Oncological feasibility of segmentectomy for inner-located lung cancer

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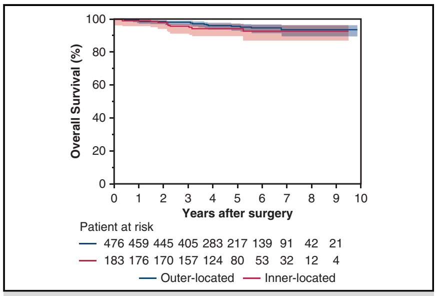
ABSTRACT

Objective: Oncological feasibility of segmentectomy for internal non–small cell lung cancer (NSCLC) has not been assessed adequately. We assessed the oncological feasibility of segmentectomy for inner-located NSCLC by investigating surgical margins and patient prognosis after undergoing the procedure.

Methods: Of the 3555 patients who underwent resection for lung cancer between 2013 and 2019 at our institution, 659 patients who underwent segmentectomy for clinical stage 0 to stage1A NSCLC were included in this study. Patients were separated into 2 groups according to whether the tumor was in the inner or outer third of the lung area. Clinical characteristics and prognoses were retrospectively compared between the groups.

Results: Of the included 659 cases, 183 (27.8%) were inner-located, and 476 (72.2%) had outer-located NSCLC. The surgical margin was significantly shorter in the inner-located group than in the outer group (median, 16 vs 25 mm; $P < .001$). The 5-year recurrence-free survival and overall survival probabilities were 91.1%/91.8% ($P = .530$) and 94.1%/95.6% ($P = .345$) for inner/outer-located groups, respectively. Multivariate analysis showed that clinical stage IA2 or 3 ($P = .043$), lymphovascular invasion ($P < .001$), and surgical margins <20 mm ($P = .017$) were independent prognostic factors for recurrence-free survival. The location of the inner or outer tumors was not related to the prognosis.

Conclusions: For clinical stage 0 to stage1A NSCLC, tumor location in the inner two-thirds of the lung was not associated with prognosis after segmentectomy. Because one of the independent prognostic factors is margin distance, segmentectomy for inner-located NSCLC would be oncologically acceptable when an adequate surgical margin is secured. (JTCVS Open 2024;18:261-75)



Comparable prognosis after segmentectomy for inner- and outer-located lung cancer.

CENTRAL MESSAGE

Apart from tumor location, surgical margin is a prognostic factor in early-stage lung cancer. Achieving adequate surgical margin can make segmentectomy oncologically feasible for inner-located tumors.

PERSPECTIVE

Segmentectomy is increasingly being used in resection for non–small cell lung cancer and has recently become a standard treatment. In this study, we demonstrated that the surgical margin, not the inner or outer location, was related to postoperative prognosis. Segmentectomy for inner and outer lung cancer is acceptable when adequate surgical margins are achieved.

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Abbreviations and Acronyms

3D	= 3-dimensional
CT	= computed tomography
C/T	= consolidation/tumor
GGO	= ground-glass opacity
JCOG	= Japan Clinical Oncology Group
NSCLC	= non–small cell lung cancer
OS	= overall survival
RFS	= recurrence-free survival
SPLC	= secondary primary lung cancer

▶ Video clip is available online.

The primary treatment for stage I lung cancer has been lobectomy since the Lung Cancer Study group reported in 1995 that sublobar resection was associated with higher mortality and locoregional recurrence rates.[1] However, with the recent development and progress of thoracic thin-section computed tomography (CT), the operative strategy has changed owing to the increased detection of small-sized lung cancer at an earlier stage. Recent exploratory clinical research has shown that tumors with ground-glass opacity (GGO) on thin-section CT have nonaggressive biological features.[2-4]

Recently published randomized controlled trial (Japan Clinical Oncology Group [JCOG] 0802/West Japan Oncology Group 4607) revealed the superiority of segmentectomy to lobectomy in terms of overall survival (OS) for peripheral solid-dominant non–small cell lung cancer (NSCLC) $\leq$2 cm in diameter while preserving pulmonary function.[5] Furthermore, the Cancer and Leukemia Group B 140,503 clinical trial comparing lobectomy and sublobar resection for peripheral NSCLC $\leq$2 cm in diameter revealed that recurrence-free survival (RFS) and OS were comparable between the 2 groups.[6] Another clinical trial (JCOG 1211) also validated the efficacy of segmentectomy for GGO-dominant tumors 2 to 3 cm in diameter.[7]

Accumulated evidence from recent clinical trials suggests that segmentectomy has become among the standard procedures for selected patients with NSCLC. Intentional segmentectomy can be considered for selected patients in terms of curative intensity while preserving pulmonary function,[8] whereas compromised segmentectomy is indicated for an impaired patient who is not a candidate for lobectomy.[9] However, the feasibility of segmentectomy for inner NSCLC has not yet been thoroughly investigated. Indeed, recent clinical trials have focused on peripheral cancers only.[5,6] It is possible that there is a group of patients with inner NSCLC for whom segmentectomy is a better indication, for example, to preserve respiratory function. One of the factors related to locoregional recurrence after segmentectomy was reported to be inadequate surgical margins.[10] It is considered that segmentectomy for inner-located lung cancer may result in shorter surgical margins due to the closer distance to adjacent segments or hilar area compared with outer-located cancer; therefore, the oncological validity of segmentectomy for inner-located NSCLC should be evaluated carefully.

In this study, we evaluated the oncological feasibility of segmentectomy for inner-located NSCLC by investigating the surgical margins and prognosis of patients after undergoing segmentectomy for NSCLC.

MATERIALS AND METHODS

Patient Collection

Of 3555 patients who underwent resection for lung cancer between 2013 and 2019 at the National Cancer Center Hospital, Tokyo, Japan, we retrospectively collected data from patients who underwent segmentectomy for clinical stage 0 to stage IA NSCLC.

After excluding patients with a current or history of treatment for other lung cancers or incomplete resection, 659 cases were included. Complete resection was defined as the resection of all macroscopic tumor tissues and a resection margin free of tumor cells upon microscopic analysis. As standard preoperative examinations, thin-slice CT and positron emission tomography scan were performed, while endobronchial ultrasound-guided transbronchial needle aspiration was performed if nodal metastasis was suspected. The lung cancer stage was defined based on the eighth edition of the TNM classification published by the Union for International Cancer Control. All clinical information was extracted from patients' medical records.

