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Segmentectomy versus lobectomy for inner-located small-sized early non-small-cell lung cancer

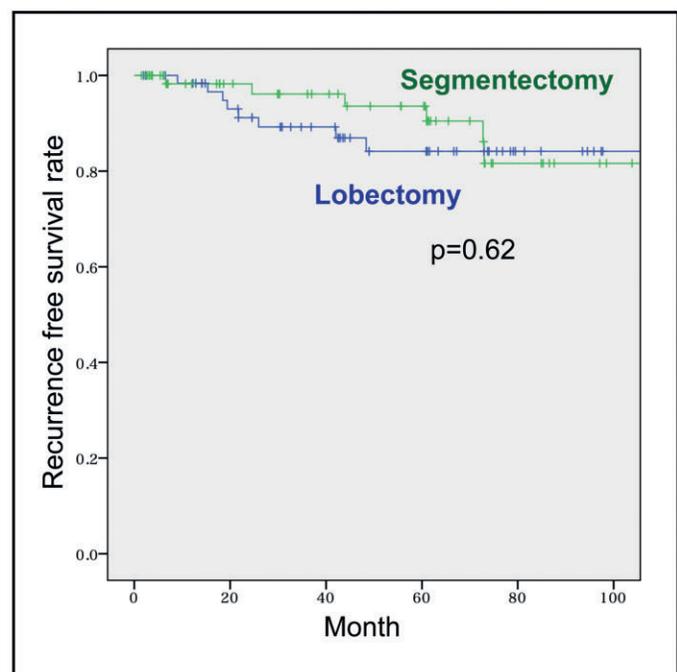
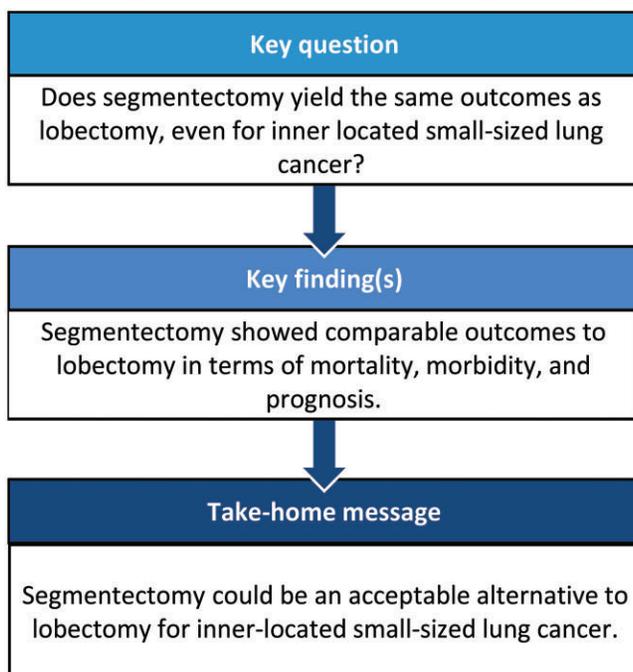
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Abstract

OBJECTIVES: Although segmentectomy is an acceptable alternative to lobectomy for peripheral small-sized non-small-cell lung cancer, the effectiveness of segmentectomy for inner lesions remains unknown. The aim of this study was to examine the feasibility of segmentectomy in comparison with lobectomy for inner lesions.

METHODS: We retrospectively analysed 570 patients with small (≤ 2 cm) cN0 non-small-cell lung cancer who underwent segmentectomy or lobectomy between January 2007 and March 2021. We focused on patients with lesions located in the inner two-thirds, which were determined using three-dimensional computed tomography ($n = 227$). After propensity score matching analysis based on sex, age, pulmonary function, serum carcinoembryonic antigen level, radiographic tumour findings and tumour location, we compared the surgical and oncological outcomes in patients who underwent segmentectomy ($n = 66$) and lobectomy ($n = 66$).

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RESULTS: Postoperative mortality or morbidity did not differ significantly between the 2 groups. The 5-year recurrence-free and overall survival rates in the segmentectomy and lobectomy groups were 93.6% vs 84.1% and 95.8% vs 87.9%, respectively. The differences between 2 groups were not significant ($P=0.62$ and $P=0.23$, respectively). The 2 groups also showed no differences in loco-regional recurrence. Multivariable Cox regression analysis revealed that segmentectomy had a comparable impact on recurrence-free survival (hazard ratio, 0.61; 95% confidence interval, 0.17–2.03; $P=0.43$).

CONCLUSIONS: Segmentectomy for inner-located small-sized non-small-cell lung tumours could be an acceptable treatment in comparison with lobectomy.

