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ORIGINAL ARTICLE

Sublobar Resection for Clinical Stage I Nonsmall Cell Lung Cancers

Tsai-Wang Huang[1], Yi-Hsi Chen[1], Kai-Hsu Huang[1], Hung Chang[1], Shih-Chun Lee[1]

[1]*Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC*

Aim: We investigated outcomes of sublobar resection in patients with clinical early-stage nonsmall cell lung cancers. **Patients and Methods:** Patients who underwent surgical resection between January 2002 and June 2013 were reviewed. The clinical data, surgical approach, and outcome were analyzed with mean follow-up of 108 months. **Results:** Of 597 patients, 108 (18.1%) underwent sublobar resection. The 5-year overall survival (OS) and disease-free survival rate for this group were 76.2% and 70.3%, respectively, compared with 79.7% and 73.0% for those undergoing anatomic resection ($P = 0.709$ and 0.618). After stratifying for tumor size <2 cm, 233 patients with T1a lesions were enrolled in this study. The 5-year OS and disease-free survival rate for 69 patients who underwent sublobar resection were 96% and 87%, respectively, compared with 93.4% and 89.7% for those undergoing anatomic resection ($P = 0.760$ and 0.868). The local recurrence rate was 3% in the sublobar resection group and 8.5% in the anatomic resection group. There were no significant differences in age, gender, histopathology type, maximum standard uptake value, lymphovascular space invasion, visceral pleural invasion, and epidermal growth factor receptor status, except in the grade of tumor differentiation and numbers of dissected lymph nodes: 13.16 ± 6.62 in the anatomic resection group and 7.34 ± 4.91 in the sublobar resection group ($P < 0.01$). In the sublobar resection group, 28 patients underwent segmentectomy without local recurrence during follow-up. **Conclusions:** The oncologic outcomes of sublobar resection were similar to anatomic resection in these patients; lymph node sampling might not compromise surgical outcomes. Further large-scale studies are necessary to clarify the difference in clinical outcome between segmentectomy and wedge resection.

Key words: Lung cancer, prognosis, surgery

INTRODUCTION

Anatomic lobectomy and mediastinal lymph node dissection are standard operations in patients with nonsmall cell lung cancer (NSCLC).[1] Lobectomy results in loss of pulmonary function and is prohibitive for patients with compromised cardiopulmonary functions. Ginsberg and Rubinstein[2] reported a randomized trial of sublobar resection for patients with clinical stage T1a NSCLC, showing that a high locoregional recurrence was associated with limited resection. Sublobar resection was considered a compromised operation in the past. With the increasing use of chest computed tomography (CT) scans, low-dose CT was more sensitive in detecting early-stage lung cancers.[3] Some retrospective studies reported sublobar resection in patients with early-stage lung cancers with similar oncologic outcomes.[4,5] The theoretical advantage of limited resection includes preservation of pulmonary function, decreased perioperative morbidity, and the ability of patients to survive the second operation. It promotes the vigorous development of sublobar resection in patients with an early-stage NSCLC. However, there are no robust data from randomized trials that document better long-term outcomes following sublobar resection or on the role of lymph node dissection. In one meta-analysis from the National Cancer Database, sublobar resection for patients with clinical Stage 1A lung cancers led to worse overall survival (OS) than did anatomic resection.[6] Inadequate positive tumor margins are the main complications involved in attempting sublobar

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Corresponding Author: Dr. Tsai-Wang Huang, Department of Surgery, Division of Thoracic Surgery, Tri-Service General Hospital, 325, Section 2, Cheng-Kung Road, Taipei 114, Taiwan, ROC. Tel: +886-2-87927167; Fax: +886-2-87927403. E-mail: chi-wang@yahoo.com.tw

