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Adaptation criterion for segmentectomy in small-sized early stage non-small cell lung cancer

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Abstract

Background: Although the utility of segmentectomy for early-stage non-small cell lung cancer (NSCLC) has been reported, the adaptation criterion for segmentectomy is unclear.

Methods: In total, 171 NSCLC patients who underwent segmentectomy or lobectomy with a consolidation tumor diameter on computed tomography of ≤20 mm were analyzed.

Results: Consolidation diameter ($p = 0.01$), consolidation to tumor ratio (CTR) ($p < 0.01$), maximum standardized uptake value (SUV_{max}) ($p < 0.01$), and segmentectomy ($p = 0.01$) were significantly different upon univariate analysis among patients stratified by recurrence. Positive correlations were observed between the consolidation diameter on CT and CEA (correlation coefficient; $r = 0.19$, $p = 0.01$), SUV_{max} ($r = 0.48$, $p < 0.01$), and CTR ($r = 0.83$, $p < 0.01$). Because there was a significant correlation among the consolidation diameter of tumors on CT, CTR, and SUV_{max} in this study, we integrated these factors into one. Consolidation, CTR, and SUV_{max} (hazard ratio [HR]: 3.77, 95% confidence interval [CI]: 1.35–11.29, $p = 0.01$) and segmentectomy (HR: 0.24, 95% CI: 0.03–0.90, $p = 0.03$) were risk factors for recurrence in a multivariate analysis. There was a significant difference between the segmentectomy and lobectomy groups (5-year relapse-free survival [RFS] 96.5% vs. 80.7%, $p = 0.02$).

Conclusions: Consolidation tumor diameter on CT, CTR, and SUV_{max} is a risk factor for recurrence. These results suggest that for patients with small-sized early stage NSCLC, this combined factor is important for determining the indication for segmentectomy.

KEYWORDS
consolidation to tumor ratio, early stage, non-small cell lung cancer, segmentectomy, standardized uptake value

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for more than 80% of all cases.[1] Several prognostic factors in patients with earlystage NSCLC have been reported.[2–9] Although the prognosis of stage IA NSCLC is considered to be good compared with that of advanced-stage disease, age, sex, carcinoembryonic antigen (CEA), tumor size, surgical procedure, surgical margin, pleural invasion, lymphatic invasion, histological type, and presence of combined pulmonary fibrosis and emphysema have been reported to be prognostic factors in patients with early-stage NSCLC. Furthermore, the risk factors are varied and are inconsistent among reports.

Although the standard treatment for early-stage NSCLC is lobectomy combined with systematic lymph node dissection,[10] some studies have reported that segmentectomy for early-stage NSCLC is not inferior to lobectomy.[11–15] 15 In particular, the Japan Clinical Oncology Group (JCOG) 0802/West Japan Oncology Group (WJOG) 4607L study, a

phase 3 trial, demonstrated the benefits of segmentectomy versus lobectomy on the overall survival of patients with small-peripheral NSCLC.[13] Although the results in JCOG0802/WJOG4706L suggested that segmentectomy should be the standard surgical procedure for clinical stage IA NSCLC patients with a tumor diameter of ≤20 mm and a consolidation-to-tumor ratio (CTR) of >0.5 on computed tomography (CT), locoregional relapse occurred more frequently in the segmentectomy group, despite no significant difference being reported for overall relapse-free survival (RFS).

In this study, we retrospectively evaluated the eligible criteria of segmentectomy for small-sized early-stage NSCLC.

METHODS

Patients

Among 589 NSCLC patients who underwent pulmonary resection at Kanazawa Medical University between 2017 and 2021, 343 patients with whole tumor size >20 mm or clinical stage IA3 or more and 75 patients who received wedge resection due to tumor size or poor performance status were excluded, and 171 patients with whole tumor diameter ≤ 20 mm on CT were enrolled in this retrospective study (Figure 1). Although the adaptation criteria of segmentectomy at our institution is tumor diameter on CT ≤20 mm and CTR on CT (CTR) < 0.5, some cases that did not meet these criteria were included because of low respiratory function or poor general condition. Postoperative patients visit our institution or affiliated hospital of our institution every 2–3 months for the first year after surgery and every 3–6 months after 1 year. This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review committee of Kanazawa Medical University approved the protocol (approval number: I392), and all patients gave written informed consent.

