



Thoracoscopic Anatomical Sublobar Resection Including Subsegmentectomy for Non-Small Cell Lung Cancer

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Abstract

Background Among anatomical sublobar resection techniques for non-small cell lung cancer (NSCLC), the clinical benefit of subsegmentectomy remains unclear. We investigated whether anatomical sublobar resection including subsegmentectomy—segmental resection with subsegmental additional resection or subsegmental resection alone—is an effective and feasible surgical procedure for NSCLC.

Methods We retrospectively reviewed data of 285 patients with clinical stage I NSCLC who underwent anatomical sublobar resection at our institution from January 2013 to March 2021 and compared surgical outcomes between patients who underwent anatomical sublobar resection including (IS; n = 50) and excluding (ES; n = 235) subsegmentectomy.

Results No significant intergroup differences were noted in terms of age, sex, smoking, comorbidities, tumor size or location, consolidation tumor ratio, and preoperative pulmonary function. The IS group had more preoperative computed tomography-guided markings (34 vs. 15%; $p = .004$) and smaller resected lung volumes converted to the total subsegment number [3 (2–4) vs. 3 (3–6); $p = .02$] than the ES group. No significant differences in margin distance [mm, 20 (15–20) vs. 20 (20–20); $p = .93$], readmission rate (2% vs. 3%; $p > .99$), and intraoperative (8% vs. 7%; $p = .77$) or postoperative (8% vs. 10%; $p = .80$) complication rates were observed, and the 5-year local recurrence-free survival (91% vs. 90%; $p = .92$) or postoperative pulmonary function change were comparable between both groups.

Conclusions Although further investigations are required, anatomical sublobar resection including subsegmentectomy for clinical stage I NSCLC could be an acceptable therapeutic option.

Abbreviations

CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
ES	Anatomical sublobar resection excluding subsegmentectomy
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
IS	Anatomical sublobar resection including subsegmentectomy
JCOG	Japan Clinical Oncology Group
LN	Lymph node
NSCLC	Non-small cell lung cancer

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OS	Overall survival
RFS	Recurrence-free survival
WJOG	West Japan Oncology Group

Introduction

As reported by the lung cancer study group in 1995, lobectomy with mediastinal lymph node (LN) dissection has been the typical technique for non-small cell lung cancer (NSCLC) [1]. However, the Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG) performed prospective randomized studies about early-stage NSCLC [2, 3] and reported that the segmentectomy was superior to lobectomy in terms of overall survival (OS) and postoperative pulmonary function preservation in 2022 [4]. Anatomical sublobar resection, as typified by segmentectomy in patients with NSCLC, requires sufficient margin distances to prevent local recurrence and minimal lung resection to preserve postoperative pulmonary function [5–14]. Nonetheless, in the case of NSCLC located close to intersegmental borders, segmentectomy alone might provide insufficient margin distances, whereas multisegmentectomy might cause excessive lung resection. Although segmentectomy with additional wedge resection on margins is widely used for such cases, additional wedge resection on margins is typically distressing owing to the absence of intraoperative anatomical landmarks used to determine appropriate resection areas of the lung parenchyma. In contrast, anatomical resection based on the subsegment (i.e., subsegmentectomy) might be a more versatile and reproducible procedure than additional wedge resection on margins because its resection area is objectively determined based on anatomical structures including pulmonary vessels or bronchi, and the application of subsegmentectomy gradually becomes widespread in some high-volume institutions [15–18].

Anatomical sublobar resection including subsegmentectomy (IS) involves segmental resection with subsegmental additional resection or subsegmental resection alone [17], and many surgeons recognize the fact that it is a technically more challenging procedure than anatomical sublobar resection excluding subsegmentectomy (ES) [15–18]. However, our previous report on anatomical sublobar resections performed in 261 patients with lung malignancies suggested that the procedures including subsegmentectomy have no negative impact on the surgical outcomes [17]. Nonetheless, in NSCLCs in particular, reports of the surgical outcomes of IS remain scarce; thus, its effectiveness and feasibility have remained unclear so

far. Therefore, we aimed to investigate whether IS can secure an adequate margin distance with minimal lung resection without impairing surgical outcomes compared to ES in patients with early-stage NSCLC.

