesting a primary tumor. In that way, PM populations were excluded from this study. Furthermore, some cases with postoperative lymph node involvement included in the MPLCs population, in which such differentiation between MPLCs and PM was difficult, were also excluded from this study.

For all 59 patients with MPLCs, we reviewed the findings of preoperative computed tomography. The size of the tumors was determined preoperatively based on the findings of thin-section CT scans. In addition, all tumors were subsequently evaluated to estimate the extent of the GGN lesion in a 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.

A GGN tumor was defined as an area with a slight, homogeneous increase in density that did not obscure the underlying vascular markings. In the current study, a "GGN" tumor was defined as a tumor in which the ratio of the maximum diameter of consolidation to the maximum

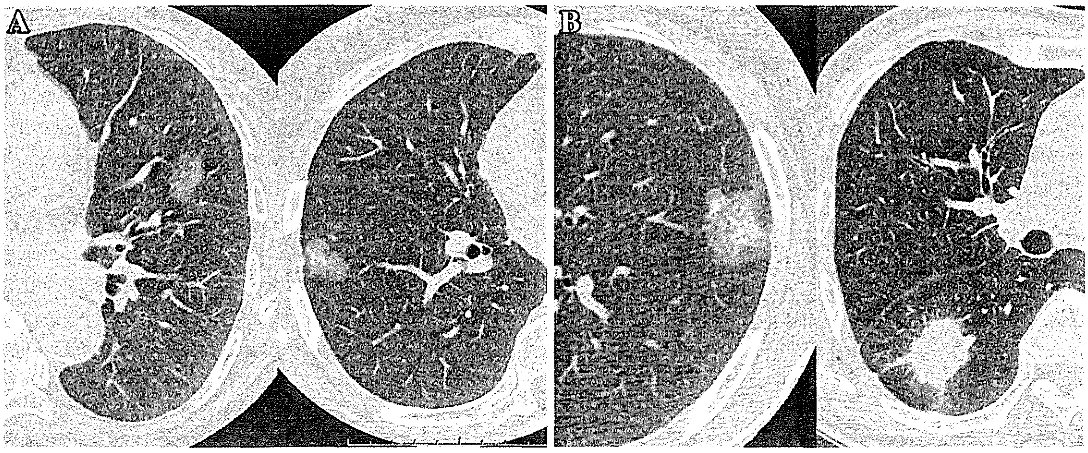


Fig. 1 Representative thin-section CT findings of GGN and solid tumors based on the ratio of the maximum consolidation diameter to the maximum tumor diameter (consolidation/tumor ratio, CTR). **a** A GGN tumor was defined as a tumor with a CTR ≤0.5. **b** a "Solid" tumor was defined as a tumor with a CTR >0.5. Furthermore, a "pure-solid" tumor was defined as a tumor with a CTR = 1.0 (*Right*)

Table 1 The classification of multiple primary lung cancer patients based on the findings of thin-section CT scans

Classification of MPLCs	Number
GGN group ($n = 29$)	
GGN tumor[a] + GGN tumor (G-G type)	11
At least one GGN tumor (G-S type)	18
Solid group ($n = 30$)	
Solid tumor[b] + Solid tumor	30

MPLCs multiple primary lung cancers, *GGN* ground glass nodule

[a] "GGN" tumor was defined as a tumor in which the ratio of the maximum diameter of consolidation to the maximum tumor diameter (consolidation/tumor ratio, CTR) ≤ 0.5

[b] A "solid" tumor was defined as a tumor with a CTR > 0.5

tumor diameter (consolidation/tumor ratio, CTR) was ≤ 0.5, whereas a "solid" tumor was defined as a tumor with a CTR >0.5. Among the solid tumors, "non pure-solid" tumors were defined as tumors with $0.5 < \mathrm{CTR} < 1.0$, whereas "pure-solid" tumors were defined as tumors with $\mathrm{CTR} = 1.0$ (Fig. 1). According to the radiological findings on thin-section CT, we categorized the patients with MPLCs into two groups based on the CTR: a Solid group and a GGN group (Table 1). In the Solid group, both the first and second lung cancers showed solid tumors, i.e., a non pure-solid or pure-solid appearance on thin-section CT scans. In contrast, in the GGN group, both the lung cancers exhibited GGN tumors (G-G type), or at least one had a GGN appearance (G-S type).