Operative Method

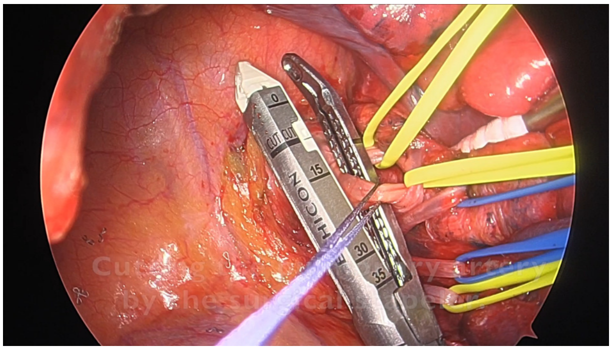
Pulmonary segmentectomy was performed via the open approach in combination with the use of a thoracoscope.[11] In most cases, the size of skin incisions was 5 to 8 cm for a thoracotomy at the fourth or fifth intercostal space and 1.5 cm for a thoracoscope at the seventh or eighth intercostal space.

During the surgery, the target segmental pulmonary arteries, veins, and bronchi were divided either using ligation or a surgical stapler. In principle, the pulmonary arteries were divided first, followed by the division of the bronchus, although the sequence of dividing these vessels and bronchi depends on the situation.

Lung inflation through the target segmental bronchus using a high-frequency jet ventilation system was performed before dividing the bronchus to depict the inflation-deflation line to identify the intersegmental plane. In patients who were operated upon after 2018, a volume of 0.25 mg/kg indocyanine green was injected intravenously after the division of all the target segmental pulmonary arteries and bronchi. After injection, the surgical field was visualized using near-infrared fluorescence imaging with a fluorescence-imaging camera (1488, 1588, or 1688 AIM Camera System; Stryker) to depict the intersegmental plane.

Based on the intersegmental plane depicted on indocyanine green fluorescence imaging, the intersegmental plane was divided using surgical staplers, and segmentectomy was completed (Video 1). When the tumor was located near the intersegmental plane, it was cut into adjacent segments to secure the surgical margin. Surgical margin was evaluated via rapid diagnosis of frozen section in almost all cases.

After segmentectomy, the presence of an air leak from the lung parenchyma or bronchus closure line was determined by inflating the lung underwater. Upon observing an air leak, manual sutures, fibrin sealant patches, polyglycolic acid sheets, or fibrin glue were applied to seal the area.



VIDEO 1. A case of S3 segmentectomy of left upper lobe for inner-located lung cancer, cT1 miN0 M0 stage IA1, approached in combination with the use of a thoracoscope. The target segmental pulmonary arteries, veins, and bronchi were divided using a surgical stapler. The intersegmental plane was divided using surgical staplers based on indocyanine green fluorescence imaging. Video available at: https://www.jtcvs.org/article/S2666-2736(24)00050-0/fulltext.

Subsequently, the lungs were inflated underwater to confirm no apparent air leak. A 28Fr chest tube was placed through the incision of the thoracoscope.

Evaluation of the Surgical Margin

We measure the distance from the tumor edge to the resection margin. Specifically for subsolid nodules, we measure from the edge of the lepidic component, not the invasive component.

Evaluation of the Location of the Tumor

Two thoracic surgeons (K.Y. and M.Y.) and a board-certified thoracic radiologist (H.W.) evaluated the preoperative chest CT images during the same session. The inner or outer location of the NSCLC was determined based on CT findings. We adopted the tumor centrality ratio based on a previous study.[12] The tumor centrality ratio was defined as the distance from the secondary carina (ie, the bifurcation of the upper lobe bronchus) to the center of the tumor, divided by the distance from the secondary carina to the visceral tumor surface (Figure 1). Tumors with a ratio <2:3 were allocated to the inner group, whereas those with a ratio >2:3 were allocated to the outer group.

CT images were evaluated in axial, sagittal, and coronal settings. In cases of uncertainty, multiplanar reconstruction images, including oblique views, were used to confirm the tumor centrality ratio by consensus. If tumor location was still uncertain, 3-dimensional (3D) CT was also used as needed (Ziostation 2; Ziosoft). The consolidation/tumor (C/T) ratio, which is the ratio of the maximum diameter of the solid component to the maximum total diameter of the tumor, including GGO, was evaluated using preoperative thin-section chest CT.

Patient Follow-up

Tumor recurrence during postsurgical follow-up was recorded. The follow-up evaluation included a physical examination, blood analysis (including carcinoembryonic antigen for adenocarcinoma), chest radiography, and CT of the chest and abdomen. In principle, these evaluations should be performed at least once a year postoperatively. Whenever patients had symptoms or signs suggestive of recurrence, further evaluations were performed using brain magnetic resonance imaging; positron emission tomography of the neck, chest, and abdomen; and/or bone scintigraphy. The date of recurrence was defined as the date when radiological features of recurrence first appeared, or when a pathological diagnosis was made on biopsy (if performed). Follow-up was conducted until the end of December 2022. All patients were censored on the date they were last known to be alive.

Radiologically, metachronous secondary primary lung cancer (SPLC) was defined as follows: multiple new pulmonary nodules with a C/T ratio > 0.5 for all nodules were defined as recurrent lesions of the initial primary lung cancer. Other multiple new pulmonary new nodules and a single new nodule that developed apart from the margins of a previous surgical resection were defined as SPLC. These definitions were based on the protocol used in studies by JCOG.[13] When the histological evaluation was performed for a new pulmonary lesion, more than 2 pathologists determined whether the new lesion was an SPLC or a recurrence by comparing the initially resected tumor and the new pulmonary lesion, following the definition reported by Martini and colleagues.[14]

Statistical Analysis

Data were presented as means, medians, counts, and percentages, as appropriate. OS and RFS probabilities were estimated using the Kaplan-Meier method, and the significance of differences between groups was analyzed using the log-rank test. All tests were 2-sided. All statistical analyses were performed using JMP 15 software (SAS Institute Inc).

Ethical Approval

The study protocol was approved by the Medical Research Ethics Committee of the National Cancer Center (IRB approval No. 2022–274; approval date: November 18, 2022), and all experiments were conducted in accordance with the Declaration of Helsinki. The committee waived the requirement for informed consent because this was a retrospective review of patient records.

RESULTS

Patient Characteristics

Of the included 659 cases, 183 (27.8%) had inner lesions, and 476 (72.2%) had outer lesions. Of the 183 inner-located cases, 44 (24.0%) were compromised and 139 (76.0%) were intentional; conversely, of the 476 outer-located cases, 37 (7.8%) were compromised and 439 (92.2%) were intentional segmentectomy. The patient and tumor characteristics are summarized in Table 1. The median age in the inner- and outer-located groups was 68 years (interquartile range [IQR], 63-75.5 years) and 70 years (IQR, 62-75 years), respectively ($P = .634$). In both groups, the median total tumor size on CT was 17 mm (IQR, 13-20.5 mm) in the inner group versus 17 to 22 mm in the outer group ($P = .100$), whereas the median consolidation tumor size on CT in the inner group was significantly smaller than that in the outer group (6 mm; IQR, 0-11.5 mm vs 10 mm; IQR, 5.75-15 mm; $P < .001$). The rate of tumors with a C/T ratio >0.5 was significantly lower in the inner-located group than in the outer-located group (27.9% vs 14.9%; $P < .001$). Tumor lobe distribution was comparable between the 2 groups.