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resection. Most mortality following surgical resection is associated with tumor recurrence. The adoption of minimally invasive techniques for sublobar resection has been one of the most important advances in thoracic surgery. Thus, video-assisted thoracoscopic surgery (VATS) segmentectomy is a safe and oncologically proven technique for patients with an early-stage NSCLC.[7] That study evaluated the VATS procedure compared with open surgery. Most studies have focused on the oncological outcomes of sublobar resection for patients with clinical T1a lesions. However, this can involve selection bias and raises ethical problems in terms of performing randomized studies. The intraoperative evaluation of lymph nodes might determine the surgeon's decision to do anatomic or sublobar resection. There are still controversies on the methods for carrying out sublobar resection, such as wedge resection versus segmentectomy and lymph node dissection versus lymph node sampling. Here, we investigated the surgical outcomes of sublobar resection for patients with clinical early-stage NSCLC using a VATS procedure and discuss the role of lymph node dissection.

PATIENTS AND METHODS

All patients who underwent anatomic resection for clinical Stage I or II NSCLC at Tri-Service General Hospital, Taiwan, between January 2002 and June 2013 were reviewed retrospectively. This study was approved by the Institutional Review Board of our hospital (TSGHIRB 2-103-05-119). The patients underwent preoperative staging workups, including chest CT scans, positron emission tomography (PET), and abdominal ultrasonography. PET was performed for the assessment of mediastinal lymph node or bone metastases. We excluded patients who had received neoadjuvant chemotherapy, those with synchronous lung cancers, or those who underwent open surgery. Determinations of cancer stage were based on the tumor-node-metastasis classification (7th edition) of the American Joint Committee on Cancer.[8] In all, 597 patients with NSCLC underwent surgical resection and mediastinal lymph node dissection after evaluation of resectability and operability. Postoperative surveillance included contrast-enhanced CT and measurements of serum carcinoembryonic antigen. CT scans were performed for tumor assessment every 4–6 months. Magnetic resonance imaging of the brain was performed as indicated clinically. Relapse (including locoregional recurrence or distant metastasis) was documented either with imaging or histopathology diagnosis for all patients.

Statistical analysis

Descriptive data are expressed as the mean ± standard deviation. Student's *t*-test was used to investigate continuous variables, and the Chi-square test was used to compare categorical variables between groups. Survival from the date of surgery was calculated using Kaplan–Meier survival analysis. SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA) was used for all analyses, and statistical significance was defined as $P < 0.05$.

RESULTS

Of 630 patients with lung cancer who underwent surgical resection, 33 were excluded as having had neoadjuvant chemotherapy, synchronous lung cancers, or open surgery, so 597 patients were enrolled finally. Of these, 108 patients (18.1%) underwent sublobar resection, and 489 underwent anatomic resection (including pneumonectomy in 5 patients, lobectomy in 476 patients, and bilobectomy in 8 patients). There was no 30-day mortality. In the anatomic resection group, there were high rates of advanced tumor stages (Stage II 33.2%; Stage III 12.9%) compared with the sublobar resection group (Stage II 15.7%; Stage III 13.9%). Of the 108 patients who underwent sublobar resection, 75% had Stage I tumors. Some of these patients underwent sublobar resection because of comorbidity and old age. The characteristics of tumors in the anatomic resection group were poorer differentiation of tumors, central location, larger tumor size, and higher maximum standard uptake value (SUV_{max}) of fluorodeoxyglucose compared with the sublobar resection group [Tables 1 and 2]. The results showed poorer outcome with lower OS rate and a higher incidence of relapse in the anatomic resection group. The mean numbers of dissected lymph nodes in the anatomic resection group (13.38 ± 6.93) were greater than in the sublobar resection group (7.58 ± 5.89; $P < 0.001$). The 5-year OS was 76.2% for patients in the sublobar resection group and 79.7% for the anatomic resection group [$P = 0.709$; Figure 1a]. The 5-year disease-free survival (DFS) was 70.3% for patients in the sublobar resection group and 73.0% for the anatomic resection group patients [$P = 0.618$, Figure 1b].