The medical record of each patient was reviewed with regard to age, gender, pack-years of smoking, total number of lung cancers, family history of any cancer, presence of double cancer, interval between the first and second operations, clinical status, histology, mean maximum tumor diameter, serum carcinoembryonic antigen level (ng/ml, CEA) and SUVmax on positron emission tomography (PET), which were taken as the higher of the values of the first and second lung cancers. The relationships between these clinical factors and the findings on thin-section CT scans based on the MPLC classifications were investigated to identify the features of resected MPLCs. Fisher's exact test was used to compare the differences between the GGN group and Solid group. The univariate analyses were used to identify the relationships between the clinical features and the findings of MPLCs based on thin-section CT scans. Several analyses were performed using the SPSS Statistics 21 software program (SPSS Inc.). Forward and backward stepwise procedures were used for the analysis. Survival was calculated by the Kaplan–Meier method, starting from the date of surgery for the second lung cancer. Differences were considered to be significant when the probability value was <0.05.

Results

Of 1112 resected non-small cell lung cancer patients, 59 underwent staged surgery for a second primary lung cancer that was detected after the operation for the first lung cancer. Among these, 30 were in the Solid group and 29 were in the GGN group based on the findings of thin-section CT scans. The MPLC classifications based on the findings of thin-section CT scans are shown in Table 1. Thirty-five patients were male and 24 were female. The patients ranged in age from 55 to 84 years, with an average of 68 years. The overall characteristics of the patients are shown in Table 2.

Regarding the clinical features of the MPLCs, a univariate analysis revealed that female gender, the presence of more than three lung tumors and a family history of any cancer was significantly more common in the GGN group, whereas smoking, the mean tumor size, an abnormal CEA titer and a high SUVmax were strongly correlated with the Solid group, as shown in Table 2.

In this study, 59 MPLC patients underwent a staged surgery for second lung cancers. The details of the surgical procedures are shown in Table 3. All the patients in the GGN group underwent limited resection (wedge resection or segmentectomy) for the first and/or the second operation. Limited resection during the second surgery was indicated for 24 patients (83 %) in the GGN group. However, lobectomy was actively selected for the second lung cancer whenever possible, even in the GGN group, if the tumors showed a solid appearance. In the Solid group, however, aggressive surgical resections were indicated for 13 patients with good risk, including 11 patients who underwent bilateral lobectomy.

The histological classification and pathological stages of MPLCs are presented in Table 4. Histologic concordance was observed in 45 patients (76.3 %). Both tumors were adenocarcinoma in 39 patients, and both tumors were squamous cell carcinoma in six patients. Regarding the pathological stages of MPLCs, the first lung cancer was stage I in 41 patients (69.5 %), and stages II and III in nine patients each (15.3 %). The pathological stage of the second lung cancers was predominantly stage I in 53 patients (89.8 %). Among them, 21 patients underwent only wedge resection of the second lung cancer without lymph node dissection. These cases were considered to have negative nodal status based on the preoperative radiological findings.

The median follow-up time was 38 months after the operation for the second lung cancer. The overall 5-year survival rate calculated from the date of the second operation was 71.7 %. The 5-year survival rate in the GGN group (89.1 %) was significantly higher than that in the Solid group (40.8 %) ($p = 0.0305$) (Fig. 2). Regarding the overall survival in the GGN group, when we divided the GGN group into G-G and G-S types, the 5-year survival

Table 2 The relationship between the clinical features and the findings of thin-section CT scans among patients with multiple primary lung cancers resected by staged surgery

Clinical features	No. of patients	GGN group (n = 29)		Solid group (n = 30)		p value*
		G-G type[a]	G-S type[b]	Non-PS type[c]	PS type[d]	
Total	59	11	18	11	19	
Gender						
Male	35	5	8	5	17	0.0259
Female	24	6	10	6	2	
Age at second tumor (years)						
Older than 70	24	3	11	3	7	0.2428
70 or younger	35	8	7	8	12	
Pack-years of smoking						
More than 30	26	3	5	6	12	0.0122
30 or fewer	33	8	13	5	7	
Interval between tumors						
More than 2 years	29	5	9	6	9	0.8946
2 years or less	30	6	9	5	10	
Mean tumor size						
Larger than 3 cm	16	1	3	3	9	0.0236
3 cm or smaller	43	10	15	8	10	
Total number of tumors						
2	43	5	12	9	17	0.0154
More than 3	16	6	6	2	2	
Family history of any cancer						
Absent	51	6	16	11	18	0.0196
Present	8	5	2	0	1	
Preceding malignancies						
Absent	40	9	11	9	11	0.8502
Present	19	2	7	2	8	
CEA (ng/ml)						
≤ 3	35	10	12	4	9	0.0110
>3	24	1	6	7	10	
SUV max						
≤ 2.5	27	11	11	2	3	<0.0001
>2.5	32	0	7	9	16	