Keywords: Non-small-cell lung cancer • Inner location • Prognosis • Segmentectomy

ABBREVIATIONS

3D-CT	Three-dimensional computed tomography
C/T	Consolidation/tumour
CT	Computed tomography
GGO	Glass ground opacity
NSCLC	Non-small-cell lung cancer
OS	Overall survival
RFS	Recurrence-free survival

INTRODUCTION

Over the last 2 decades, segmentectomy has gained popularity among thoracic surgeons. Accumulated evidence has suggested that segmentectomy could be an alternative to lobectomy for small-sized non-small-cell lung cancer (NSCLC) [1]. A recent ongoing randomized controlled trial to confirm the noninferiority of segmentectomy to lobectomy in terms of prognosis among patients with peripheral small NSCLC (JCOG0802/WJOG4607L) revealed a significantly better overall survival (OS) and pulmonary function with segmentectomy, indicating that segmentectomy could be the standard treatment procedure instead of lobectomy for this population [2, 3]. However, it is not clear whether segmentectomy is also feasible for inner-located small-sized NSCLC.

We previously investigated whether segmentectomy for inner small-sized NSCLC is defined by a novel three-dimensional measurement method with feasible oncological outcomes in comparison with segmentectomy for outer lesions [4]. In that study, tumour invasiveness, but not tumour centrality, was shown to be the most important prognostic factor of recurrence-free survival (RFS) with segmentectomy. However, to further establish the feasibility of segmentectomy for inner lesions, segmentectomy should be compared with lobectomy, since this comparison is more relevant than that between inner and outer lesions. However, to date, no study has compared the prognosis of segmentectomy with that of lobectomy for inner-located NSCLC.

Therefore, we aimed to elucidate whether segmentectomy could show acceptable oncological outcomes in comparison with lobectomy for inner-located ≤ 2 -cm NSCLC. To compare these 2 procedures, we conducted a propensity match based on sex, age, pulmonary function, the presence of glass ground opacity (GGO) and the resected location, with an exact match for tumour centrality. The recurrence rates and long-term survival outcomes after segmentectomy were compared with those after lobectomy to confirm that segmentectomy

could be a feasible option even for inner-located small-sized NSCLC.

MATERIALS AND METHODS

Ethical statement

The Hyogo Cancer Center Institutional Review Board approved the study (Institutional Review Board number: G-240; approved on 27 December 2021), and each participant provided informed consent.

Patient collection

The study reviewed and analysed the clinicopathological data and prognosis of patients who underwent segmentectomy or lobectomy for small-sized NSCLC (≤ 2 cm) between January 2007 and March 2021 at Hyogo Cancer Center. A detailed flowchart depicting the selection of the study population is shown in Fig. 1. Preoperative evaluations, including chest computed tomography (CT), whole-body ^{18}F -fluorodeoxyglucose positron emission tomography/CT, brain magnetic resonance imaging and pulmonary function tests, were performed to determine the clinical stage and treatment strategies. The inclusion criteria were the ability to tolerate lobectomy, as evaluated by cardiopulmonary function tests, and no history of thoracic surgery or other cancers. Patients who had undergone middle-lobe lobectomy, bronchoplasty, induction therapy or incomplete resection were excluded.

Operative procedure

At the beginning of the study period, the operative procedure, including lobectomy and segmentectomy, was performed by muscle-sparing mini-thoracotomy (posterolateral or serratus anterior incision) under thoracoscopic guidance. In the latter period of the study, most procedures were performed via the thoracoscopic approach, as described elsewhere [5].

Generally, both segmentectomies and lobectomies involved selective mediastinal lymphadenectomy. For compromised patients, intraoperative hilar or mediastinal node sampling was only performed in cases where the nodes exhibited ^{18}F -fluorodeoxyglucose uptake preoperatively. If positive lymph nodes were suspected by intraoperative visualization, pathological node assessments were performed using frozen-section analysis. When the lymph nodes submitted for frozen-section analyses showed positive results, we converted segmentectomy to lobectomy.