Data including clinical factors such as sex, age, comorbidities, smoking history, CEA, maximum standardized uptake value (SUV_{max}) on 18F-fluoro-2-deoxy-glucose positron emission tomography, and lung cancer lobe involvement were collected. Comorbidities were evaluated using the Charlson comorbidity index (CCI).[16] Smoking history was assessed using the Brinkman index, which was calculated by multiplying the number of cigarettes smoked per day by the number of years the patients had been smoking.[17] Respiratory function parameters, such as the percent-predicted vital capacity (%VC) and forced expiratory volume in 1 s as a percentage of forced vital capacity (FEV_1%), were collected.

Surgical factors and postoperative complications

Surgical procedures were stratified into two categories: segmentectomy or lobectomy. Wound length and surgery time were measured. Postoperative complications were categorized into five grades in accordance with the Clavien–Dindo classification system, which was established in 1992 and is a simple and feasible grading system for all types of postoperative complications.[18] In 2004, it was modified to allow for the grading of life-threatening complications and long-term disability caused by a complication.[19] This revised version defines five grades of severity with subgrades (grades I, II, IIIa, IIIb, IVa, IVb, and V), with the suffix "d" (for "disability") used to denote any postoperative impairment.

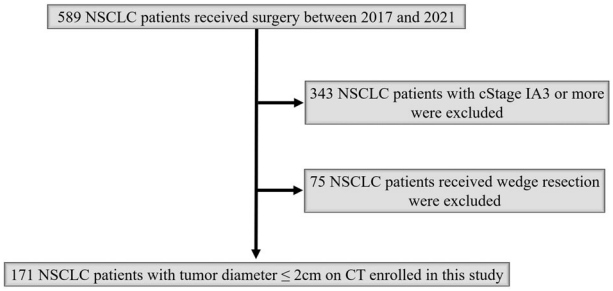

FIGURE 1 Patient flow diagram.

Pathological factors

Lymphatic invasion, vascular invasion, histological type, and pathological stage were collected.

Statistical analysis

We used Pearson's chi-squared test of independence to compare the frequencies of the variables. The correlation coefficient was evaluated by Spearman's rank correlation coefficient. Relapse-free survival (RFS) was calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. The cutoff values of factors associated with recurrence were calculated using receiver operating characteristic (ROC) curve analysis, and prognostic analyses were performed according to these cutoff values. Univariate and multivariate analyses using a Cox proportional hazards model were conducted to determine the risk factors for RFS. All statistical analyses were two-sided, with the statistical significance set at $p < 0.05$. Statistical analyses were performed using JMP software v13.2 (SAS Institute Inc.).

RESULTS

Patient characteristics

The clinicopathological characteristics of the 171 NSCLC patients with a tumor diameter of less than 2 cm are listed in Table 1. Sixty-eight patients underwent segmentectomy and 103 underwent lobectomy. Among patients who received lobectomy, there were significantly more men ($p < 0.01$), the Brinkman index was higher ($p = 0.01$), the consolidation diameter on CT was larger ($p < 0.01$), CTR was