Materials and methods

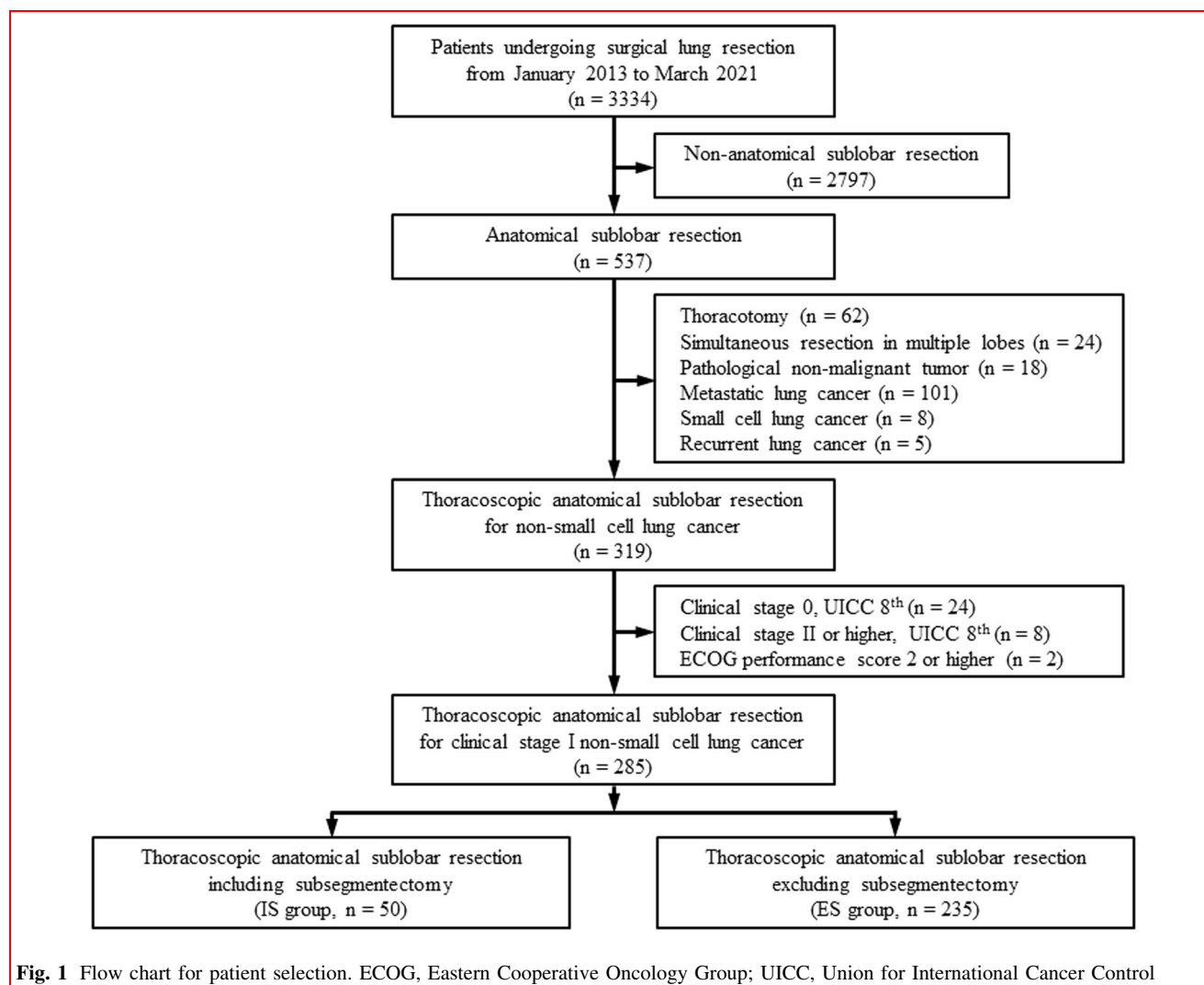
Research participants and design

The Institutional Review Board of Aichi Cancer Center approved this retrospective research on January 27, 2022 (approval number: 2021-0-179). We reviewed patients who had anatomical sublobar resection at our institution from January 2013 to March 2021 among the 3334 patients who had pulmonary resection during that period (Fig. 1). Surgical indications and preoperative markings were decided through our multidisciplinary tumor board, and each patient's written informed consent was obtained preoperatively [17, 19, 20]. The excluded criteria were as listed: (1) thoracotomy, (2) simultaneous excision in multiple lobes, (3) pathological diagnoses other than primary NSCLC, (4) clinical stage other than I, and (5) Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2 . Patients were then divided into two groups according to whether subsegmentectomy was included in the surgical procedure: IS (i.e., anatomical sublobar resection including subsegmentectomy; $n = 50$) and ES (i.e., anatomical sublobar resection excluding subsegmentectomy; $n = 235$) groups. Only one case of procedure conversion from the IS group was included in the ES group.

Clinicopathological data were collected from the medical records. All participants were assessed using biochemistry including tumor markers, electrocardiography, echocardiography, pulmonary function tests, high-resolution enhanced computed tomography (CT), brain magnetic resonance imaging, and 18-fluorodeoxyglucose positron emission tomography CT within 6 weeks before surgery [2–4]. NSCLC patients were staged per the *Tumor, Nodes, and Metastasis Classification of Malignant Tumors* (eighth edition) [21]. Surgical outcomes included the surgery duration, bleeding, margin distance, perioperative morbidity or mortality, period of hospitalization or drainage, and postoperative respiratory function.