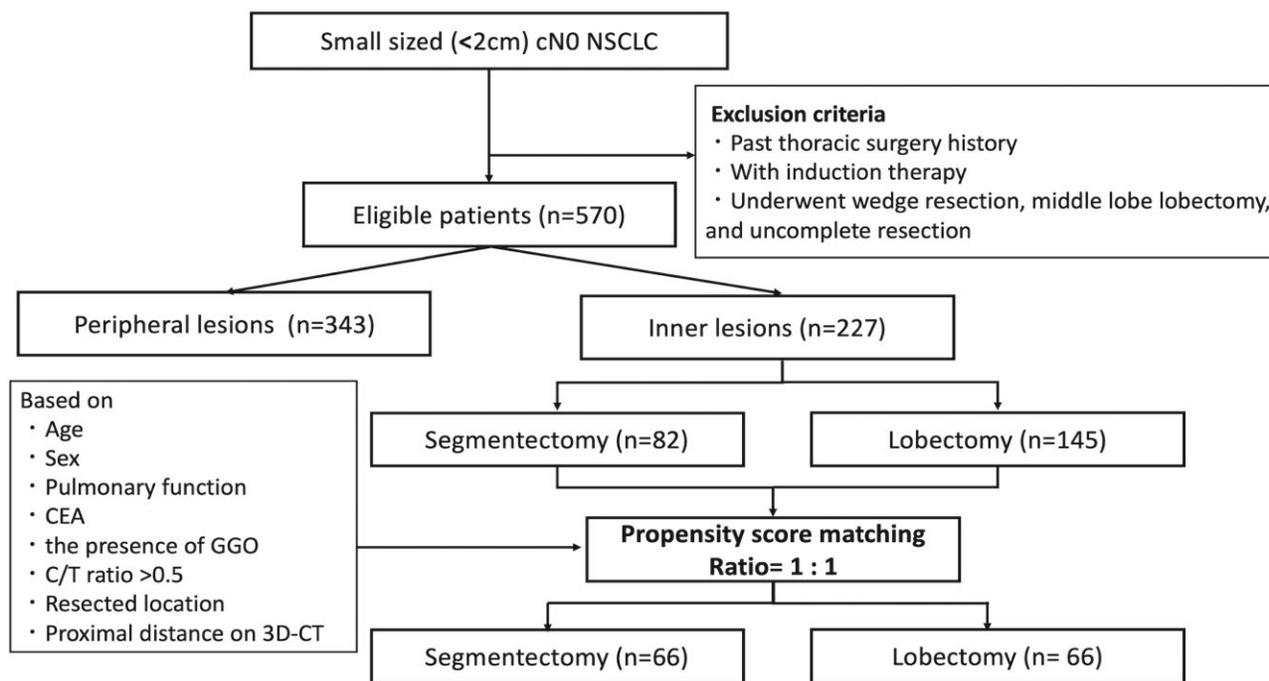


Figure 1: Flowchart of study population selection. 3D-CT: three-dimensional computed tomography; CEA: carcinoembryonic antigen; C/T: consolidation/tumour; GGO: grass-ground opacity; NSCLC: non-small-cell lung cancer.

Measurement of the proximal margin from the tumour on three-dimensional computed tomography

A representative image is shown in Fig. 2A. Imaging reconstruction was performed for CT data using the Synapse Vincent software program (Fujifilm Corp, Tokyo, Japan). The 'tumour centrality ratio', defined as the distance from the secondary carina to the centre of the tumour divided by the distance from the secondary carina to visceral surface, was measured on three-dimensional computed tomography (3D-CT). Tumours with ratio values below 2/3 were categorized as 'inner lesions', while those with ratio values above 2/3 were categorized as 'outer lesions'.

Tumour origin in the bronchioalveolar anatomy

The resected specimens were evaluated by experienced pathologists. The origin of lung tumours was classified according to the following criteria as described previously [6]:

Central type: Tumours arising from large nominate bronchi extending from the origin of the main bronchus to the point of division of the segmental bronchi.

Intermediate type: Tumours arising from the smaller bronchi, which included all branches of the large nominate bronchi that were visible with the naked eye.

Peripheral type: Tumours arising from the minute bronchi, bronchioles and alveoli themselves.

Follow-up evaluations

As an adjuvant chemotherapy, oral tegafur uracil administration was administered for pathological stage I, and platinum-based chemotherapy were used for pathological stage II or above. For

2 years after the surgical intervention, systemic and local examinations, including blood tests, chest and abdominal CT examinations, head magnetic resonance imaging and bone scintigraphy, were performed at 6-month intervals. Between 3 and 5 years postsurgery, intensive examinations were performed once a year. To identify the tumour recurrence, observational follow-up was continued indefinitely or for at least 5 years. Local recurrence was defined as a recurrent tumour within the same lobe (i.e. surgical stump and intrapulmonary metastases). Regional recurrence was defined as involvement of the mediastinal or hilar lymph nodes or a different ipsilateral lobe from the location of the segmentectomy. Distant recurrence was defined as distant metastasis to other organs with diffuse pleural disease.