CEA carcinoembryonic antigen, *SUV* standardized uptake value

* p value in χ^2 test or Fisher's exact test for the comparison between the GGN and Solid groups

[a] G-G type indicates tumors where both of the lung cancers exhibited GGN type tumors

[b] G-S type indicates tumors where at least one of the lung cancers had a GGN appearance

[c] Non-PS type indicates tumors where at least one cancer had a non pure-solid type tumor

[d] PS type indicates tumors where both of the lung cancers exhibited pure-solid tumors

Table 3 Characteristics of the surgical procedure in staged surgery among patients with multiple primary lung cancers based on the findings of thin-section CT scans

Variables	Patients
Surgical procedures for the first tumor/second tumor in the GGN group	
G-G type (N = 11)	
Wedge resection/wedge resection	1
Wedge resection/lobectomy	1
Segmentectomy/segmentectomy	1
Segmentectomy/lobectomy	2
Lobectomy/wedge resection	2
Lobectomy/segmentectomy	4
G-S type (N = 18)	
Wedge resection/wedge resection	2
Wedge resection/segmentectomy	1
Wedge resection/lobectomy	2
Segmentectomy/segmentectomy	1
Lobectomy/wedge resection	5
Lobectomy/segmentectomy	6
Pneumonectomy/wedge resection	1
Surgical procedures for the first tumor/second tumor in the Solid group	
Wedge resection/wedge resection	1
Segmentectomy/lobectomy	2
Lobectomy/wedge resection	9
Lobectomy/segmentectomy	5
Lobectomy/completion pneumonectomy	2
Bilateral bilobectomy	11

rate in the patients with the former type was 90.9 %, and that in the patient with the latter type was 87.4 %, and this difference was not significant (p = 0.8851) (Fig. 3).

Among the patients in the GGN group, new GGN lesions (range, one to four new nodules) developed in seven patients (24 %), giving a total of 12 lesions in the GGN group after the second operations, all of which remained small and were carefully observed. Among the patients in the GGN group, seven (24 %) showed pure-solid tumors in this cohort.

In contrast, when we divided the Solid group into the S type and PS types, i.e., at least one was a non pure-solid tumor (non-PS type), or both the lung cancers were pure-solid tumors (PS type), the 5-year survival rate in the patients with the non-PS type tumors was 60.6 %, and that in the patients with the PS type tumors was 35.1 % (p = 0.6085). No significant difference was observed, but the 5-year survival rate of the patients with the PS type tumors was low.

Among the patients in the Solid group, 28 (93 %) showed at least one pure-solid tumor. Moreover, in a subgroup analysis in the Solid group based on the surgical procedures, the 5-year survival rate in patients who underwent bilateral lobectomy was 53.9 %, whereas the

3-year survival rate in patients who did not undergo bilateral lobectomy was 32.4 % ($p = 0.6649$) (Fig. 4). In addition, the 5-year cancer-specific survival rate in patients who underwent bilateral lobectomy was 59.3 %, whereas the 3-year survival rate in patients who did not undergo bilateral lobectomy was 32.7 % ($p = 0.4952$).

Table 4 The histological characteristics and stages of the multiple primary lung cancer patients

Variables	Patients
Histological characteristics of the first tumor/second tumor	
Adenocarcinoma	
Adenocarcinoma	39
Squamous cell carcinoma	1
Adenosquamous cell carcinoma	1
Large cell neuroendocrine carcinoma	1
Squamous cell carcinoma	
Adenocarcinoma	3
Squamous cell carcinoma	6
Small cell carcinoma	2
Adenosquamous cell carcinoma	
Squamous cell carcinoma	2
Large cell carcinoma	1
Small cell carcinoma	
Adenocarcinoma	1
Pathological stages of the first tumor/second tumor	
Stage I/stage I	37
Stage I/stage II	2
Stage I/stage III	2
Stage II/stage I	9
Stage III/stage I	7
Stage III/stage II	2