Surgery technique and histopathological samples

Four experienced attending general thoracic surgeons exclusively performed thoracoscopic view surgeries typically with four ports. Preoperative CT-guided marking using an indigo carmine and lipiodol mixture was conducted as necessary by experienced radiologists [19, 20].



Endoscopic surgical staplers were mainly utilized for the intersegmental and intersubsegmental dissections.

The macroscopic distance between the surgical margin and the nearest tumor edge on a collapsed lung was determined post-staple removal. If required, frozen sections of the margins were microscopically assessed. If the tumor reached the margin or the distance between the tumor and margin was $< 1000 \mu\text{m}$, it was considered positive or close, respectively. In cases with positive or close margins, additional surgery for ensuring sufficient margin distances was conducted whenever possible.

Follow-up evaluation

The Common Terminology Criteria for Adverse Events version 5.0 was employed to evaluate complications, and all grade ≥ 2 (moderate) complications were analyzed [2, 3, 17, 20]. Patient follow-up started from the day of surgery with physical and biochemical examinations,

thoracoabdominal CT, and brain magnetic resonance imaging at 3–6 month intervals during the initial 5 years and then once annually [2–4, 20]. Pulmonary function was reassessed at 6 and 12 months postoperatively, excluding cases requiring conversion to thoracotomy [3, 17, 20, 22]. Readmission was defined as admission within 30 days of discharge postoperatively [3]. Perioperative mortality was defined as death within the first 30 postoperative days [3, 17, 20]. Local recurrence was determined as recurrence of tumor in the ipsilateral thorax, including hilar or mediastinal LNs, malignant pleural effusion, and the surgical margin of the lung or bronchus [4]. If necessary, a biopsy was conducted to histologically confirm local recurrence; otherwise, the institutional multidisciplinary tumor board accepted imaging demonstration on local recurrence, involving positron emission tomography CT.

Analysis of statistics

All data were displayed as numbers (percentages) or medians (first and third quartiles of the distribution). Intergroup differences were estimated with Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Time-dependent functional changes about forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured. The repeated-measures analysis of variance was utilized to compare FVC and FEV1 changes. The Kaplan–Meier method was employed to evaluate local recurrence-free survival (RFS), and the log-rank test was utilized to determine the intergroup differences. JMP software for Windows version 14.0 (SAS Institute, Cary, NC, USA) was used for all statistical calculations. A two-sided p value of < 0.05 indicated statistical significance.

Results

Altogether, 537 patients were evaluated (Fig. 1), and those with thoracotomy ($n = 62$), simultaneous excision in multiple lobes ($n = 24$), pathological nonmalignant diseases ($n = 18$), and metastatic lung ($n = 101$), small cell lung ($n = 8$), or recurrent lung ($n = 5$) cancers were excluded. Furthermore, patients with clinical stage 0 ($n = 24$), clinical stage \geq II ($n = 8$), and ECOG performance score ≥ 2 ($n = 2$) were excluded. Finally, 285 patients were included, with 50 (18%) and 235 (82%) belonging to the IS and ES groups, with a median follow-up of 51 and 50 months for each.

The patient characteristics were relatively balanced between both groups (Table 1). The IS group had a significantly higher percentage of ECOG performance score of 1 (12% vs. 4%; $p = 0.03$) than the ES group. No significant differences in age, sex, body mass index, smoking, tumor location, comorbidities, preoperative pulmonary function, and clinical stage were found between both groups. On CT images, no significant differences in tumor diameter, consolidation tumor ratio, or tumor depth from the nearest pleura were seen between the groups.

Figure 2 describes the segment of tumor location and top 10 most frequently resected segment(s) or subsegment(s) of both groups. The subsegmental resections around the right superior, left superior, and left apicoposterior segments were frequently performed in the IS group (Fig. 2a). The resection of the left upper division ($n = 62$, 26%) and the left apicoposterior segment ($n = 28$, 12%) were often conducted in the ES group (Fig. 2b).

The IS group had significantly more preoperative CT-guided markings ($n = 17$, 34%) than the ES group ($n = 36$, 15%) ($p = 0.004$) (Table 2). None of the markings

adversely affected general anesthesia or caused surgery postponement. No significant intergroup differences in surgery duration [min, 180 (148–210) vs. 178 (149–211); $p = 0.72$], bleeding [mL, 5 (1–10) vs. 5 (1–10); $p = 0.82$], margin distance [mm, 20 (15–20) vs. 20 (20–20); $p = 0.93$], and additional resection rate (6% vs. 3%; $p = 0.39$) based on intraoperative margin evaluation were observed. The IS group had significantly smaller lung resections converted to the total subsegment number [3 (2–4) vs. 3 (3–6); $p = 0.02$] and fewer dissected LNs [2 (0–3) vs. 3 (1–9); $p < 0.001$] or LN sites [1 (1–3) vs. 2 (1–4); $p = 0.002$] than the ES group. No significant intergroup differences in duration of hospitalization [days, 3 (2–5) vs. 3 (2–4); $p = 0.63$], length of drainage [days, 0 (0–1) vs. 0 (0–1); $p = 0.83$], and readmission rate (2% vs. 3%; $p > 0.99$) were found. Finally, both groups had no perioperative mortality and comparable local recurrence rates (4% vs. 4%; $p > 0.99$) during follow-up.