Statistical analysis

To compare segmentectomy with lobectomy and to reduce selection bias, we used propensity score matching based on age, sex, proximal distance, resected lobe, presence of GGO, consolidation/tumour (C/T) ratio, serum carcinoembryonic antigen level and preoperative pulmonary function. Matching was performed with a ratio and calliper distance of 1:1 and 0.20, respectively. Match balance between the groups was assessed with standardized mean differences of all variables included in the propensity score estimation and was considered appropriate if none of the standardized mean differences exceeded 0.1. Segmentectomy and lobectomy were compared with regard to the clinicopathological findings. The Mann-Whitney *U* test was performed to compare continuous variables, and Fisher's exact test was used to compare nominal variables. For the matched populations, Wilcoxon signed-rank sum test was used to compare continuous variables and McNemar test was used to compare nominal variables. RFS and OS were estimated using Kaplan-Meier analysis, and differences were determined using log-rank analysis.

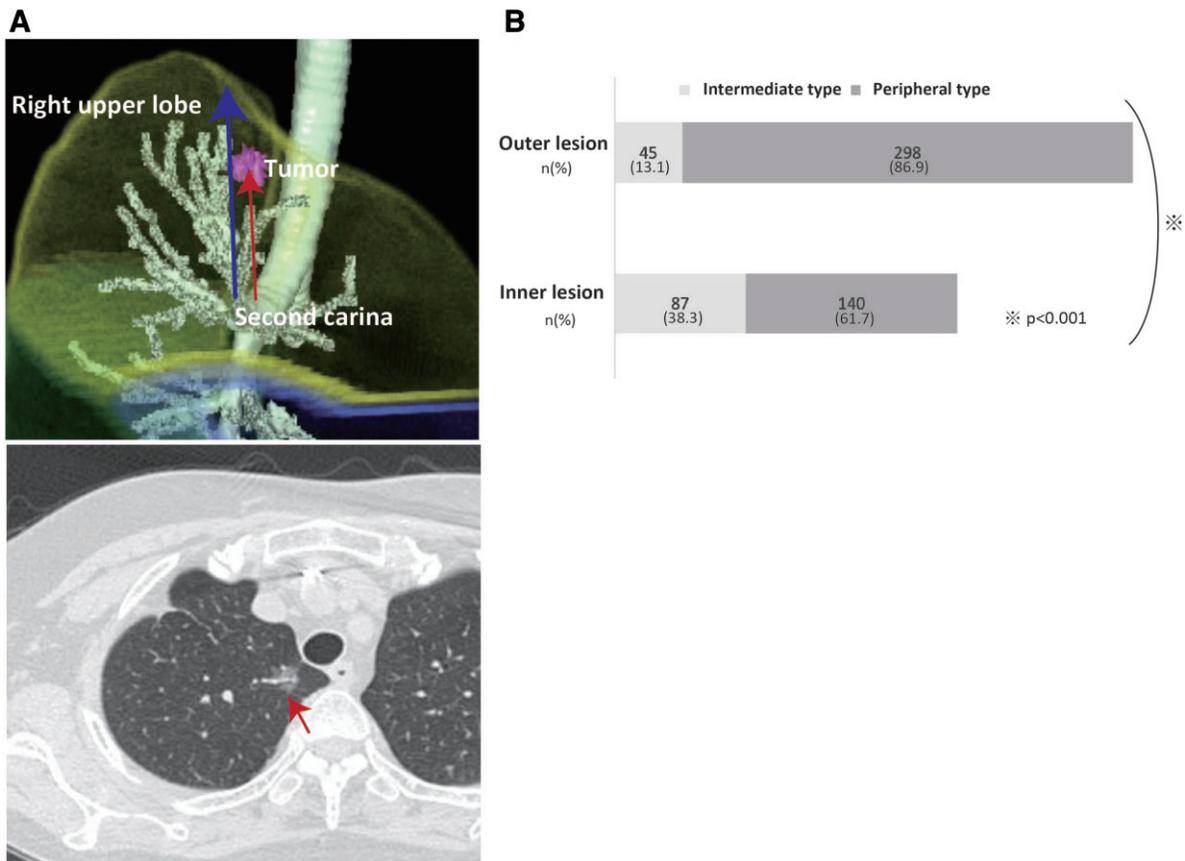


Figure 2: (A) Representative case measuring the tumour centrality ratio. The tumour centrality ratio, defined as the distance from the secondary carina to the centre of the tumour (red arrow) divided by the distance from the secondary carina to the visceral surface (blue arrow). (B) The distribution of the tumour origin among the inner and outer lesions (A color version of this figure appears in the online version of this article).

Multivariable analysis was performed using the Cox proportional-hazard regression model to identify significant prognostic factors for RFS. For the matched population, the random-effects Cox proportional-hazard regression was used. All statistical analyses were performed using JMP software (version 16, SAS Inc., Cary, NC, USA). All values were expressed as mean \pm standard deviation.