TABLE 1 Patient characteristics

Variables	Segmentectomy ($n = 68$)	Lobectomy ($n = 103$)	p-value
Gender (male/female)	24/44	64/39	<0.01
Age, median, range (years)	71.8 (42–82)	69.7 (22–82)	0.05
Comorbidity	42 (61.7%)	75 (72.8%)	0.12
Charlson comorbidity index (0/1/2/3/4)	41/10/14/2/1	55/21/18/8/1	0.55
Brinkman index, median, range	0 (0–2760)	450 (0–2520)	0.01
CEA, median, range (ng/ml)	2.6 (0.5–12.3)	3.1 (0.7–54.9)	0.07
%VC, median, range	107.0 (76.3–177.7)	102.3 (74.4–145.6)	0.08
FEV_1%, median, range	74.5 (48.2–89.1)	72.8 (46.8–87.1)	0.13
Tumor diameter on CT, median, range (mm)	14 (6.5–19)	14 (6–20)	0.93
Consolidation diameter on CT, median, range (mm)	9 (0–19)	11 (0–20)	<0.01
Consolidation to tumor ratio, median, range	0.62 (0–1)	0.84 (0–1)	<0.01
SUV_{max} of tumor	1.42 (0–16)	2.21 (0–12.4)	<0.01
Lobe of tumor (RU/RM/RL/LU/LL)	27/2/13/16/10	30/5/27/27/14	0.59
Wound length, median, range (mm)	4.5 (3–15)	5 (3–12)	0.96
Operation time, median, range (min)	133 (61–209)	155 (37–247)	<0.01
Morbidity (%)	13.2	24.2	0.07
Clavien-Dindo grade (0/1/2/3a/3b)	59/0/2/7/0	78/0/6/17/2	0.20
Postoperative hospital-stay, median, range (days)	8 (3–15)	8 (3–71)	0.34
Histological type (Ad/Sq/LCNEC/Pleo/Carci/Large)	63/4/0/1/0/0	85/7/9/0/1/1	0.09
Pathological stage (0/IA1/IA2/IA3/IB/IIA/IIB/IIIA)	15/31/11/8/2/0/1/0	9/34/30/25/3/0/1/1	0.03
Lymphatic invasion (0/1)	57/11	71/32	0.02
Vascular invasion (0/1)	55/13	69/34	0.05
Postoperative follow-up period, median, range (days)	840 (62–1800)	750 (34–1807)	0.59
Recurrence site (local/locoreg/locoreg+distant/distant)	0/1/3/4	0/1/2/4	0.27

Abbreviations: Ad, adenocarcinoma; AdSq, adenosquamous cell carcinoma; Carci, carcinoid; CEA, carcinoembryonic antigen; CT, computed tomography; FEV_1%, forced expiratory volume % in 1 s; Large, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; LL, left lower; Lob, lobectomy; locoreg, locoregional; LU, left upper; Pleo, pleomorphic carcinoma; RL, right lower; RM, right middle; RU, right upper; Seg, segmentectomy; Sq, squamous cell carcinoma; SUV_{max}, maximum of standardized uptake value; VC, vital capacity; Wed, wedge resection.

higher ($p < 0.01$), SUV_{max} was higher ($p < 0.01$), surgery time was longer ($p < 0.01$), and lymphatic invasion was greater ($p = 0.02$).

Correlation coefficient

The correlation coefficients are shown in Table 2. Positive correlations were observed between the consolidation diameter on CT and Brinkman index (correlation coefficient; $r = 0.29$, $p < 0.01$), CEA ($r = 0.19$, $p = 0.01$), FEV_1% ($r = -0.21$, $p < 0.01$), SUV_{max} ($r = 0.48$, $p < 0.01$), and CTR ($r = 0.83$, $p < 0.01$). Furthermore, SUV_{max} was positively correlated with Brinkman index ($r = 0.19$, $p = 0.01$), CEA ($r = 0.24$, $p < 0.01$), FEV_1% ($r = -0.19$, $p = 0.01$), and CTR ($r = 0.47$, $p < 0.01$).

Univariate and multivariate analyses

Relationships between clinicopathological characteristics or surgical factors of the patients and recurrence

TABLE 2 Correlation among variables

Variables	Correlation coefficient	p-value
Correlation with consolidation diameter on CT		
Age	0.0513	0.50
Brinkman index	0.2989	<0.01
CEA	0.1923	0.01
%VC	0.0167	0.82
FEV_1%	−0.2154	<0.01
SUV_{max}	0.4826	<0.01
CTR	0.8303	<0.01
Correlation with SUV_{max}		
Age	−0.0221	0.77
Brinkman index	0.1907	0.01
CEA	0.2482	<0.01
%VC	−0.0209	0.78
FEV_1%	−0.1910	0.01
CTR	0.4715	<0.01

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; CTR, consolidation to tumor ratio; FEV_1%, forced expiratory volume % in one second; SUV_{max}, maximum of standardized uptake value; VC, vital capacity.