No significant differences in the intraoperative (8 vs. 7%; $p = 0.77$) and postoperative (8 vs. 10%; $p = 0.80$) complication rates were observed between the groups (Table 3). Four intraoperative complications were observed in the IS group, including three cases of pulmonary vascular injuries and one case of anatomical misidentification, wherein a branch of the pulmonary artery was accidentally dissected.

Although pathological tumor sizes [mm, 14 (10–18) vs. 15 (11–21); $p = 0.11$] were comparable in both groups, the IS group had significantly smaller invasive sizes [mm, 7 (2–12) vs. 10 (4–16); $p = 0.01$] than the ES group (Table 4). Pathologically, two (1%) and four (2%) patients in the ES group had positive and close margins, respectively; none in the IS group ($p > 0.99$). Among the two positive margin cases in the ES group, one had a 15-mm ground-glass nodule with partially solid component on directly contacting the visceral pleura and the other had an 8-mm solid nodule localized 12 mm from the nearest visceral pleura. The ES group had four (2%) cases with spread through air spaces, whereas the IS group had none ($p > 0.99$). During the postoperative course, only 213 (75%) patients were able to reassess their pulmonary function at both 6 and 12 months (Fig. 3). No significant intergroup differences in the postoperative-to-preoperative ratios of FVC ($p = 0.26$; Fig. 3a) and FEV1 ($p = 0.24$; Fig. 3b) were observed.

The 5-year local RFS rate for all patients in this study was 90%. No significant difference in the 5-year local RFS rate (91 vs. 90%; $p = 0.92$) was observed between the groups (Fig. 4).

Table 1 Clinical factors of thoracoscopic anatomical sublobar resection including (IS) and excluding (ES) subsegmentectomy for clinical stage I non-small cell lung cancer

Variables	All patients (n = 285)		
	IS group (n = 50)	ES group (n = 235)	p value
Age, year	71 (65–78)	72 (65–78)	.99
Sex	29 (58)	134 (57)	> .99
Female	21 (42)	101 (43)	
Male			
Body mass index	23 (20–25)	22 (20–25)	.52
ECOG performance score	44 (88)	226 (96)	.03
0	6 (12)	9 (4)	
1			
Smoking, never	25 (50)	124 (53)	.76
Tumor location lobe	10 (20)	50 (21)	.30
Right upper	8 (16)	45 (19)	
Right lower	17 (34)	98 (42)	
Left upper	15 (30)	42 (18)	
Left lower			
Comorbidities	3 (6)	28 (12)	.32
Chronic obstructive pulmonary disease	3 (6)	27 (11)	.32
Interstitial pneumonitis	9 (18)	39 (17)	.84
Diabetes mellitus	8 (16)	25 (11)	.33
Cardiovascular dysfunction	3 (6)	18 (8)	
Renal dysfunction			
Pulmonary function Forced vital capacity, L	2.7 (2.3–3.1)	2.8 (2.4–3.4)	.21
Forced expiratory volume in 1 s, L	2.0 (1.6–2.4)	2.1 (1.7–2.5)	.26
Emphysema on CT	9 (18)	54 (23)	.57
Tumor diameter on CT, mm	16 (14–20)	18 (13–24)	.28
Consolidation tumor ratio	7 (14)	33 (14)	.22
≤ 0.25	22 (44)	71 (30)	
0.25 to ≤ 0.5	11 (22)	56 (24)	
0.5 to < 1	10 (20)	75 (32)	
1			
Tumor depth from the pleura, mm	0 (0–9)	0 (0–6)	.26
Clinical stage	31 (62)	124 (53)	.39
IA1	16 (32)	76 (32)	
IA2	2 (4)	27 (11)	
IA3	1 (2)	8 (3)	
IB			

Note: Values are n (%) or median (the first and third quartiles)

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group

Discussion

The JCOG0802/WJOG4607L findings indicated that lobectomy in patients with early-stage NSCLC may adversely affect not only a patient's postoperative pulmonary function but also life expectancy from its high invasiveness due to excessive lung resection [4]. Therefore,

anatomical sublobar resection as typified by segmentectomy should be selected to reduce invasiveness for such patients. However, segmentectomy alone might not provide adequate margin distances to prevent local recurrence in the case of small NSCLCs located near intersegmental borders. Surgical options for such NSCLCs include segmentectomy with additional wedge resection on margins,