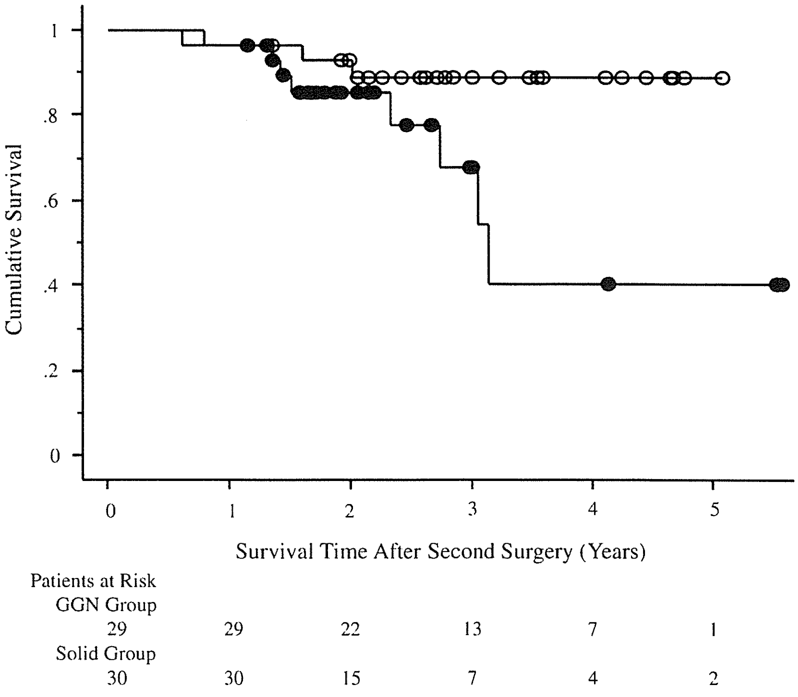
Comment

Recently, there has been a rapid increase in the likelihood of encountering patients with second lung cancers as a result of long-term survival after resection of the first lung cancer and improvements in the instruments used for early detection, such as thin-section CT and PET. Although several investigators have reported acceptable outcomes for the surgical treatment of MPLCs [3–16], the appropriate therapeutic strategies remain controversial, since the surgical strategies for second lung cancers depend on various clinical factors, including the extent and site of the second lesion, the initial surgical procedure and the patient's pulmonary functional reserve.

When multiple lung tumors are present, it is difficult to differentiate multicentric lung cancer from a single lung cancer with intrapulmonary metastasis. Genetic and molecular profiles have only very recently begun to be incorporated into the diagnosis of MPLCs [19–22]. However, there is still no definitive method for identifying MPLCs before treatment [23]. Thus, determining a way to improve the preoperative diagnosis of MPLCs would be helpful for selecting the proper treatment strategy.

While the first and second lung cancers show various radiological features on thin-section CT scans, the patterns

Fig. 2 The survival curves for patients with surgically resected second primary lung cancers based on the thin-section CT findings. A statistically significant difference was observed between the outcomes in the GGN group and the Solid group (log-rank test, $p = 0.0305$)