TABLE 3 Univariate analysis and multivariate analysis of risk factor for relapse-free survival

Univariate analysis				Multivariate analysis		
Variables	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Gender						
Male	1.18	0.426–3.397	0.73			
Age						
≥75	1.28	0.399–3.622	0.65			
Charlson comorbidity index						
≥3	2.16	0.338–7.877	0.35			
Smoking status						
BI > 200	0.58	0.181–1.640	0.31			
CEA						
>3	0.68	0.270–2.238	0.68			
Consolidation diameter on CT						
>10	4.07	1.293–17.898	0.01			
CTR						
1	5.11	1.748–18.458	<0.01			
SUV_{max}						
>2.0	4.73	1.502–20.768	<0.01			
Consolidation and CTR and SUV_{max}						
>10 and 1 and >2.0	4.25	1.535–12.708	<0.01	3.77	1.353–11.298	0.01
Operative procedure						
Segmentectomy	0.21	0.033–0.774	0.01	0.24	0.038–0.904	0.03
Clavian-Dindo grade						
≥3a	0.42	0.023–2.130	0.35			
Histological type						
Adenocarcinoma	0.56	0.179–2.477	0.40			
Lymphatic invasion						
Present	1.64	0.512–4.644	0.37			
Vascular invasion						
Present	1.46	0.455–4.125	0.49			

Abbreviations: BI, Brinkman index; BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; CTR, consolidation to tumor ratio on CT; HR, hazard ration; SUV_{max}, maximum of standardized uptake value.

were analyzed (Table 3). The cutoff values of factors associated with recurrence were calculated using ROC curve analysis. The following cutoff values were determined: Age, 75 years; Brinkman index, 200; CEA, 3 ng/ml; consolidation diameter on CT, 1 cm; CTR, 1; and SUV_{max}, 2.0. Consolidation diameter ($p = 0.01$), CTR ($p < 0.01$), SUV_{max} ($p < 0.01$), and segmentectomy ($p = 0.01$) were significantly different in the univariate analysis among patients stratified by recurrence. Because there was a significant correlation between the consolidation diameter, CTR, and SUV_{max}, we integrated these factors into one, such as consolidation diameter >1 cm, CTR >1, and SUV_{max} >2.0. Consolidation, CTR, and SUV_{max} (hazard ratio [HR]: 3.77, 95% confidence interval [CI]: 1.35–11.29, $p = 0.01$) and segmentectomy (HR: 0.24, 95% CI: 0.03–0.90, $p = 0.03$) were risk factors for recurrence in multivariate analysis.

Subanalysis

Patient was matched by propensity scores and we performed comparative analysis to reduce the selection bias. The clinicopathological characteristics of the 126 NSCLC patients are listed in Table 4. There were no significant differences between the segmentectomy and the lobectomy groups. The risk factors for recurrence were analyzed by multivariate analysis (Table 5). Consolidation diameter >1 cm, CTR >1, and SUV_{max} >2.0. (HR: 4.04, 95% CI: 1.11–14.70, $p = 0.03$) and segmentectomy (HR: 0.22, 95% CI: 0.03–0.90, $p = 0.03$) were risk factors for recurrence in multivariate analysis

Survival analysis

RFS for 126 NSCLC patient propensity score matched is shown in Figure 2. There was a significant difference

TABLE 4 Patient characteristics propensity score matched

Variables	Segmentectomy ($n = 63$)	Lobectomy ($n = 63$)	p-value
Gender (male/female)	23/40	66/37	0.58
Age, median, range (years)	71.8 (42–82)	71.5 (49–82)	0.27
Comorbidity	25 (39.7%)	24 (38.1%)	0.68
Charlson comorbidity index (0/1/2/3/4)	38/9/13/2/1	39/11/12/0/1	0.68
Brinkman index, median, range	0 (0–2760)	0 (0–2280)	0.94
CEA, median, range (ng/ml)	2.5 (0.5–12.3)	2.8 (0.7–9.8)	0.42
%VC, median, range	106.3 (76.3–177.7)	101.4 (74.4–133.6)	0.13
FEV_1%, median, range	75.0 (48.2–89.1)	74.8 (46.8–86.8)	0.68
Tumor diameter on CT, median, range (mm)	14 (6.5–19)	13 (6–19)	0.39
Consolidation diameter on CT, median, range (mm)	9 (0–18)	10 (0–18)	0.37
Consolidation to tumor ratio, median, range	0.64 (0–1)	0.70 (0–1)	0.45
SUV_{max} of tumor	1.41 (0.42–16)	1.71 (0–12.4)	0.31
Lobe of tumor (RU/RM/RL/LU/LL)	24/2/12/15/10	19/4/19/12/9	0.52
Morbidity (%)	12.7	12.7	1.00
Clavien-Dindo grade (0/1/2/3a/3b)	59/0/2/6/0	55/0/2/6/0	1.00
Postoperative hospital stay, median, range (days)	8 (3–15)	8 (3–71)	0.34
Histological type (Ad/Sq)	59/4	58/5	0.72
Pathological stage (0/IA1/IA2/IA3/IB/IIA/IIB/IIIA)	14/28/11/8/1/0/1/0	5/25/20/10/1/0/1/1	0.21
Lymphatic invasion (0/1)	53/10	52/11	0.81
Vascular invasion (0/1)	51/12	50/13	0.82
Postoperative follow-up period, median, range (days)	804 (90–1798)	750 (34–1807)	0.76