RESULTS

The validity of tumour centrality ratio

Among 570 consecutive patients who underwent segmentectomy or lobectomy for cN0 small-sized NSCLC, tumour centrality ratios below 2/3 (inner lesion) and above 2/3 (outer lesion) were observed in 227 and 343 patients, respectively. On the basis of pathological evaluations, 'intermediate' and 'peripheral' lesions were identified in 87 and 140 cases with inner lesions, respectively and 45 and 298 cases with outer lesions, respectively. No 'central type' lesions were identified in these populations. The 'intermediate type' was significantly more frequent in cases with inner lesions ($P < 0.001$), indicating that the tumour centrality ratio measured from 3D-CT reflected the accurate tumour location (Fig. 2B). The rate of unforeseen lymph node evaluation did not differ significantly between the inner and outer lesions (7.4% vs 6.8%, $P = 0.78$).

Operative outcomes

Next, we focused only on patients with inner lesions. The proximal distance to the tumour was 45 ± 16 mm in the segmentectomy group and 46 ± 15 mm in the lobectomy group ($P < 0.001$). Notably, in the segmentectomy group, the proximal distance exceeded 20 mm in all cases. Among the 145 patients who underwent lobectomy and 82 patients who underwent segmentectomy, 66 patients were matched in order to reduce selection bias (Table 1).

Patient characteristics and operative outcomes of the overall ($n = 227$) and matched cohort ($n = 132$) are shown in Tables 2 and 3. Within the matched cohort, the overall postoperative complication rate, including prolonged air leak, did not differ significantly between segmentectomy and lobectomy (15.1% vs 10.6%, $P = 0.46$). No postoperative deaths occurred in any patient population. Three patients converted from segmentectomy to lobectomy during surgery and were included in the lobectomy group because the surgical decision may have influenced the postoperative outcomes. The reasons for conversion were insufficient margin ($n = 1$) and nodal upstaging during operation ($n = 2$). All 3 patients had lesions located in the lower lobe.

Oncological outcomes

Pathological nodal upstaging was reported in 2 cases (3.0%) in the segmentectomy cases and 10 cases (15.2%) in the matched

Table 1: Patient characteristics with inner-located non-small-cell lung cancer before and after propensity score matching analysis

Clinical variables	Before propensity score matching				After propensity score matching			
	Segmentectomy (n = 82)	Lobectomy (n = 145)	P-Value	SMD	Segmentectomy (n = 66)	Lobectomy (n = 66)	P-Value	SMD
Sex (male/female)	47/35	83/62	0.99	0.002	39/27	41/25	0.72	0.062
Age (years)	68.5 ± 8.7	68.7 ± 8.4	0.84	<0.001	68.6 ± 8.5	68.1 ± 8.6	0.72	0.002
FEV1.0/FVC (%)	73.7 ± 10.8	74.1 ± 9.2	0.75	<0.001	74.2 ± 11.5	73.8 ± 7.7	0.76	0.002
CEA (>5 ng/ml)	12/70	27/118	0.44	0.11	12/54	10/56	0.64	0.081
The presence of GGO	51/33	83/62	0.47	0.10	37/29	39/27	0.72	0.061
C/T ratio >0.5	52/30	116/29	0.007	0.37	50/16	52/14	0.68	0.072
Tumour location, RUL/RLL/LUL/LLL	11/22/30/19	67/31/22/25	<0.001	0.23	11/21/17/17	11/19/18/18	0.98	0.001
Proximal distance on 3D-CT (mm)	45 ± 16	45 ± 15	0.067	<0.001	45 ± 15	46 ± 16	0.84	0.002

Values are n, mean ± SD, or n (%).

3D-CT: three-dimensional computed tomography; CEA: preoperative carcinoembryonic antigen; C/T: consolidation/tumour; GGO: ground-glass-opacity; FEV1.0: forced expiratory volume in 1 s; FVC: forced vital capacity; LLL: left lower lobe; LUL: left upper lobe; RLL: right lower lobe; RUL: right upper lobe; SD: standard deviation; SMD: standardized mean difference.

Table 2: Surgical and oncological outcomes of the unmatched cohort

	Segmentectomy (n = 82)	Lobectomy (n = 145)	P-Value
Surgical approach, thoracoscopy/thoracotomy	51/31	90/55	0.95
Resected site			<0.001
RUL	12	67	
S1	3		
S2	7		
S3	1		
S2b + S3a	1		
RLL	22	31	
S6	15		
S8	4		
S10	2		
Basal	1		
LUL	29	22	
S1 + 2	4		
S1 + 2 + 3	20		
S4 + 5	5		
LLL	19	25	
S6	14		
S8	3		
S10	1		
Basal	1		
Operation time (min)	184 ± 56	173 ± 47	0.11
Blood loss volume (ml)	75 ± 90	109 ± 147	0.06
Overall postoperative complication (%)	17 (20.7)	25 (17.2)	0.52
Prolonged air leak (%)	7 (8.5)	11 (7.6)	0.80
Histology (Ad/non-Ad)	75/7	132/13	0.91
Lymph node metastasis (yes/no)	2	15	0.018
Vascular invasion (yes/no)	8/74	31/114	0.021
Lymphatic invasion (yes/no)	11/71	41/104	0.008
Pathological stage			0.43
I	80	129	
II	1	8	
III	1	8	
Adjuvant chemotherapy (%)	10 (12.2)	26 (17.9)	
Recurrence			0.56
Regional	2	3	
Distance	3	4	
Regional + distance	1	7	

Values are n, mean ± SD.