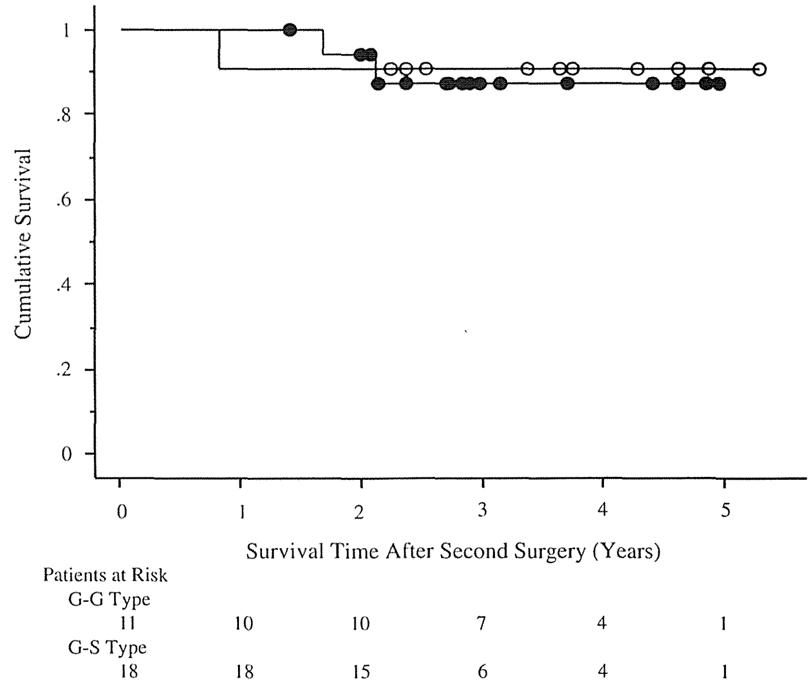


Fig. 3 The survival curves of the patients in the GGN group according to the thin-section CT findings. No statistically significant difference was observed between the outcomes for the G-G type and G-S type (log-rank test, $p = 0.8851$)

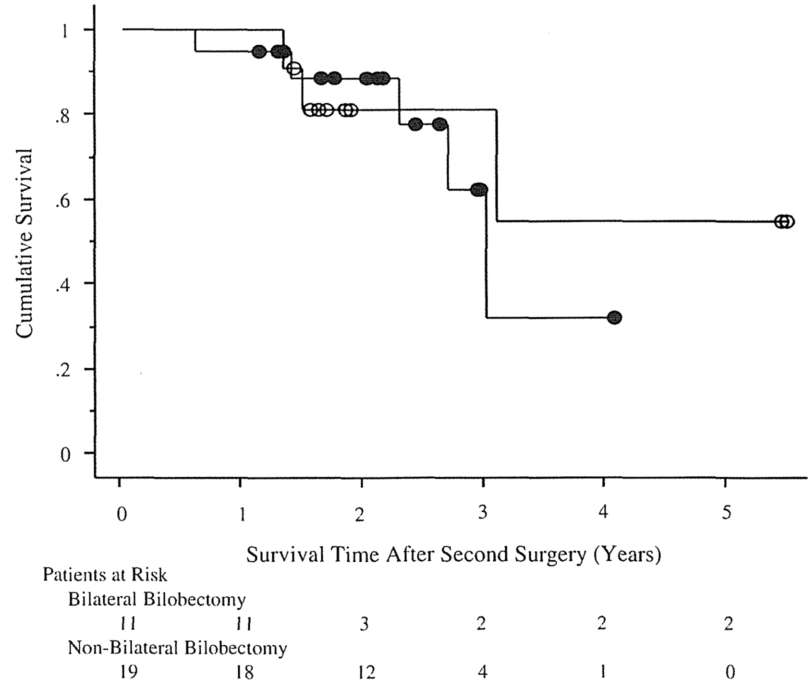


Fig. 4 The survival curves of the patients in the Solid group according to the surgical procedure. No statistically significant difference was observed between the outcomes for bilateral lobectomy and other operations (log-rank test, $p = 0.6649$)

or sequences of the expression of MPLCs, which could be an important factor in the selection of the proper surgical strategy, have not yet been identified. Knowledge regarding the tendencies of second malignancies and their predictive factors based on the results of a thin-section CT scan would better equip thoracic surgeons to design follow-up plans and surgical management strategies for second lung cancers. Thus, in the present study, we investigated the clinical features of MPLCs and tried to identify appropriate surgical strategies for second lung cancers.

In the current study, 59 eligible patients with MPLCs underwent staged surgery for second lung cancers. Based on the results of a univariate analysis investigating the relationship between several clinical factors and the findings of thin-section CT scans in patients with MPLCs, the patients in the GGN group were found to be more likely to have more than three lung tumors developed during their follow-up period after the first operation. On the other hand, the patients in the Solid group were significantly more likely to be cigarette smokers, to have a larger mean tumor size, an abnormal CEA titer and high SUVmax, which indicate higher tumor invasiveness.

The 5-year survival rate in the GGN group (89.1 %) was significantly better than that in the Solid group (40.8 %), as indicated in Fig. 2. Furthermore, there was no significant difference in the survival between the G-G and G-S types within the GGN group, which indicated that all the multiple primary lung cancer patients with GGO tumors had an excellent survival outcome. Moreover, this result suggests that the G-S type patients who had solid, i.e., non pure-solid or pure-solid tumors as the first tumor had a better survival than the other solid tumor patients, because the patients survived long enough to experience a second tumor. In addition, it was considered that the CTR was larger in the solid tumors in the Solid group than those of the G-S subgroup within the GGN group. Pure-solid lung cancer is considered to be highly invasive, even when the tumor is small [24, 25]. In our study, more than 90 % of the patients in the Solid group showed a pure-solid tumor for at least one of the tumors (first or second), pure-solid lung cancer was uncommon in the GGN group. In the Solid group, the 5-year survival rate in patients who underwent bilateral lobectomy was 53.9 %, whereas the 3-year survival rate in patients who did not undergo bilateral lobectomy was 32.4 %. With regard to the surgical strategy for bilateral solid type lung cancers, aggressive surgical resection could be acceptable as a radical resection for second lung cancer, provided that patients can tolerate lobectomy and have a good performance status.