Perioperative Outcomes

We compared the perioperative outcomes between the 2 groups (Table 2). The median operative time in the inner location group was significantly longer, although the difference was only slight (114 minutes vs 109 minutes; $P = .011$). There were 170 (92.9%) and 441 (92.6%) adenocarcinoma cases in the inner- and outer-located groups, respectively.

TABLE 1. Comparison of patient characteristics between segmentectomy for inner-located and outer-located non–small cell lung cancer

Characteristic	Value: Inner-located (n = 183)	Value: Outer-located (n = 476)	*P* value
Age at operation (y)	68 (63-75.5)	70 (62-75)	.634
Sex			
Female	98 (53.6)	272 (57.1)	.405
Male	85 (46.4)	204 (42.9)	
Smoking habit			
Present	97 (53.0)	224 (47.1)	.171
Absent	86 (47.0)	252 (52.9)	
Comorbidities			
Present	109 (59.6)	286 (60.0)	.902
Absent	74 (40.4)	190 (40.0)	
Respiratory disease	13 (7.1)	30 (6.3)	
Cerebrovascular disease	5 (2.7)	24 (5.0)	
Liver or gastrointestinal function disorder	3 (1.6)	15 (3.2)	
Renal function disorder	4 (2.2)	8 (1.7)	
Ischemic heart failure	8 (4.4)	17 (3.6)	
Hypertension	68 (37.2)	177 (37.2)	
Diabetes	25 (13.7)	66 (13.9)	
Other diseases	19 (10.4)	42 (8.8)	
Pulmonary function			
Median FEV1 (mL)	2170 (1745-2717.5)	2110 (1715-2662.5)	.628
Median FVC (mL)	2970 (2360-3555)	2780 (2300-3480)	.233
Total tumor size on CT			
Median (mm)	17 (13-20.5)	17 (14-22)	.100
Consolidation size on CT			
Median (mm)	6 (0-11.5)	10 (5.75-15)	<.001
C/T ratio			
≤0.25	66 (36.1)	98 (20.6)	<.001
>0.25, ≤ 0.5	45 (24.6)	104 (21.8)	.467
>0.5	30 (16.4)	121 (25.4)	.013
1	42 (23.0)	153 (32.1)	.022
Clinical stage (%)			
0	51 (27.9)	71 (14.9)	<.001
IA1	79 (43.2)	183 (38.4)	.287
IA2	43 (23.5)	178 (37.4)	<.001
IA3	10 (5.5)	44 (9.2)	.152
Tumor location			
Right upper lobe	46 (25.1)	123 (25.9)	.921
Right lower lobe	38 (20.1)	122 (25.6)	.244
Left upper lobe	68 (37.2)	159 (32.9)	.362
Left lower lobe	31 (16.9)	72 (14.9)	.552

Values are presented as median (interquartile range) or n (%). *FEV1*, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *CT*, computed tomography; *C/T*, consolidation/tumor.

One or more postoperative complications of grade 3 or worse occurred significantly more frequently in the inner-located group (10.4% vs 5.3%; $P = .018$). One patient in the inner location group died within 30 days as the result of a stroke. A box chart of the surgical margins in each group is shown in Figure 2. The surgical margin was significantly shorter in the inner-located group than in the outer group (median, 16 mm; IQR, 10-24.5 mm vs median 25 mm; IQR,19-32 mm; $P < .001$).

Recurrence and Mortality

The incidence of recurrence and mortality according to tumor location are summarized in Table 3. The median follow-up period for both groups was 54.2 months. During

TABLE 2. Comparison of perioperative and pathological outcomes between the 2 groups

Characteristic	Value Inner-located (n = 183)	Outer-located (n = 476)	P value
Resected segment			.233*
Right	84 (45.9)	245 (51.5)	
S1/S2/S3	11 (6.0)/20 (10.9)/14 (7.7)	45 (9.4)/50 (10.5)/27 (5.7)	
S6/S8/S9	26 (14.2)/7 (3.8)/1 (0.5)	67 (14.0)/29 (6.1)/4 (0.8)	
S10/other	0 (0.0)/5 (2.7)	7 (1.5)/16 (3.4)	
Left	99 (54.1)	231 (48.5)	
S1+2/S3/S1+2 + 3	12 (6.6)/4 (2.2)/41 (22.4)	34 (7.1)/13 (2.7)/82 (17.2)	
Lingular/S6/S8	11 (6.0)/15 (8.2)/6 (3.3)	30 (6.3)/45 (9.5)/10 (2.1)	
S9/S10/other	2 (1.1)/1 (0.5)/7 (3.8)	1 (0.2)/5 (1.1)/11 (2.3)	
Operation duration (min)	114 (101-126)	109 (98-121)	.011
Blood loss (mL)	17 (8.5-32.5)	18 (8-31)	.798
Histology			
Adeno/squamous/others	170 (92.9)/5 (2.7)/8 (4.4)	441 (92.6)/24 (5.0)/11 (2.3)	.179
Surgical margin distance (mm)			
Median	16 (10–24.5)	25 (19-32)	<.001
Lymph node dissection			.491
No dissection	17 (9.3)	32 (6.7)	
Hilar	153 (83.6)	405 (85.1)	
Mediastinal	13 (7.1)	39 (8.2)	
Complete resection			
R0/R1	181 (98.9)/2 (1.1)	474 (99.6)/2 (0.4)	.319
Lymphovascular invasion			
Present/absent	22 (12.0)/161 (88.0)	73 (15.3)/403 (84.7)	.278
Lymph node metastasis			
Present/absent	3 (1.6)/180 (98.4)	11 (2.5)/465 (97.5)	.592
Postoperative hospital stay (d)	4 (3-4)	4 (3-4)	.404
Postoperative morbidities†			
Present/absent	19 (10.4)/164 (89.6)	25 (5.3)/451 (94.7)	.018
Fistula/pulmonary	9 (4.9)	13 (2.7)	
Pneumonia	3 (1.6)	4 (0.8)	
Stroke	1 (0.5)	2 (0.4)	
Heart failure	1 (0.5)	0 (0)	
Ischemic heart disease	0 (0)	1 (0.2)	
Arrhythmia	2 (1.1)	0 (0)	
Hemorrhage	1 (0.5)	1 (0.2)	
Infection	1 (0.5)	1 (0.2)	
Others	1 (0.5)	3 (0.6)	
30-d mortality	1 (0.5)	0 (0)	

Values are presented as n (%) or median (interquartile range). *Comparison between the 2 groups using the χ^2 test for the right side or left side. †Clavien-Dindo grade ≥3.

the follow-up time, cancer recurrence occurred in 8 (4.4%) and 24 (5.0%) patients in the inner- and outer-located groups, respectively (P = .720). No significant differences were observed between the methods of recurrence. During the follow-up period, 11 (6.0%) and 20 (4.2%) patients died in the inner- and outer-located groups (P = .326), respectively. More patients in the inner-located group died from causes other than cancer (P = .032).