Ad: adenocarcinoma; LLL: left lower lobe; LUL: left upper lobe; non-Ad: non-adenocarcinoma; RLL: right lower lobe; RUL: right upper lobe; SD: standard deviation.

Table 3: Surgical and oncological outcomes of the matched cohort

	Segmentectomy (n = 66)	Lobectomy (n = 66)	P-Value
Surgical approach thoracoscopy/thoracotomy	39/27	38/28	0.43
Resected site			0.98
RUL	11	11	
S1	2		
S2	8		
S2b + S3a	1		
RLL	21	19	
S6	15		
S8	3		
S10	2		
Basal	1		
LUL	18	18	
S1 + 2	2		
S1 + 2 + 3	10		
S4 + 5	6		
LLL	17	17	
S6	13		
S8	3		
Basal	1		
Operation time (min)	182 ± 55	176 ± 47	0.50
Blood loss volume (ml)	81 ± 96	105 ± 161	0.11
Overall postoperative complication (%)	11 (15.1)	7 (10.6)	0.46
Prolonged air leak (%)	6 (9.1)	4 (6.0)	0.51
Histology (Ad/non-Ad)	59/7	61/5	0.23
Lymph node metastasis (yes/no)	2/64	10/56	0.41
Vascular invasion (yes/no)	10/56	18/48	0.34
Lymphatic invasion (yes/no)	6/60	15/51	0.53
Pathological stage			0.41
I	64	56	
II	1	4	
III	1	6	
Adjuvant chemotherapy (%)	10 (15.1)	15 (22.7)	0.56
Recurrence			0.20
Regional	2 (3.0)	1 (1.5)	
Distance	3 (4.5)	3 (4.5)	
Regional + distance	1 (1.5)	4 (6.0)	

Values are n, mean ± SD, or n (%).

Ad: adenocarcinoma; LLL: left lower lobe; LUL: left upper lobe; non-Ad: non-adenocarcinoma; RLL: right lower lobe; RUL: right upper lobe; SD: standard deviation.

cohort. In the segmentectomy cases, 1 patient showed hilar lymph node metastasis and 1 patient showed skip mediastinal lymph node metastasis. In the lobectomy cases, 3 patients showed skip mediastinal lymph node metastasis, 4 patients showed hilar lymph node metastasis and 3 patients showed hilar and mediastinal lymph node metastasis. The rate of nodal upstaging was significantly higher in lobectomy than in segmentectomy ($P=0.001$).

The mean follow-up period was 50 ± 34 months. As for the prognosis of the overall patients with inner lesions, the RFS was not statistically significant different between segmentectomy and lobectomy ($P=0.94$), and 5-year survival rates were 87.7% and 89.5%, respectively. Moreover, the OS curves did not differ significantly between the 2 groups ($P=0.44$); and 5-year survival rates were 94.6% vs 89.2%, respectively (Fig. 3A and B).

When limiting to the matched patients with inner lesions, the 5-year RFS and OS rates in the segmentectomy and lobectomy groups were 93.6% vs 84.1% and 95.8% vs 87.9%, respectively. These differences between 2 groups were not significant ($P=0.62$ and $P=0.23$, respectively) (Fig. 3C and D).

As shown in [Supplementary Material, Table S1](#), the multivariable analysis revealed that the presence of GGO was an independent

predictive factor for RFS (hazard ratio, 0.16; 95% confidence interval 0.04–0.62; $P=0.008$), while surgical procedure (segmentectomy versus lobectomy) did not show significant differences (hazard ratio, 0.61; 95% confidence interval 0.18–2.07; $P=0.43$).

The recurrence patterns of the matched patients are shown in [Table 3](#). During the follow-up assessments, 14 of the 132 patients showed disease recurrence (10.6%). No local recurrence was observed in either group. Regional recurrence was noted in 2 patients (the residual lobe in 1 patient and the hilar and mediastinal lymph nodes in 1 patient) in the segmentectomy group and 1 patient (pleural dissemination) in the lobectomy group. Distant metastasis or combined distant and local recurrence was observed in 4 patients in the segmentectomy group and 5 patients in the lobectomy group.