These results suggest that patients in the GGN group, i.e., patients with at least one GGN tumor on thin-section CT, may have more than three lung cancers at the second surgery and a higher likelihood of new lesions emerging in the future. However, the survival rate in the GGN group was excellent, as shown in Fig. 3. In this group, the surgical strategy for the second lung cancer might influence the survival prognosis. In principal, especially for GGO dominant tumors, limited resection at the second surgery should be performed whenever possible to preserve the lung function, due to the high likelihood of a third lung cancer developing. However, complete resection is still mandatory for the second lung cancer whenever possible. Therefore, lobectomy should be actively selected for second lung cancer even in the GGN group, if the tumor shows a solid appearance. With regard to the efficacy of segmentectomy for second lung cancer with a non pure-solid or pure-solid appearance, the most appropriate surgical method should be selected based on the result of ongoing clinical trials [such as the Japan Clinical Oncology Group (JCOG 0802)].

In contrast, for patients in the Solid group, both the overall survival rate and cancer-specific survival rate in patients who underwent bilateral major lung resection were not inferior to that in patients who could not undergo this aggressive procedure, although no significant difference was observed, as shown in Fig. 4. This is probably due to the differences in the performance status between these two subgroups. Radiologically, "pure-solid" tumors are considered to be more invasive compared to "non pure-solid" tumors on thin-section CT scans because of their potential risk for postoperative nodal metastasis [24, 25]. Based on these results, limited surgical resections or radiation therapy without careful consideration should be strictly avoided for second lung cancers in the Solid group if the patient can tolerate lobectomy with adequate pulmonary and cardiac function. Limited surgical resection should be applied with great caution for pure-solid tumors even in patients with MPLCs. Although the MPLC patients in the Solid group showed a poor survival, radical resection should be actively considered whenever possible even for second lung cancers if patients show a good performance and can tolerate lobectomy, due to the low likelihood of there being more than three tumors in this group.

Generally, a curative but limited-extent operation should be considered for second lung cancers [14]. The classification of MPLCs based on thin-section CT is warranted to determine the optimal indications for surgical strategies for second lung cancers. Future studies will be needed to identify predictive clinical factors that can be used to differentiate MPLCs and intrapulmonary metastasis for early detection and diagnosis, which should improve the overall survival associated with MPLCs.

This study was limited by a relatively short median follow-up time after the surgery for the second lung cancer. Further investigations are warranted regarding the longer-term outcomes. Moreover, in the assessment of second lung cancers, the first and second lung cancers showed various radiological patterns on thin-section CT scans, as indicated in Table 1, and no consensus regarding the proper classification of MPLCs is currently available regarding this challenging problem. Controversies still remain with regard to the clinical characteristics of MPLCs, which have not yet been resolved. Several clinical factors can be used to evaluate the patients with MPLCs, such as the tumor size, GGN component and surgical interval. Future studies will be needed to address these matters in the future.

In conclusion, although the MPLC patients in the Solid group showed a poor survival, radical resection should be actively considered whenever possible. On the other hand, due to the possible presence of more than three lung cancers but better survival in the GGN group, limited resection should be performed as much as possible to preserve the lung function.

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Conflict of interest Aritoshi Hattori and co-authors have no conflicts of interest.