Abbreviations: Ad, adenocarcinoma; CEA, carcinoembryonic antigen; CT, computed tomography; FEV_1%, forced expiratory volume % in one second; LL, left lower; Lob, lobectomy; LU, left upper; RL, right lower; RM, right middle; RU, right upper; Seg, segmentectomy; Sq, squamous cell carcinoma; SUV_{max}, maximum of standardized uptake value; VC, vital capacity; Wed, wedge resection.

between the segmentectomy and lobectomy groups (5-year RFS 96.2% vs. 80.3%, $p = 0.05$). Furthermore, RFS in the high- and low-risk groups is shown in Figure 3. The high-risk group was defined as having a consolidation diameter > 10 mm, a CTR of 1, and SUV_{max} >2.0. There was a significant difference between the high- and low-risk groups (5-year RFS 93.5% vs. 69.7%, $p = 0.02$).

DISCUSSION

In this study, we analyzed the risk factors for patients with small-sized early-stage NSCLC who underwent pulmonary resection. Our findings demonstrated that consolidation tumor diameter on CT, CTR, and SUV_{max} were significant risk factors for recurrence in small-sized early stage NSCLC. SUV_{max} has been reported to be a predictor of recurrence in patients with surgically resected early-stage NSCLC.[20,21] Furthermore, CTR in CT has been reported to be a prognostic factor for early-stage NSCLC.[22–25] Because there was a significant correlation between consolidation tumor diameter on CT, CTR, and SUV_{max} in this study, we integrated these factors into one and analyzed whether it is a risk factor in recurrence. This factor was revealed as a significant risk factor in multivariate analysis and in survival curves in this study. After a meta-analysis in Japan showed that adjuvant chemotherapy with oral tegafur/uracil (UFT) was beneficial in patients with tumors >20 mm without node metastasis,[26,27] UFT was recommended for NSCLC patients with pathological stage IA3 to IB disease. Therefore, consolidation tumor diameter on CT, CTR, and SUV_{max} may be an adaptation criterion for adjuvant chemotherapy such as UFT in early-stage NSCLC patients.

Although it has been reported that segmentectomy is not inferior to lobectomy for early-stage NSCLC patients, tumor diameter ≤ 20 mm has been reported as an adaptation criterion.[13,15] Furthermore, overall survival and postoperative respiratory function were superior in the segmentectomy group rather than the lobectomy group.[13] Because RFS of the segmentectomy group was significantly better than that of the lobectomy group in this study, it was suggested that tumor diameter ≤ 20 mm is an adaptation criterion of segmentectomy for early-stage NSCLC. Although locoregional relapse was not detected in the segmentectomy group in this study, it occurred more frequently in the segmentectomy group, despite no significant difference being reported in overall RFS in JCOG0802/WJOG4706L.[13] In this study, the adaptation criterion of segmentectomy was CTR <0.5; however, NSCLC patients with CTR >0.5 participated in JCOG0802/WJOG4706L. Therefore, a discussion of the adaptation criterion of segmentectomy for early-stage NSCLC in the future is required.