DISCUSSION

Growing evidence suggests that segmentectomy is an acceptable alternative to lobectomy for peripheral small NSCLC. Recently, the JCOG0802/WJOG4607L trial revealed that segmentectomy for small-sized NSCLC (tumour size ≤ 2 cm, C/T ratio >0.5) showed

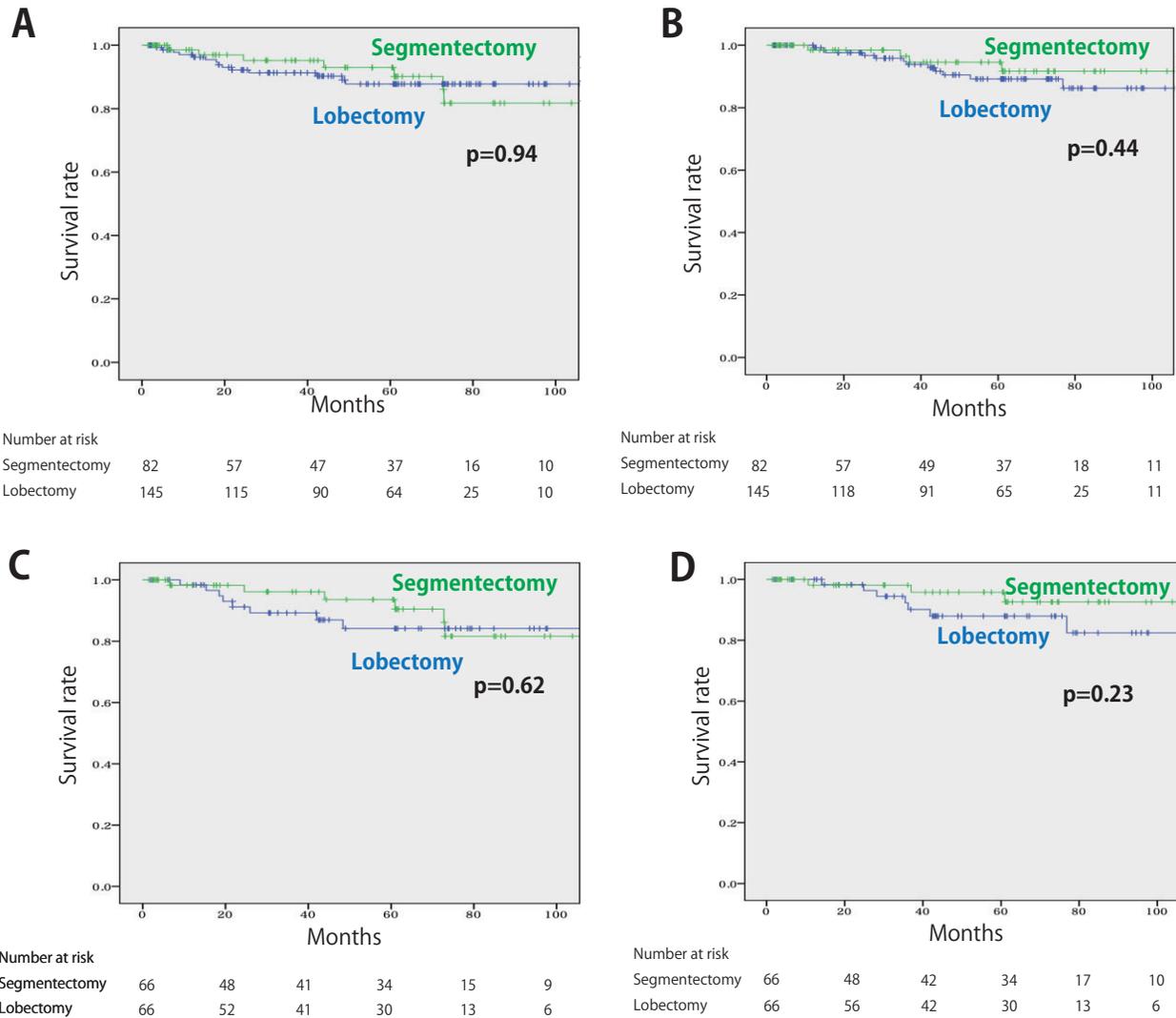


Figure 3: (A) Recurrence-free survival of the overall cohort. (B) Overall survival of the overall cohort. (C) Recurrence-free survival of the matched cohort. (D) Overall survival of the matched cohort.

oncologic noninferiority to lobectomy. However, this trial was based on peripheral lesions alone [2, 3]. Thus, the viability of segmentectomy as a standard care even for inner-located lesions remains unknown. However, no previous studies have compared segmentectomy and lobectomy for inner-located NSCLC.