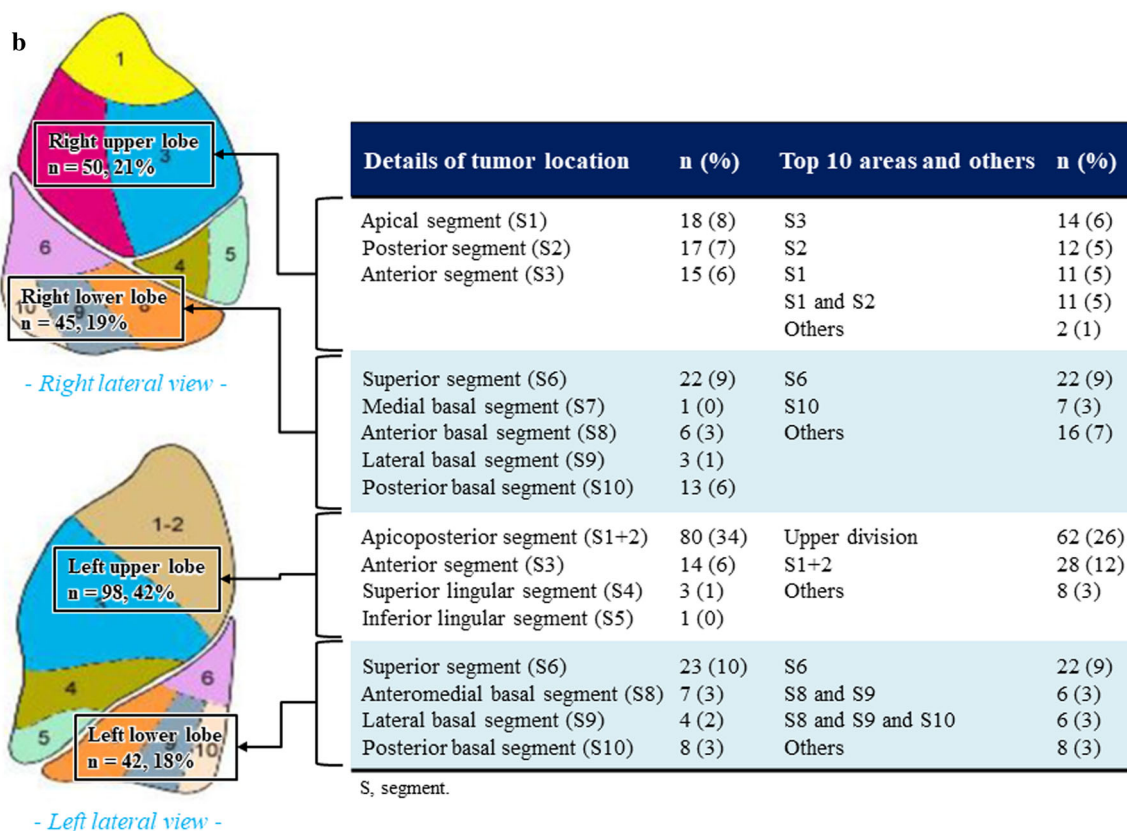
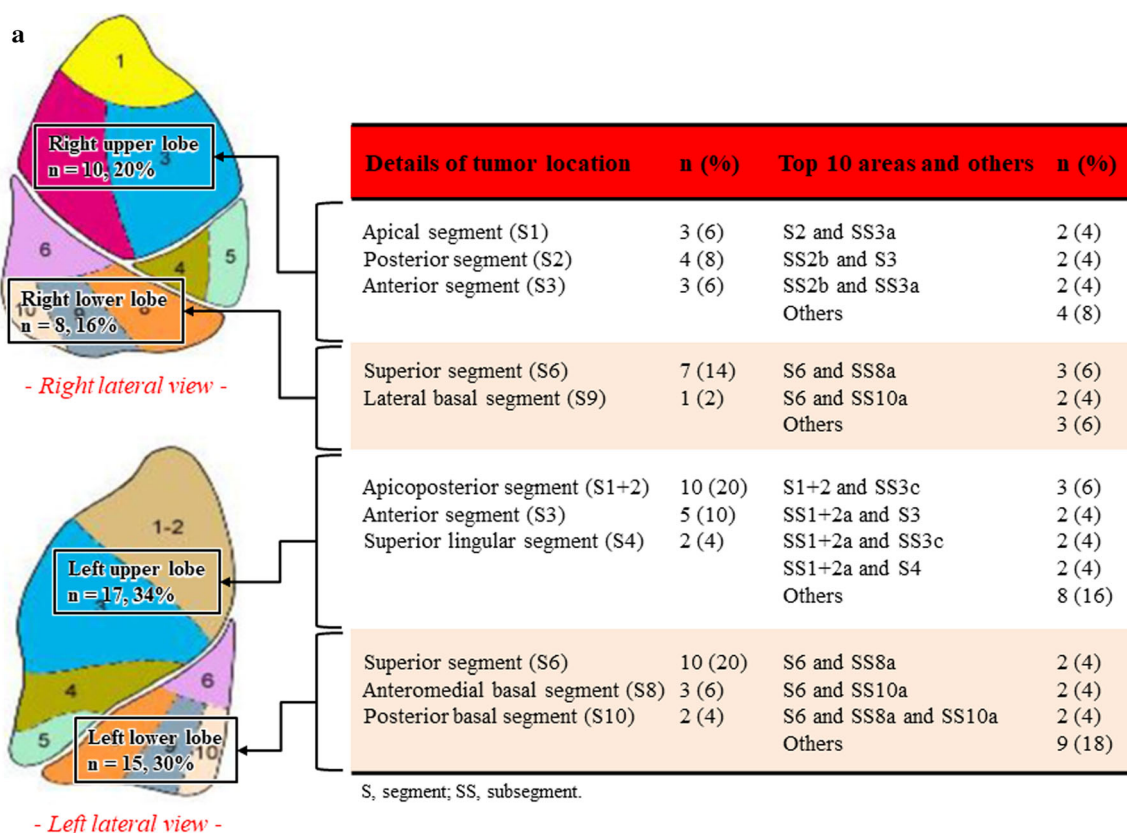