After stratifying patients according to T1a lesions (tumor size <2 cm), 233 were included in the study; 164 (70.4%) underwent anatomic resection and 69 (29.6%) underwent sublobar resection after intraoperative node examination with free metastases. Three patients with preoperative PET–CT-negative N status had lymph node involvement, and this finding changed the operation (sublobar resections were converted to anatomic resections). There were no significant differences in age, gender balance, tumor histopathology type, SUV_{max} of tumor, lymphovascular space invasion (LVSI), visceral pleural invasion, or epidermal growth factor receptor gene mutation status, except in terms of the grade of tumor differentiation and the numbers of dissected lymph

Table 1: Characteristics of patients with or without tumor recurrence after resection for clinical Stage I nonsmall cell lung cancer

	Anatomic resection, *n*=489 (%)	Sublobar resection, *n*=108 (%)	*P*[a]
Gender			
Male	224 (45.8)	47 (43.5)	0.373
Female	265 (54.2)	61 (56.5)	
Histopathology			
Adenocarcinoma	417 (85.3)	103 (95.4)	0.017
SCC	36 (7.4)	3 (2.8)	
Others	36 (7.4)	2 (1.9)	
Differentiation			
Good	183 (37.4)	69 (63.9)	**<0.001**
Moderate	201 (41.1)	27 (25.0)	
Poor	105 (21.5)	12 (11.1)	
Location			
Central	283 (57.9)	41 (38.0)	**<0.001**
Peripheral	206 (41.1)	67 (62.0)	
Adjuvant chemotherapy			
Yes	192 (39.3)	34 (31.5)	0.154
No	297 (60.7)	74 (68.5)	
Adjuvant radiotherapy			
Yes	59 (12.1)	6 (5.6)	0.059
No	430 (87.9)	102 (94.4)	
Survival			
Yes	414 (84.7)	100 (92.6)	0.003
No	75 (15.3)	8 (7.4)	
Smoking			
Yes	121 (24.7)	22 (20.4)	0.662
No	332 (67.9)	80 (74.1)	
Ex-smoker	36 (7.4)	6 (5.6)	
Relapse			
Yes	100 (20.4)	8 (13.0)	0.008
No	389 (79.6)	100 (87.0)	
LVSI			
Absent	442 (90.4)	101 (93.5)	0.358
Present	47 (9.6)	7 (6.5)	
VPI			
Absent	471 (96.3)	102 (94.4)	0.414
Present	18 (3.7)	6 (5.6)	
P-stage			
0	3 (6.1)	2 (1.85)	0.006
I	255 (52.1)	73 (67.59)	
II	162 (33.1)	17 (15.74)	
III	63 (12.88)	15 (13.89)	
IV	6 (1.22)	1 (0.93)	

Statistically significant *P* values are depicted in bold print. [a]Significance was assessed using Chi-square tests. SCC=Squamous cell carcinoma; LVSI=Lymphovascular space invasion; P-stage=Pathology stage; VPI=Visceral pleural invasion

Table 2: Characteristics of patients with or without recurrence after surgical resection for clinical Stage I nonsmall cell lung cancer

Variable	Anatomic resection (*n*=489)	Sublobar resection (*n*=108)	*P*[a]
Age (year)	61.30±11.41	64.64±11.83	0.007
SUV_{max} of tumor	5.04±4.78	2.82±2.61	**<0.001**
Tumor size (cm)	2.60±1.48	1.40±0.81	**<0.001**
CEA (ng/mL)	7.08±27.05	3.66±5.88	0.015
Dissected lymph nodes	13.38±6.93	7.58±5.89	**<0.001**
Dissected N1	5.46±4.00	1.57±2.62	0.002
Dissected N2	7.73±5.54	5.96±4.63	**<0.001**