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ORIGINAL ARTICLE

High-quality 3-dimensional image simulation for pulmonary lobectomy and segmentectomy: results of preoperative assessment of pulmonary vessels and short-term surgical outcomes in consecutive patients undergoing video-assisted thoracic surgery[†]

Masaru Hagiwara[a], Yoshihisa Shimada[a,*], Yasufumi Kato[a], Kimitoshi Nawa[a], Yojiro Makino[a], Hideyuki Furumoto[a], Soichi Akata[b], Masatoshi Kakihana[a], Naohiro Kajiwara[a], Tatsuo Ohira[a], Hisashi Saji[c] and Norihiko Ikeda[a]

[a] First Department of Surgery, Tokyo Medical University Hospital, Tokyo, Japan
[b] Department of Radiology, Tokyo Medical University Hospital, Tokyo, Japan
[c] Department of Chest Surgery, St. Marianna University School of Medicine, Yokohama, Japan

* Corresponding author. First Department of Surgery, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Tel: +81-3-33426111; fax: +81-3-33426203; e-mail: zenkyu@za3.so-net.ne.jp (Y. Shimada).

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Abstract

OBJECTIVES: The aim of this study was to evaluate the effectiveness of 3-dimensional computed tomography (3D-CT) software in short-term surgical outcomes and the assessment of variations of pulmonary vessel branching patterns on performing video-assisted thoracic surgery (VATS).

METHODS: The study included 179 consecutive patients who had undergone VATS anatomical lung resection, of which 172 were lobectomies (96%) and 7 were segmentectomies (4%), from May 2011 through January 2013. There were 124 patients (69%) in whom 3D-CT was performed and 55 patients (31%) who had not undergone 3D-CT. Observed actual pulmonary vessel branching patterns by intraoperative findings or footage were compared with the 3D image findings. Various surgical outcomes, including the occurrence of postoperative complications, in this study defined as those of Grade 2 or above under the Clavien–Dindo classification system, and total operative time, were retrieved from available clinical records.

RESULTS: Among the 124 patients with preoperative 3D imaging, there were 5 (4%) conversions from VATS to thoracotomy. The incidence rate of patients with postoperative complications was 8% ($n = 10$), and there were no 30-day or 90-day mortalities. Pulmonary artery (PA) branches were precisely identified for 97.8% (309 of 316) of branches on 3D images, and the sizes of the seven undetected branches (five in the right upper lobe, two in the left upper lobe) ranged from 1 to 2 mm. The 3D images accurately revealed 15 cases (12%) of anomalous or unusual PA branches and 5 cases (4%) of variant pulmonary veins. Multivariate logistic regression analysis of the association with postoperative complications and operative time in 165 lung cancer patients demonstrated that male gender was the only statistically significant independent predictor of complications (risk ratio: 5.432, $P = 0.013$), and patients without 3D imaging tended to have operative complications (risk ratio: 2.852, $P = 0.074$), whereas conducting the 3D-CT (risk ratio: 2.282, $P = 0.021$) as well as intraoperative bleeding amount (risk ratio: 1.005, $P = 0.005$) had significant association with operative time.

CONCLUSIONS: High-quality 3D-CT images clearly revealed the anatomies of pulmonary vessels, which could play important roles in safe and efficient VATS anatomical resection.

Keywords: 3-Dimensional computed tomography • Simulation • Video-assisted thoracic surgery • Lobectomy • Pulmonary vessels

INTRODUCTION

Video-assisted thoracic surgery (VATS) lobectomy and segmentectomy have been established as standard surgical techniques for the treatment of lung cancer, metastatic lung tumours and benign lung tumours. A number of reports have documented the safety and effectiveness of a thoracoscopic approach, which has less morbidity, better postoperative respiratory function and equivalent oncological outcomes to conventional thoracotomy [1–4]. Anatomical variants of pulmonary vessels can cause serious problems such as unexpected bleeding in patients undergoing VATS [5, 6]. Detailed preoperative understanding and simulations of the surgical anatomy using image modalities would greatly contribute to safely performing VATS.

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Multidetector computed tomography (MDCT) allows surgeons to construct 3-dimensional (3D) images of lung structures. We have used 3D lung modelling based on CT images taken using the Fujifilm Synapse Vincent system (Fujifilm Corporation, Tokyo, Japan) to obtain 3D images of the pulmonary vessels and the tracheobronchial tree for surgical simulations [7, 8]. Several reports have addressed the usefulness of pre- or intraoperative use of 3D evaluations in the field of thoracic surgery [7–12]. However, the influence of 3D simulation on perioperative surgical outcomes in VATS has not been well described. The aim of this study was to evaluate the effectiveness of 3D software in short-term surgical outcomes and the preoperative assessment of variations of pulmonary vessel branching patterns for safely performing VATS.