Fig. 2 Details of tumor location and top 10 most frequently resected areas for thoracoscopic anatomical sublobar resection including (IS; **a**) and excluding (ES; **b**) subsegmentectomy for clinical stage I non-small cell lung cancer

multisegmentectomy, or IS. The advantage of IS over segmentectomy with additional wedge resection on margins is the ability to objectively determine the resection area of the lung parenchyma based on anatomical structures including pulmonary vessels or bronchi. Preoperative usage of the anatomical evaluation of pulmonary vessels and bronchi with three-dimensional reconstruction images is a key factor in our procedures, as previously reported [17, 19, 20]. In contrast, the advantage of IS over multisegmentectomy is the ability to determine the minimal resection area based on the subsegment smaller anatomical

unit of the lung than the segment. In this study, the IS group had significantly smaller resected lung volumes converted to the total number of subsegments than the ES group, whereas margin distances were comparable between both groups. IS might be a more helpful procedure than ES (involving multisegmentectomy) in patients with early-stage NSCLC for securing appropriate margin distances with minimal lung resection.

Because IS requires techniques to identify and dissect fine subsegmental vessels and bronchi, many surgeons have avoided performing it for fear that its technical complexity would lead to poor surgical outcomes. However, this research showed no significant differences between the IS and ES groups in surgery duration, bleeding, perioperative morbidity or mortality, and margin distance. Although the IS group tended to have more

Table 2 Perioperative outcomes of thoracoscopic anatomical sublobar resection including (IS) and excluding (ES) subsegmentectomy for clinical stage I non-small cell lung cancer

Variables	All patients (n = 285)		
	IS group (n = 50)	ES group (n = 235)	p value
<i>Preoperative factors</i>			
Diagnosis	2 (4)	13 (6)	> .99
Computed tomography-guided marking	17 (34)	36 (15)	.004
<i>Intraoperative factors</i>			
Operative time, minutes	180 (148–210)	178 (149–211)	.72
Blood loss, mL	5 (1–10)	5 (1–10)	.82
Conversion to thoracotomy	0 (0)	1 (0)	> .99
Transfusion	0 (0)	1 (0)	> .99
Resected lung volume ^a	3 (2–4)	3 (3–6)	.02
Margin distance, mm	20 (15–20)	20 (20–20)	.93
Additional margin resection	3 (6)	7 (3)	.39
Polyglycolic acid sheet	47 (94)	217 (92)	> .99
Fibrin glue	48 (96)	220 (94)	.75
Dissected lymph nodes	2 (0–3)	3 (1–9)	< .001
Dissected lymph node sites	1 (1–3)	2 (1–4)	.002
Staples ^b	4 (3–4)	3 (3–4)	.09
<i>Postoperative factors</i>			
Hospital stay, days	3 (2–5)	3 (2–4)	.63
Drainage, days	0 (0–1)	0 (0–1)	.83
Drain removal on the operative day	34 (68)	164 (70)	.87
Drain reinsertion	2 (4)	6 (3)	.63
Readmission	1 (2)	8 (3)	> .99
Mortality	0 (0)	0 (0)	> .99
Adjuvant therapy	1 (2)	3 (1)	.54
Local recurrence	2 (4)	9 (4)	> .99

Values are n (%) or median (the first and third quartiles)

^aTotal number of subsegments in the resected lung. ^bTotal number of staples for intersegmental and/or intersubsegmental formations

Table 3 Complications of thoracoscopic anatomical sublobar resection including (IS) and excluding (ES) subsegmentectomy for clinical stage I non-small cell lung cancer