Statistically significant *P* values are depicted in bold print. [a]Significance was assessed using Student's *t*-tests. SUV_{max}=Maximum standard uptake value of FDG; CEA=Carcinoembryonic antigen; FDG=Fluorodeoxyglucose

node [Tables 3 and 4]. In the sublobar resection group, 74% of the patients had well-differentiated tumors, compared with 53.0% in the anatomic resection group ($P = 0.015$). There were more dissected lymph nodes in the anatomic resection group (13.16 ± 6.62) than in the sublobar resection group (7.34 ± 4.91; $P < 0.001$). The 5-year OS and DFS were 96% and 87% for the 69 patients who underwent sublobar resection versus 93.4% and 89.7% for the anatomic resection group ($P = 0.760$ and 0.868, respectively; [Figure 2a and b]). One local recurrence was found in 2 of the 69 patients with sublobar resection (3%) and in 14 of the 164 patients who underwent anatomic resection (8.5%). In the sublobar resection group, 28 patients underwent VATS-aided segmentectomy without any local recurrence [Figure 3]. The 5-year OS and DFS of segmentectomy patients had trends of better oncologic outcomes in the short-term follow-up.

DISCUSSION

Lung cancer remains the leading cause of cancer-related death. Despite advances in molecular markers and new drugs, long-term survival is unsatisfactory. Anatomic lobectomy is the gold standard in surgical treatment of patients with a

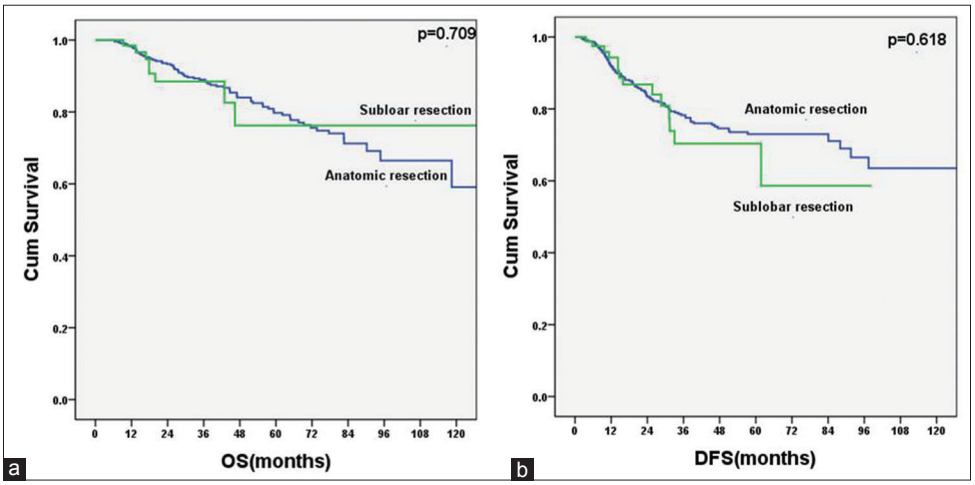

Figure 1: (a) Overall patient survival curves following anatomic or sublobar resection. (b) Disease-free patient survival curves following anatomic or sublobar resection

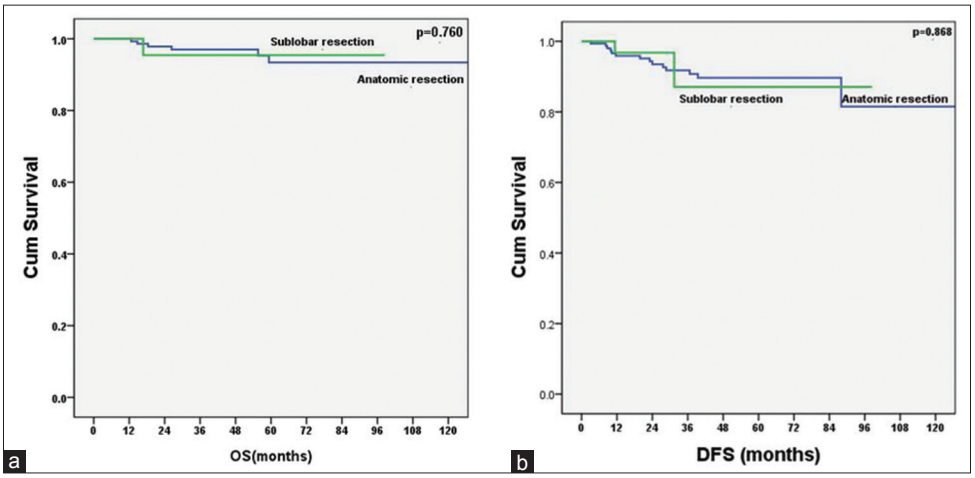

Figure 2: (a) Overall survival curves of patients with T1a lesions following anatomic or sublobar resection. (b) Disease-free patients with T1a lesions survival curves following anatomic or sublobar resection