The concerns associated with the use of segmentectomy for inner lesions are the difficulty in securing the proximal margin and the high dominance of lymph node metastasis. Regarding the proximal margin, although there are no accepted criteria to prevent loco-regional relapse, margins of 15 mm for a deflated lung and 20 mm for an inflated lung would be acceptable according to the previous literature [7, 8]. In our institution, segmentectomy has been allowed in cases where a 20-mm distance can be secured from the hilum on preoperative evaluation. In addition, in cases involving a tumour closer to the hilum, we do not hesitate to sacrifice the intersegmental vein and dissect towards the neighboring segment to be preserved, with the aim of securing the tumour margin. As a result, there was no loco-regional recurrence among patients with inner NSCLC who underwent segmentectomy in the current cohort.

The inner-located NSCLC has been recognized with a dominance of lymph node metastasis in comparison with peripheral lesions [9]. Decaluwe *et al.* [10] reported that central tumour location demonstrated 4-fold higher odds for lymph node metastasis (21%) in patients with cN0 NSCLC who underwent lung resection, including sublobar resection. However, inner lesions showed a comparable rate of lymph node metastasis to outer lesions in the current cohort, including segmentectomy and lobectomy. Since our cohort was limited to small-sized early NSCLC and the tumours in most of our cases were located in the middle third of the lung field without bronchoplasty, tumour invasiveness rather than tumour location might contribute to the lymph node metastatic status.

In addition, when limiting the findings to inner-located lesions, the rate of lymph node metastasis in lobectomy was significantly higher than that in the segmentectomy group. This result may have been partly influenced by the cases where segmentectomy was converted to lobectomy due to nodal upstaging during operation. Interestingly, all of these cases involved lesions located in the lower lobe. According to the study reported by Handa *et al.*

[11], cases where complex segmentectomy was converted to lobectomy because of nodal upstaging showed a predominance of the lower lobe, which is consistent with the findings of the current study. One possible explanation for this observation is that the lower lobe has a more complex lymphatic pathway than the upper lobe (i.e. the tumour located in the apical segment of the lower lobe is associated with a higher incidence of superior mediastinal metastases than tumours in basal segments and fewer subcarinal metastases) [12]. Indeed, a recent study by Jones *et al.* [13] reported that the prognosis differed by segmentectomy location and that S6 segmentectomy was associated with worse survival compared with other segmentectomies. Thus, attention should be paid to unforeseen lymph node upstaging, particularly in lower lobe segmentectomy.

The postoperative complications after segmentectomy also require consideration. According to the JCOG0802 trial, the overall complication rate did not differ significantly between segmentectomy and lobectomy [14]. However, the rate of prolonged air leak was significantly higher after segmentectomy than after lobectomy. In the current study, the rate of postoperative complications, including air leak after segmentectomy, showed comparable outcomes to those after lobectomy. To prevent postoperative air leakage, the intersegmental plane should be dissected with a mechanical stapler, the line of which should be aimed at minimizing the number of junctional points. If fistulae of the bronchioles are identified, they should be sutured thoroughly. In this study, fibrin glue and polyglycolic acid mesh were applied to the raw surfaces of the remaining lung. Thus, we assumed that these procedures might have contributed to the prevention of postoperative complications after segmentectomy.

Limitations

This study had several limitations. First, this was a single-centre retrospective study, and the study population was small. Moreover, due to the lack of randomization, the study design may have been influenced by patient selection and other biases, although segmentectomy cases were matched with lobectomy cases using propensity score matching analysis to reduce bias. Second, pathological margin data were not included in this study. Nonetheless, if the nearest surgical margin seemed close to the tumour, a negative surgical margin was confirmed by frozen-section cytodiagnosis. In addition, we confirmed the negative invasion of hilar peribronchovascular soft tissue (Sheath+) in all cases, which was routinely examined at our institution [15]. Third, the study population was not classified using the most recent revision of TNM staging (eighth edition) based on the size of the solid component. However, we measured and categorized the C/T ratios in all cases.

CONCLUSION

In conclusion, our study revealed that segmentectomy could be an acceptable treatment for small-sized NSCLC defined using a novel 3D-CT method. The prognosis was influenced by the tumour invasiveness, not the surgical procedure.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: none declared.

Data availability

Data are available on request.

Author contributions

Shinya Tane: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing. **Yoshitaka Kitamura:** Writing—review & editing. **Kenji Kimura:** Writing—review & editing. **Nahoko Shimizu:** Writing—review & editing. **Gaku Matsumoto:** Writing—review & editing. **Kazuya Uchino:** Writing—review & editing. **Wataru Nishio:** Supervision; Writing—review & editing.

Reviewer information

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