RFS and OS According to Tumor Location

As shown in Figure 3, *A* and *B*, the 5-year OS probabilities were 94.1% (95% CI, 89.3-96.8%) in the inner-located group and 95.6% (95% CI, 92.9-97.3%) in the outer-located group (P = .345). The 5-year RFS probabilities were 91.1% (95% CI, 88.4-94.2%) in the inner-located group and 91.8% (95% CI, 85.2-94.7%) in the outer-located group (P = .530).

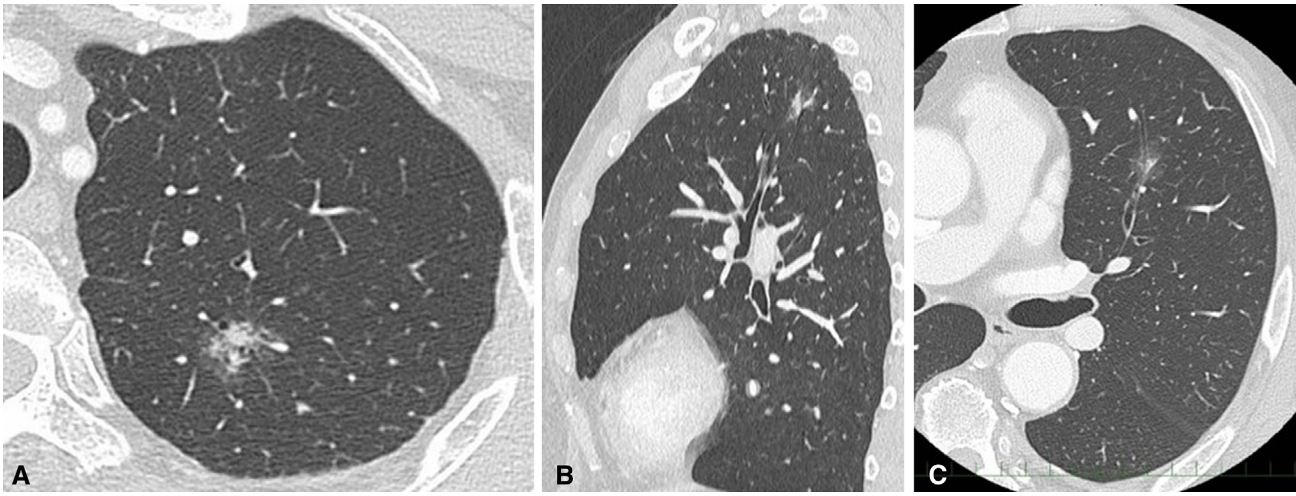


FIGURE 1. Computed tomography (*CT*) images of representative cases that underwent segmentectomy. A, Axial computed tomography (*CT*) image of outer-located lung cancer case. It was difficult to determine if this was inner-located or outer-located based on the image. B, Sagittal CT image of the same case, in which it was feasible to determine this case as an outer-located group. C, Axial CT image of inner-located lung cancer.

RFS and OS According to Tumor Location Stratified by C/T Ratio

Because significantly more GGO-predominant patients were present in the inner-located group, we stratified the group by C/T 0.5 and examined the prognosis. The patient characteristics and perioperative outcomes of patients with C/T $\leq$ 0.5 or C/T $>$ 0.5 are shown in Tables E1 and E2. Notably, in the group of patients with C/T $\leq$ 0.5, only 6 patients had lymphovascular invasion, and only 2 developed recurrences during the follow-up period. As shown in Figure 3, *C* and *D*, 5-year OS probabilities of the patients with C/T $\leq$ 0.5 were 97.2% (95% CI, 91.6%-99.1%) in the inner-located group and 97.5% (95% CI, 93.2%-99.1%) in the outer-located group (*P* = .662). As shown in Figure 3, *E* and *F*, 5-year OS probabilities of the patients with C/T > 0.5 were 89.2% (95% CI, 78.7%-94.7%) in the inner-located group and 94.2% (95% CI, 90.1%-96.6%) in the outer-located group (*P* = .129).

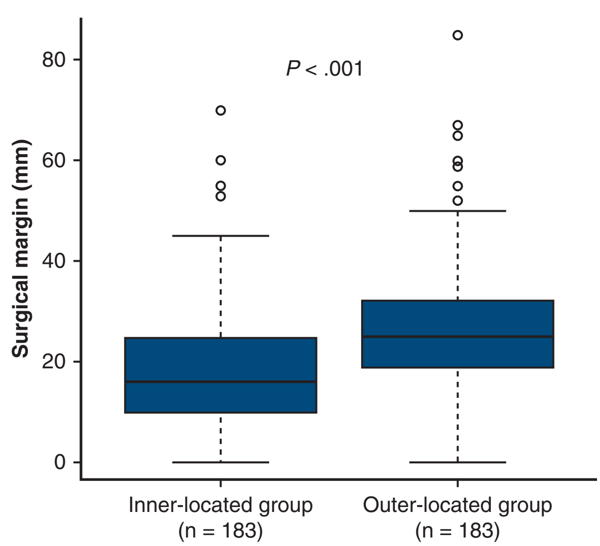


FIGURE 2. Box chart of surgical margin comparing inner-located group and outer-located group. The *lower* and *upper borders* of the box represent the lower and upper quartiles (25th percentile and 75th percentile). The *middle horizontal line* represents the median. The *lower* and *upper* whiskers represent the minimum and maximum values of nonoutliers. Extra *dots* represent outliers. Outliers are greater than the third quartile + 1.5 interquartile range (*IQR*) or less than the first quartile – 1.5 IQR in this chart. The median surgical margins in the inner-located group and outer-located group were 16 mm (IQR, 10-24.5 mm) and 25 mm (IQR, 19-32 mm), respectively (*P* < .001).

Univariate and Multivariate Analysis for RFS

Univariate and multivariate analyses of RFS are summarized in Table 4. Univariate analysis indicated that age >75 years (*P* < .001), male sex (*P* = .009), left side (*P* = .026), smoking habit (*P* = .014), clinical stage IA2 or 3 (*P* < .001), presence of lymphovascular invasion (*P* < .001), and surgical margin <20 mm (*P* = .017) were prognostic factors for RFS. Tumor location was not a prognostic factor for RFS. In the multivariate analysis, clinical stage IA2 or 3 (*P* = .043), lymphovascular invasion (*P* < .001), and surgical margins shorter than 20 mm (*P* = .017) were found to be significant prognostic factors for RFS. The results of univariate and multivariate analyses of RFS for patients with C/T > 0.5 are shown in Table E3. In the multivariate analysis, the presence of lymphovascular invasion (hazard ratio [HR], 7.20; 95% CI, 3.30-15.68; *P* < .001), surgical margin shorter than 20 mm (HR, 2.40; 95% CI, 1.25-4.62; *P* < .001) and the presence of smoking habit (HR, 2.92; 95% CI, 1.06-8.01; *P* = .038) were found to be significant prognostic factor for RFS.