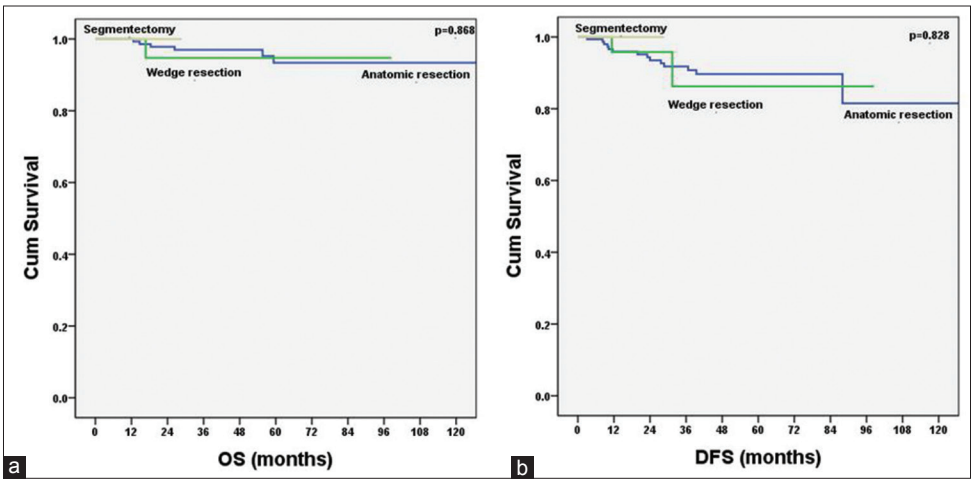

Figure 3: (a) Overall survival curves of patients with T1a lesions according to the surgical procedure used. (b) Disease-free patient survival curves of patients with T1a lesions according to the surgical procedure used

Table 3: Characteristics of patients with or without tumor recurrence after resection for clinical T1a nonsmall cell lung cancer

	Anatomic resection, ***n***=164 (%)	Sublobar resection, ***n***=69 (%)	*P* [a]
Gender			
Male	62 (37.8)	33 (48)	0.189
Female	102 (62.2)	36 (52)	
Histopathology			
Adenocarcinoma	151 (92.1)	66 (96)	0.377
SCC	4 (2.4)	2 (3)	
Others	9 (5.5)	1 (1)	
Differentiation			
Good	87 (53.0)	50 (74)	0.015
Moderate	62 (37.8)	14 (21)	
Poor	15 (9.1)	4 (6)	
Location			
Central	61 (37.2)	28 (40.6)	0.659
Peripheral	103 (62.8)	41 (59.4)	
Adjuvant chemotherapy			
Yes	11 (6.7)	8 (12)	0.162
No	153 (93.3)	61 (88)	
Adjuvant radiotherapy			
Yes	3 (1.8)	0	0.557
No	161 (98.2)	69 (100)	
Survival			
Yes	157 (95.7)	68 (98)	0.442
No	7 (4.3)	1 (1)	
Smoking			
Yes	121 (24.7)	22 (20)	0.662
No	332 (67.9)	80 (74)	
Ex-smoker	36 (7.4)	6 (6)	
Relapse			
Yes	14 (8.5)	2 (3)	0.097
No	150 (91.5)	67 (97)	
LVSI			
Absent	161 (98.2)	68 (99)	0.659
Present	3 (1.8)	1 (1.4)	
VPI			
Absent	163 (99.4)	69 (100)	0.704
Present	1 (0.6)	0	
EGFR gene mutation			
Wild type	46 (51.1)	24 (46)	0.604
Mutation	44 (48.9)	28 (54)	