TABLE 5 Univariate analysis and multivariate analysis of risk factor for relapse-free survival propensity score match

Univariate analysis				Multivariate analysis		
Variables	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Gender						
Male	0.72	0.156–2.623	0.63			
Age						
≥75	0.92	0.199–3.358	0.91			
Charlson comorbidity index						
NA						
Smoking status						
NA						
CEA						
>3	0.67	0.144–2.420	0.55			
Consolidation diameter on CT						
>10	6.19	1.548–41.069	<0.01			
CTR						
1	3.96	1.129–15.536	0.03			
SUV_{max}						
>2.0	3.33	0.926–15.471	0.06			
Consolidation and CTR and SUV_{max}						
>10 and 1 and >2.0	3.72	1.035–13.417	0.04	4.04	1.116–14.708	0.03
Operative procedure						
Segmentectomy	0.24	0.036–0.975	0.04	0.22	0.034–0.909	0.03
Clavian-Dindo grade						
≥3a	NA					
Histological type						
Adenocarcinoma	NA					
Lymphatic invasion						
Present	1.56	0.234–6.311	0.59			
Vascular invasion						
Present	1.16	0.175–4.680	0.84			

Abbreviations: BI, Brinkman index; BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; CTR, consolidation to tumor ratio on CT; HR, hazard ration; SUV_{max}, maximum of standardized uptake value.

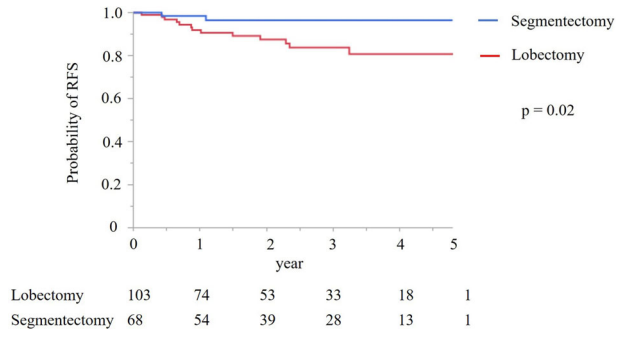

FIGURE 2 Relapse-free survival (RFS) for non-small cell lung cancer patients with tumor diameter less than 2 cm. There was a significant difference between the segmentectomy and lobectomy groups (5-year RFS 96.5% vs. 80.7%, respectively, $p = 0.02$).

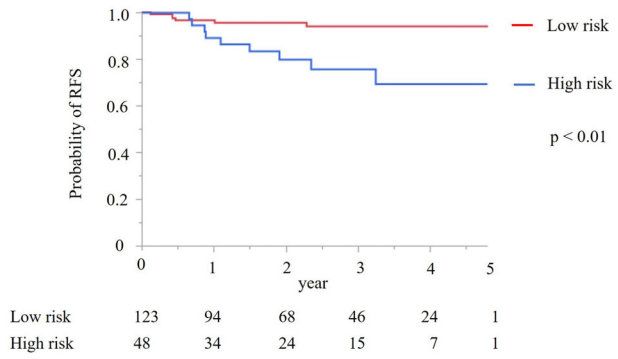

FIGURE 3 Relapse-free survival (RFS) by high-and low-risk group. The high-risk group was defined as consolidation diameter > 10 mm and consolidation to tumor ratio is 1 and SUV_{max} >2.0. There was a significant difference between the high- and low-risk groups (5-year RFS 93.9% vs. 69.4%, $p < 0.01$).

This study had some limitations. First, it was retrospective in nature and potentially involved unobserved cofounding and selection biases. Second, the study was performed at a single institution, and the study population was relatively small.

In summary, our findings describe risk factors of recurrence in patients with small-sized early-stage NSCLC who underwent lobectomy and segmentectomy. This study revealed that consolidation tumor diameter on CT, CTR, and SUV_{max} combined is a risk factor for recurrence. These results suggest that for patients with small-sized early-stage NSCLC, this combined factor is important for determining the indication for segmentectomy. Furthermore, the adaptation criterion of segmentectomy for early-stage NSCLC requires further study.

AUTHOR CONTRIBUTIONS

N. M. performed the research, collected and analyzed the data and wrote the paper. T.M., M.I., S. I., and Y.I. contributed to sample collection. H. U. contributed to supervision of this study and revision of the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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