TABLE 3. Comparison of recurrence and mortality between the 2 groups

Characteristic	Value		P value
	Inner-located (n = 183)	Outer-located (n = 476)	
Recurrence			
Total	8 (4.4)	24 (5.0)	.720
Local recurrence	2 (1.1)	4 (0.8)	.672
Regional recurrence	4 (2.2)	17 (3.6)	.463
Distant recurrence	2 (1.1)	3 (0.6)	.621
Mortality			
Total	11 (6.0)	20 (4.2)	.326
Lung cancer deaths	3 (1.6)	8 (1.7)	1.000
Other cancer deaths	2 (1.1)	8 (1.7)	.734
Other causes	6 (3.3)	4 (0.8)	.032

Values are presented as n (%).

RFS and OS According to the Tumor Location and Surgical Margin Stratified by C/T Ratio

Because significantly more GGO-predominant patients were present in the inner-located group, we stratified the group by C/T 0.5 and examined the prognosis. As shown in Figure E1, *A*, 5-year RFS probabilities of the patients with C/T $\leq$ 0.5 were not significant different among the inner-located and surgical margin $\geq$20 mm group, the inner-located and surgical margin <20 mm group, the outer-located and surgical margin $\geq$20 mm group and the outer-located and surgical margin < 20 mm group ($P = .867$). As shown in Figure E1, *B*, 5-year RFS probabilities of the patients with C/T > 0.5 were not also significant different among the same 4 groups ($P = .061$).

DISCUSSION

We found that the prognosis after segmentectomy for inner NSCLC was not significantly different from that for outer NSCLC. In a previous report, Tane and colleagues[12] reported that segmentectomy for inner-located NSCLC was comparable to peripheral NSCLC in terms of RFS. In the current study, we showed that both RFS and OS were comparable between inner- and outer-located cancers and demonstrated that margin distance is a more important prognostic indicator than tumor location (inner or outer). A graphical abstract of the study is shown in Figure 4.

Ensuring adequate surgical margins is among the most important points when performing segmentectomy.[15-17] Sawabata and colleagues[16] reported that the margin distance should be greater than the maximum tumor diameter to prevent margin relapse. We attempted to secure an adequate surgical margin by sacrificing the intersegmental vein or cutting into the adjacent segment with a stapler if the tumor was around the intersegmental area. However, securing adequate surgical margin distance was still more challenging in some cases. In this study, the median surgical margin of segmentectomy for inner-located tumors was 16 mm, and cases with insufficient margin distance were more frequent in inner-located tumors.

Higher likelihood of lobectomy was performed for inner-located lesions compared with outer-located lesions due to the difficulty in achieving adequate surgical margin. However, for inner tumors, lobectomy does not always provide a sufficient margin distance compared with segmentectomy because the distance between the lobar bronchus and segmental bronchus is small. Thus, it has been reported that the prognosis of inner-located tumors is the same between lobectomy and segmentectomy.[18] Although every effort should be made to maximize the margin distance, shorter margins are considered inevitable in some inner-located tumors. Because margin distance is a more direct prognostic factor than tumor location, patients who undergo segmentectomy for inner NSCLC should be carefully selected. Prediction of the expected surgical margin through measurement of the distance to the intersegmental vein is important, especially for inner-located lesions. The use of 3D CT reconstruction may also allow prediction of the expected surgical margin based on accurate localization of the tumor while extracting the vasculature,[19] thereby enabling surgeons to make better decisions when selecting the surgical procedure. It is also important if possible to palpate the tumor intraoperatively to confirm its localization. This study revealed that inner-located and solid-dominant NSCLC cases with inadequate margins have a poor prognosis. If an adequate margin distance is expected, segmentectomy for inner NSCLC is acceptable.

Considering that inner-located NSCLC cases had significantly more GGO-dominant lesions in this study, we stratified the analysis according to whether the C/T ratio of the tumor was >0.5. GGO-dominant NSCLC was found to have a favorable prognosis regardless of the tumor location, indicating that a shorter surgical margin might be acceptable for GGO-dominant tumors. In fact, inadequate margins