Variables	All patients (n = 285)		
	IS group (n = 50)	ES group (n = 235)	p value
<i>Intraoperative complications</i>			
Any complication (grade ≥ 2)	4 (8)	17 (7)	.77
Any organ injury	3 (6)	17 (7)	> .99
Aorta	0 (0)	1 (0)	> .99
Pulmonary artery	2 (4)	5 (2)	.36
Pulmonary vein	1 (2)	2 (1)	.44
Bronchus	0 (0)	2 (1)	> .99
Phrenic nerve	0 (0)	1 (0)	> .99
Recurrent nerve	0 (0)	1 (0)	> .99
Atelectasis	0 (0)	4 (2)	> .99
Anatomical misidentification	1 (2)	0 (0)	.18
<i>Postoperative complications</i>			
Any complication (grade ≥ 2)	4 (8)	24 (10)	
Pulmonary fistula (> 5 days)	1 (2)	9 (4)	.80
Respiratory disorder	2 (4)	9 (4)	> .99
Pneumonitis	0 (0)	3 (1)	> .99
Pleural effusion	1 (2)	5 (2)	> .99
Pneumothorax	0 (0)	1 (0)	> .99
Atelectasis	0 (0)	1 (0)	> .99
Acute exacerbation of interstitial pneumonitis	0 (0)	3 (1)	> .99
Pleural hemorrhage	0 (0)	1 (0)	> .99
Wound infection	0 (0)	1 (0)	> .99
Atrial fibrillation	1 (2)	0 (0)	> .99
Hepatic failure	0 (0)	1 (0)	.18
Pulmonary embolism	1 (2)	0 (0)	> .99
Nervous system disorder	0 (0)	2 (1)	.18
Delirium	0 (0)	2 (1)	> .99

Note: Values are n (%)

pulmonary vascular injuries, vascular repairs were easily completed and did not adversely affect perioperative outcomes because all injured vessels were small peripheral subsegmental branches. The present findings suggests that surgeons do not need to avoid performing IS for fear of poor surgical outcomes. In contrast, IS was significantly more accompanied by preoperative CT-guided marking (which have been reported to be helpful in reducing the operative time of complex segmentectomy) [17, 20], than ES. Thus, the difference in preoperative marking frequency might have affected the operative time of both procedures.

The ability of IS to minimize lung resection was expected to improve postoperative pulmonary function. Actually, although the IS group tended to have consistently better FVC and FEV1 during the postoperative course than the ES group, no significant differences in these parameters

were found between the groups. In this research, only 213 (75%) patients (43 in the IS group) were able to reassess pulmonary function at both 6 and 12 months postoperatively. If reassessment pulmonary function data had been obtained from all patients, postoperative pulmonary function changes would have been more accurately evaluated. Future comparisons involving more cases need to be performed to obtain more accurate results.

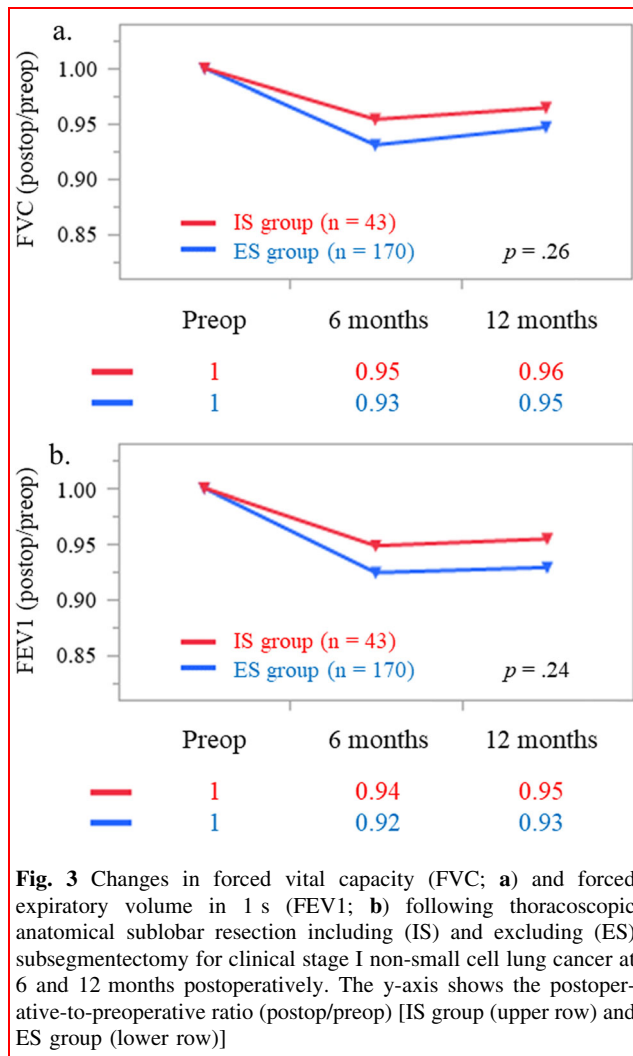
Limitations

The present study has several limitations. First, this study was conducted retrospectively on a relatively limited number of participants at a single institution. Second, the resected lung volume was converted to the total number of subsegments contained in the resected lung. Third, some