PATIENTS AND METHODS

Patients

From May 2011 to January 2013, 561 patients underwent pulmonary resection at our department. Among them, 179 (31.9%) consecutive patients who had undergone VATS anatomical lung resections were included in this retrospective study. Our original indications of VATS anatomical resection for malignancies were for peripheral tumours less than 5 cm in diameter without nodal involvement. However, we have applied the VATS procedure in patients with multiple comorbidities who would otherwise not be suitable candidates for the conventional thoracotomy approach. We have preoperatively constructed 3D lung modelling based on CT images of lung structures taken using the Synapse Vincent system for the majority of patients scheduled for VATS lobectomy or segmentectomy. Data collection and analyses were approved and the need to obtain written informed consent from each patient was waived by the Institutional Review Board of Tokyo Medical University.

Preoperative 3D image construction and simulation

Patients underwent CT imaging with a 64-channel MDCT (Light Speed VCT, GE Medical Systems, Milwaukee, WI, USA) set at the following parameters: gantry rotation speed of 0.4 s per rotation, collimation of 0.625 mm, table incrementation speed of 39.37 mm/s with a helical pitch of 0.984, tube voltage of 120 kV, and the tube current was used with an automatic exposure control system. Axial sections (1.25 mm in thickness) were reconstructed at intervals of 1.0 mm. A total of 100 ml of iohexol (Omnipaque, 300 mg of iodine per ml; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was injected by a mechanical injector (Dual Shot GX7; Nemoto Kyorindo, Tokyo, Japan) at a rate of 1.5–2.0 ml/s without an injection of saline solution afterwards. Each CT image was acquired within 1 breath hold of about 5 s, after a delay of 70 s during which the contrast media injection took effect. The presented CT scan protocol has been used for not only the 3D image construction but also standard staging for lung cancer patients to be suitable for contrast radiography. These digital imaging and communication in medicine data were transferred to a workstation with the volume-rendering reconstruction software. After this step, a surgeon can construct 3D images completed within approximately 5 min for surgical simulations. We have performed VATS with double monitor guidance: one was a thoracoscopy television monitor, and the other was the 3D imaging system. The simulation system was implemented as a plug-in in the processing workstation (Dell Precision T5500, Windows 7 Professional, 64-bit, 12 GB, DDR3 RDIMM).

Operative procedure

Operations were performed with the patient in the lateral decubitus position under general anaesthesia with one-lung ventilation. Three or four incisions were used in each patient. A 10-mm camera port was placed in the sixth intercostal space (ICS) at the midaxillary line, through which a 30-degree thoracoscope was positioned. An access incision of 3 cm was placed in the fourth ICS and centred at the anterior axillary line, and a 10-mm accessory port was placed in the sixth ICS at the anterior axillary line. A 15-mm assist port was placed at the tip of the scapula. Rib resection or rib spreading was not performed.

Analysing evaluation data

To determine the ability of 3D images to enable the assessment of pulmonary artery (PA) branching patterns involved in operation, vascular size, the route of the pulmonary vein (PV) and the results of all examinations were interpreted by two surgeons (at least one of whom was a board-certified thoracic surgeon) and one chest radiologist (Soichi Akata) in consensus. The intraoperative footage was postoperatively evaluated by two surgeons, who were blinded to patient identification. When pulmonary vessels identified by the footage could not be visualized in the 3D images, they were considered 'undetected' vessel branches. Short-term outcomes, such as operating time, approximate blood loss, mortality rate and postoperative complications, were retrieved from available clinical records. The development of postoperative complications in this study was defined as Grade 2 or above for severe complications under the Clavien–Dindo classification system.

Statistical analysis

The χ^2 test and Fisher's exact or Student's *t*-test were used to compare proportions and continuous variables in analysing the frequency of occurrence of postoperative complications and operative time. Multivariate analyses were performed using the multiple logistic regression analysis, and we checked the validity of the model using the Hosmer–Lemeshow χ^2 test (a larger *P* value signifies greater reliability) on an external validation data set. All tests were two-sided, and *P*-values less than 0.05 were considered to indicate a statistically significant difference between the two groups. All statistical calculations were performed using the SPSS statistical software package (version 21.0; DDR3 RDIMM, SPSS, Inc., Chicago, IL, USA).

RESULTS

The characteristics of the patients who underwent VATS anatomical lung resection during this study period are summarized in Table 1. The study cohort of 179 patients included 88 men and 91 women, of whom 165 (92%) had primary lung cancer and 172