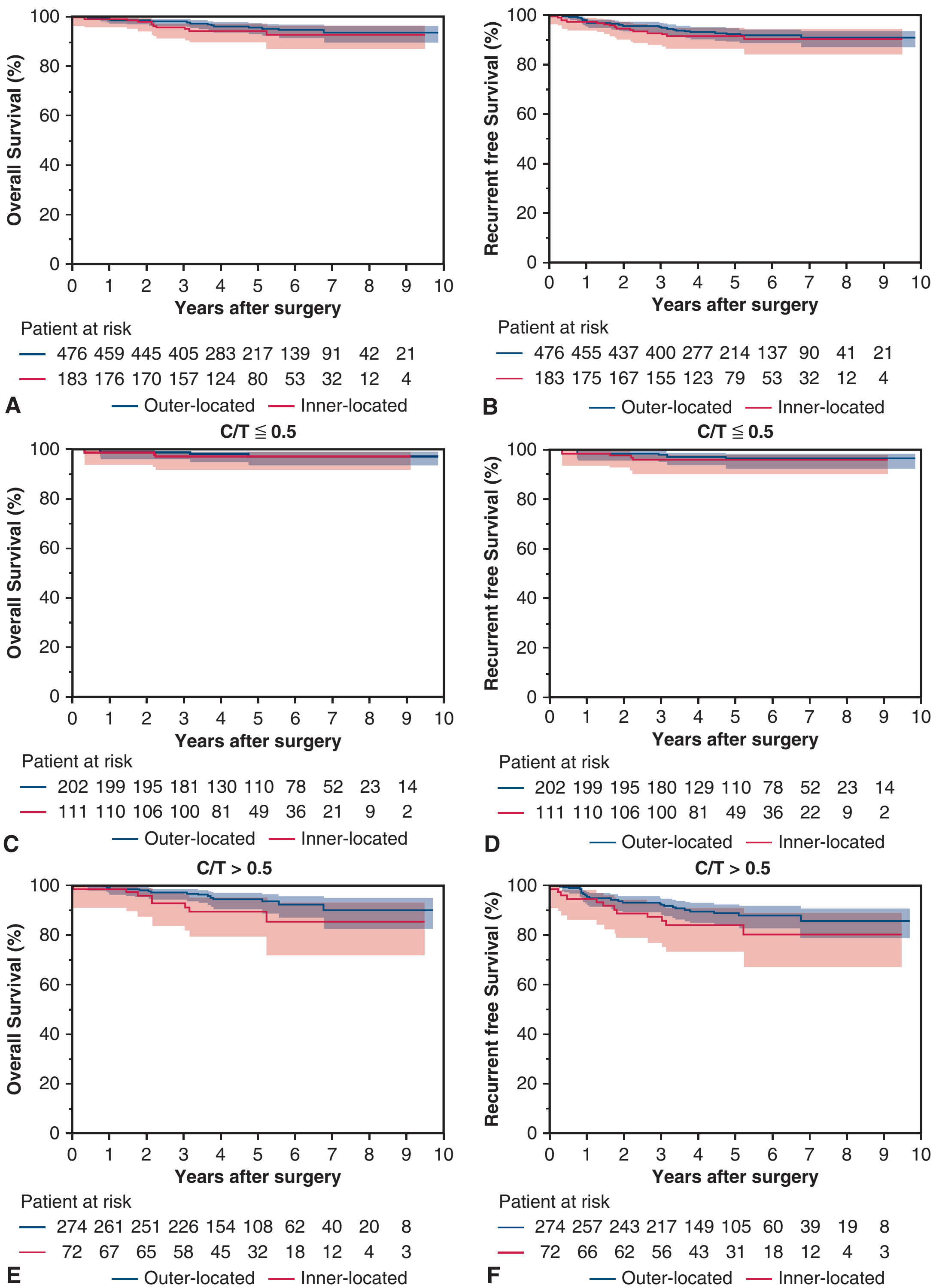


FIGURE 3. Prognosis after segmentectomy between the inner-located group and outer-located groups. A, Overall survival (*OS*) after segmentectomy with 95% CI. The 5-year OS probabilities were 94.1% in the inner-located group and 95.6% in the outer-located group ($P = .345$). B, Recurrence-free survival (*RFS*) after segmentectomy with 95% CI. The 5-year RFS probabilities were 91.1% in the inner-located group and 91.8% in the outer-located group ($P = .530$). C, OS after segmentectomy of consolidation/tumor (*C/T*) ratio $\leq$ 0.5 cases with 95% CI. The 5-year OS probabilities were 97.2% in the inner-located group and 97.5% in the outer-located group ($P = .662$). D, RFS after segmentectomy of C/T ratio $\leq$ 0.5 cases with 95% CI. The 5-year RFS probabilities were 96.3% in the inner-located group and 96.9% in the outer-located group ($P = .555$). E, OS after segmentectomy of C/T ratio >0.5 cases. The 5-year OS probabilities were 89.2% in the inner-located group and 94.2% in the outer-located group ($P = .129$). F, RFS after segmentectomy of C/T ratio >0.5 cases. The 5-year RFS probabilities were 83.8% in the inner-located group and 96.9% in the outer-located group ($P = .166$).

TABLE 4. Analyses of factors associated with recurrence-free survival after segmentectomy

Characteristic	Univariate analysis: Hazard ratio (95% CI)	Univariate analysis: *P* value	Multivariate analysis: Hazard ratio (95% CI)	Multivariate analysis: *P* value
Age at operation				
≥75 y	2.60 (1.49-4.54)	<.001	1.44 (0.76-2.73)	.264
<75 y	1		1	
Sex				
Male	2.13 (1.20-3.77)	.009	1.10 (0.54-2.27)	.79
Female	1		1	
Side				
Left	1.95 (1.08-3.49)	.026	1.55 (0.84-2.87)	.165
Right	1		1	
Tumor location				
Inner	1.21 (0.67-2.21)	.511		
Outer	1			
Smoking habit				
Present	2.81 (1.52-5.21)	.014	2.06 (0.94-4.50)	.07
Absent	1		1	
Comorbidities				
Present	2.27 (1.18-4.34)	.014	1.16 (0.55-2.47)	.7
Absent	1		1	
Clinical stage				
IA2 or more	5.05 (2.64-9.68)	<.001	2.21 (1.03-4.78)	.043
IA1 or less	1		1	
Lymphovascular invasion				
Present	13.63 (7.64-24.33)	<.001	7.75 (3.94-15.24)	<.001
Absent	1		1	
Surgical margin				
<20 mm	2.03 (1.14-3.64)	.017	2.09 (1.14-3.82)	.017
≥20 mm	1		1	

have little effect on patient prognosis as shown in Figure E1, *A*. Wide wedge resection is difficult for inner-located lesions, and lobectomy would be too invasive; therefore, inner-located GGO-dominant NSCLC may be a good candidate for segmentectomy.

In the present study, there was no significant difference in the rate of lymph node metastasis between the inner and outer lesions, even in solid-dominant tumors. However, several reports indicated that the cases of central lung tumors had significantly more occult mediastinal lymph node metastases.[20-22] Lymph node staging is recommended for inner-located NSCLC even <3 cm diameter, especially for solid-dominant lesions.[23] Segmentectomy is an anatomic lung resection along with the lymphatic drainage system, including segmental vessels and bronchus, and the hilar lymph nodes are dissected.[24] Although it is possible to add mediastinal lymph node dissection to segmentectomy for inner-located lesions with solid dominance if needed, it is not clear whether it would help improve the prognosis. Further investigations are required to assess the appropriate extent of lymph node dissection during segmentectomy.

This study had some limitations. First, definitive criteria for deciding the application of either segmentectomy or other procedures have not been established; therefore, selection bias cannot be ruled out. In addition, segmentectomy can be indicated as either compromised or intentional, although the difference is sometimes ambiguous. In an effort to overcome this limitation, we stratified the patients by C/T ratio to align with patient characteristics. Second, our cohort showed an imbalance of histological types, with adenocarcinoma dominating the cases in our study. However, the association between adequate surgical margin and prognosis was also evident in the subgroup of patients with C/T > 0.5, who are anticipated to be relatively poorly differentiated, and we anticipate that this study can be applied to other histologic types as well. Third, although the radiologist decided to divide the lesions into inner- and outer-located groups, some borderline lesions were difficult to classify. We tried to evaluate objectively by using 3D CT