Table 4 Pathological features of thoracoscopic anatomical sublobar resection including (IS) and excluding (ES) subsegmentectomy for clinical stage I non-small cell lung cancer

Variables	All patients (n = 285)		
	IS group (n = 50)	ES group (n = 235)	<i>p</i> value
Histological subtype			
Adenocarcinoma in situ	7 (14)	16 (7)	.13
Minimally invasive adenocarcinoma	14 (28)	45 (19)	
Invasive adenocarcinoma	27 (54)	146 (62)	
Squamous cell carcinoma	1 (2)	20 (9)	.11
Large cell carcinoma	0 (0)	5 (2)	
Others	1 (2)	3 (1)	
Tumor size, mm	14 (10–18)	15 (11–21)	.11
Invasive size, mm	7 (2–12)	10 (4–16)	.01
Margin assessment			
Negative	50 (100)	229 (97)	> .99
Close	0 (0)	4 (2)	
Positive	0 (0)	2 (1)	
Pathological stage			
0	7 (14)	16 (7)	.10
I A1	27 (54)	107 (46)	
IA2	14 (28)	74 (31)	
IA3	1 (2)	16 (7)	.02
IB	0 (0)	17 (7)	
≥ IIA	1 (2)	5 (2)	
Pathological nodal status			
Negative	36 (72)	199 (85)	.07
Positive	1 (2)	5 (2)	
Unknown	13 (26)	31 (13)	
Lymphatic invasion, positive	8 (16)	81 (34)	.02
Vascular invasion, positive	4 (8)	40 (17)	.28
Pleural invasion, positive	0 (0)	15 (6)	.15
Resection status			
R0	50 (100)	233 (99)	> .99
R1	0 (0)	2 (1)	
Tumor spread through air spaces	0 (0)	4 (2)	

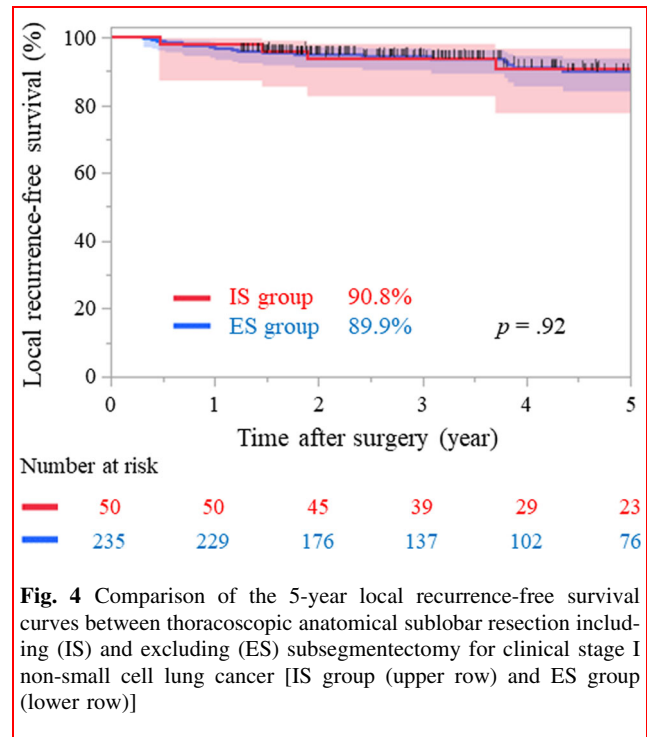
Values are n (%) or median (the first and third quartiles)



cases could not reassess their respiratory function postoperatively. Forth, the follow-up duration was inadequate for precise analysis of calculating the OS rates.

Conclusion

Although future multicenter prospective studies are needed to validate our findings, anatomical sublobar resection including subsegmentectomy may be an acceptable treatment option for clinical stage I NSCLCs.



Declarations

Conflicts of interest Drs. Takuya Matsui, Yusuke Takahashi, Takeo Nakada, Yusuke Sugita, Shuichi Shinohara, Ayumi Suzuki, Noriaki Sakakura, Takatsugu Takano, Kensuke Chiba, Ryuji Nakamura, Risa Oda, Tsutomu Tatematsu, Keisuke Yokota, Kotaro Mizuno, Hiroshi Haneda, Katsuhiko Okuda, and Hiroaki Kuroda have no conflicts of interest or financial ties to disclose.

Ethics approval The Institutional Review Board of Aichi Cancer Center approved this retrospective research on January 27, 2022 (approval number: 2021-0-179).

Informed consent Informed written consent was obtained from all research participants prior to research enrollment.

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