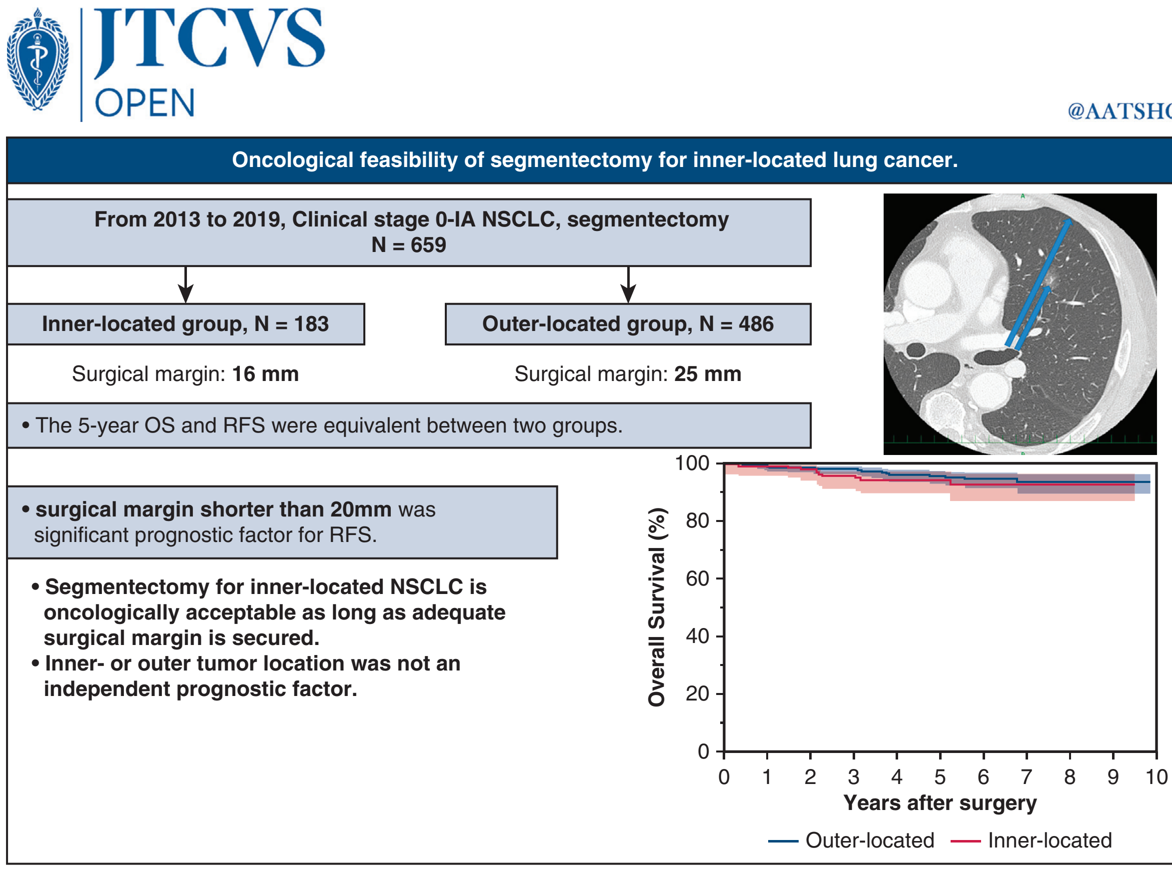


FIGURE 4. Graphic abstract.

when necessary. And, this study showed that not tumor location but adequate surgical margin was prognostic factor after segmentectomy, and the classification of inner or outer is not considered important. Fourth, because this was a retrospective study, it is assumed that some patients underwent other surgical procedures (lobectomy or wedge resection) for various reasons, and there may a selection bias in the patients who underwent segmentectomy. A prospective study is warranted for further productive analysis. Fifth, there were no multivariate analyses related to OS. The small number of death events related to lung cancer (11 cases) made it difficult to identify prognostic factors.

CONCLUSIONS

Our study demonstrated that the prognostic factors for NSCLC after segmentectomy are advanced clinical stage, lymphovascular invasion, and inadequate surgical margins. The location of the inner or outer tumor was not an independent prognostic factor. Segmentectomy for inner NSCLC should be considered to be oncologically acceptable in cases where an adequate surgical margin is expected to be secured.

Conflict of Interest Statement

Dr Yatabe reports personal fees from AstraZeneca, Daiichi-Sankyo, MSD, Amgen, AstraZeneca, Chugai Pharma, MSD, Novartis, Pfizer, Thermo Fisher Scientific, and Konika Minolta outside of this work. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: segmentectomy, non–small cell lung cancer, inner-located lung cancer, prognosis, surgical margin

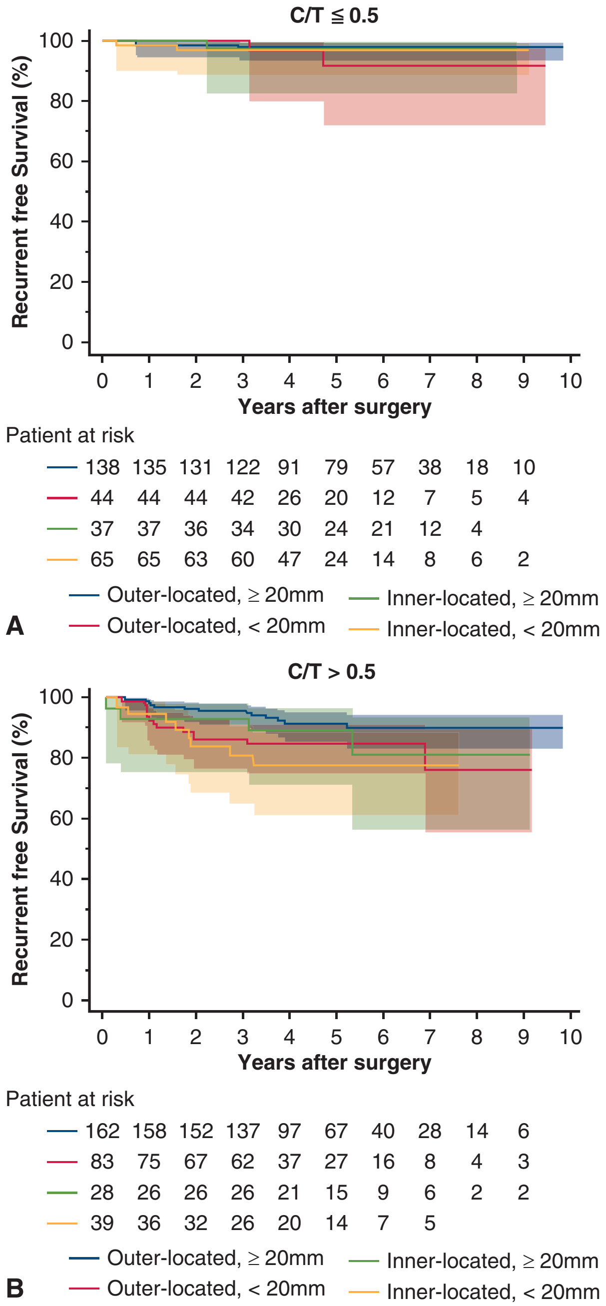

FIGURE E1. Prognosis after segmentectomy among the inner-located and surgical margin ≥20 mm group, and the inner-located and surgical margin <20 mm group, the outer-located and surgical margin ≥20 mm group and outer-located and surgical margin <20 mm group, stratified by consolidation to tumor (*C/T*) ratio. A, Recurrence-free survival (*RFS*) after segmentectomy of C/T ratio ≤0.5 cases. The 5-year RFS probabilities were 97.1% (95% CI, 81.4-99.6%) in the inner-located and surgical margin ≥20 mm group, 96.9% (95% CI, 81.4-99.2%) in the inner-located and fsurgical margin <20 mm group, 97.7% (95% CI, 93.2-99.3%) in the outer-located and surgical margin ≥20 mm group and 91.8% (95% CI, 70.4-98.0%) in the outer-located and surgical margin <20 mm group ($P = .867$). B, RFS after segmentectomy of C/T ratio >0.5 cases. The 5-year RFS probabilities were 89.1% (95% CI, 70.0-96.4%) in the inner-located and surgical margin ≥20 mm group, 77.5% (95% CI, 59.9-88.1%) in the inner-located and surgical margin <20 mm group, 91.5% (95% CI, 85.4-95.1%) in the outer-located and surgical margin ≥20 mm group and 84.7% (95% CI, 74.6-91.0%) in the outer-located and surgical margin <20 mm group ($P = .061$).

TABLE E1. Comparison of patient characteristics and perioperative outcomes between the 2 groups of consolidation/tumor ratio ≤0.5 cases

	Value		
Characteristic	Inner-located (n = 111)	Outer-located (n = 202)	*P* value
Age at operation (y)	69 (63.5-76)	69 (62-73.75)	.232
Sex			
Female/male	61 (55.0)/50 (45.0)	118 (58.4)/84 (41.6)	.633
Smoking habit			
Present/absent	57 (51.4)/54 (48.6)	85 (42.1)/117 (57.9)	.124
Comorbidities			
Present/absent	64 (57.7)/47 (42.3)	105 (52.0)/97 (48.0)	.346
Pulmonary function (mL)			
FEV1	2240 (1750-2740)	2160 (1805-2700)	.758
FVC	2940 (2311-3570)	2780 (2325-3740)	.865
Total tumor size on CT (mm)	17 (1-21)	18 (14.25-22)	.093
Consolidation size on CT (mm)	3 (0-6)	5 (0-8)	.009
Clinical stage			
0	51 (45.9)	71 (35.1)	.070
IA1	54 (48.6)	116 (57.4)	.155
IA2	6 (5.4)	15 (7.4)	.638
IA3	0 (0)	0 (0)	
Tumor location			
Right upper lobe	32 (28.8)	64 (31.7)	.701
Right lower lobe	25 (22.5)	38 (18.8)	.463
Left upper lobe	40 (36.0)	80 (39.6)	.546
Left lower lobe	14 (12.6)	20 (9.9)	.455
Surgical margin distance (mm)	3 (0-6)	5 (0-8)	.009
Lymphovascular invasion			
Present/absent	4 (3.6)/107 (96.4)	2 (1.0)/200 (99.0)	.191
Lymph node metastasis			
Present/absent	0 (0)/111 (100)	0 (0)/202 (100)	
Postoperative morbidities*			
Present/absent	13 (11.7)/98 (88.3)	8 (4.0)/194 (96.0)	.016
Recurrence			
Total	1 (0.9)	1 (0.5)	1.000
Mortality			
Total	3 (2.7)	7 (3.5)	1.000

Values are presented as n (%) or median (interquartile range). *FEV1*, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *CT*, computed tomography; *C/T*, consolidation/tumor. *Clavien-Dindo grade≥3.

TABLE E2. Comparison of patient characteristics and perioperative outcomes between the 2 groups of consolidation to tumor ratio >0.5 cases

Characteristic	Value		*P* value
	Inner-located (n = 72)	Outer-located (n = 274)	
Age at operation (y)	68 (61-74.25)	70 (62-77)	.124
Sex			
Female/male	37 (42.9)/35 (57.1)	154 (46.4)/120 (53.6)	.507
Smoking habit			
Present/absent	40 (47.1)/32 (52.9)	139 (53.0)/135 (47.0)	.509
Comorbities			
Present/absent	45 (60.0)/27 (40.0)	181 (59.6)/93 (40.4)	.580
Pulmonary function (mL)			
FEV1	2060 (1745-2660)	2060 (1680-2615)	.621
FVC	3040 (2460-3385)	2780 (2280-3360)	.184
Total tumor size on CT (mm)	15.5 (11-19)	16 (13-22)	.094
Consolidation size on CT (mm)	13 (9.75-17)	14 (11-17.75)	.153
Clinical stage			
0	0 (0)	0 (0)	
IA1	25 (34.7)	67 (24.5)	.099
IA2	37 (51.4)	163 (59.5)	.230
IA3	10 (13.9)	44 (16.1)	.719
Tumor location			
Right upper lobe	14 (19.4)	59 (21.5)	.748
Right lower lobe	13 (18.1)	84 (30.7)	.039
Left upper lobe	28 (38.9)	79 (28.8)	.155
Left lower lobe	17 (23.6)	52 (19.0)	.408
Surgical margin distance (mm)	17 (11-25)	24 (18-32)	<.001
Lymphovascular invasion			
Present/absent	18 (25.0)/54 (75.0)	71 (25.9)/203 (74.1)	1.000
Lymph node metastasis			
Present/absent	3 (4.2)/69 (95.8)	11 (4.0)/263 (96.0)	1.000
Postoperative morbidities*			
Present/absent	6 (8.3)/66 (91.7)	17 (6.2)/257 (93.8)	.594
Recurrence			
Total	7 (9.7)	23 (8.4)	.814
Mortality			
Total	8 (11.1)	16 (5.8)	.123

Values are presented as median (interquartile range) or n (%). *FEV1*, Forced expiratory volume in one second; *FVC*, forced vital capacity; *CT*, computed tomography. *Clavien-Dindo grade ≥ 3.

TABLE E3. Analyses of factors associated with recurrence-free survival after segmentectomy for consolidation/tumor ratio >0.5 cases

Characteristic	Univariate analysis Hazard ratio (95% CI)	Univariate analysis *P* value	Multivariate analysis Hazard ratio (95% CI)	Multivariate analysis *P* value
Age at operation				
≥75 y	1.68 (0.90-3.12)	.105		
<75 y	1			
Sex				
Male	3.56 (1.78-7.10)	<.001	1.47 (0.61-3.53)	.384
Female	1		1	
Side				
Left	1.90 (1.00-3.63)	.05	1.44 (0.73-2.86)	.296
Right	1			
Tumor location				
Inner	1.60 (0.82-3.14)	.17		
Outer	1			
Smoking habit				
Present	4.93 (2.18-11.12)	<.001	2.92 (1.06-8.01)	.038
Absent	1		1	
Comorbidities				
Present	2.09 (1.00-4.39)	.05	1.28 (0.55-3.00)	.569
Absent			1	
Clinical stage				
IA2 or more	3.00 (1.18-7.65)	.021	1.90 (0.71-5.05)	.201
IA1 or less	1		1	
Lymphovascular invasion				
Present	11.56 (5.66-23.62)	<.001	7.20 (3.30-15.68)	<.001
Absent	1		1	
Surgical margin				
<20 mm	2.18 (1.15-4.13)	.017	2.40 (1.25-4.62)	<.001
≥20 mm	1		1	