[a]Significance was assessed using Chi-square tests. SCC=Squamous cell carcinoma; LVSI=Lymphovascular space invasion; P-stage=Pathology stage; VPI=Visceral pleural invasion; EGFR=Epidermal growth factor receptor

Table 4: Characteristics of patients with or without recurrence after surgical resection for clinical T1a nonsmall cell lung cancer

Variable	Anatomic resection (*n*=164)	Sublobar resection (*n*=69)	*P* [a]
Age (year)	59.57±10.68	62.06±11.82	0.117
SUV_{max} of tumor	2.29±2.14	2.68±2.41	0.398
CEA (ng/mL)	2.43±2.96	2.21±1.75	0.589
Dissected lymph nodes	13.16±6.62	7.34±4.91	**<0.001**
Dissected N1	5.35±3.61	1.44±2.43	**<0.001**
Dissected N2	7.56±5.44	5.93±4.01	**0.027**

Statistically significant *P* values are depicted in bold print. [a]Significance was assessed using Student's *t*-tests. SUV_{max}=Maximum standard uptake value of FDG; CEA=Carcinoembryonic antigen; FDG=Fluorodeoxyglucose

resectable NSCLC. Mortality following surgical resection is most often associated with tumor relapse.[8,9] In our previous study, tumor differentiation and LVSI were independent factors for postoperative relapse after surgical resection for patients with clinical Stage I NSCLC; 17 of 261 patients (6.5%) developed a local recurrence. Anatomic or sublobar resection did not affect the recurrence rate.[10]

The oncologic outcome of sublobar resection remains a controversial issue. This approach including wedge resection and segmentectomy had a trend for equal OS and DFS.[11] That study focused on T1a lesions (tumor size <2 cm). However, sublobar resection has been found to be an independent predictor of locoregional recurrence.[12] Bando *et al*.[13] reported that a higher recurrence rate was associated with sublobar resection in patients with tumors >2 cm (locoregional recurrence rate of 1.9% for tumors <2 cm compared with 33% in patients with tumors >2 cm). Regarding anatomic or sublobar resection approaches, the tumor size is important for postoperative outcome. In our study, the 5-year OS and DFS were no different between the two groups [Figure 1a and b]. Although this was the retrospective study, some patients underwent sublobar resections because of comorbidity and old age in early period of this study. The recurrence rate was 13% in the whole cohort of sublobar resection. The recurrence rate was still lower than in a previous report.[13] After stratifying for a tumor size <2 cm, there were still no differences between the groups in terms of the 5-year OS and DFS [Figure 2a and b]. The surgical outcome was better for patients with T1a lesions; the postoperative recurrence rate was 3% in the sublobar resection group versus 8.5% for patients who underwent anatomic resection.

Cerfolio *et al*. reported that a high SUV_{max} was correlated with tumor stage and with recurrence and survival rates.[14] A SUV_{max} of ≥10 was an independent predictor of DFS and OS. In published study, a SUV_{max} of ≥4.5 was found to be an independent predictor of recurrence after resection, with an odds ratio of 5.45 in 310 patients with Stages I and II disease.[15]

The metabolic activity of tumors has been shown to contribute significant information in terms of prognosis. However, the cutoff values of SUV_{max} measurements vary widely, making their clinical application difficult. In the present study, there was no significant difference of SUV_{max} between the two groups after we stratified the tumor size to <2 cm. A SUV_{max} cutoff of 3.3 based on our previous study[16] did not show statistical significance in predicting postoperative recurrence. The SUV_{max} as a parameter used in determining the decision to apply anatomic or sublobar resection has not been evaluated rigorously and here we showed that it was not a prognostic factor for T1a lesions.

In this study, the characteristics of tumors in the anatomic resection group were poorer differentiation of tumors, central location, larger tumor size, and higher SUV_{max} of compared with the sublobar resection group. The study was designed as retrospective study. It was the possible reason why the surgeon preferred the sublobar resection for peripheral lesions. It was easier to get tumor-free margin for peripheral lesions. In anatomic group, the grade of tumor differentiation was high than sublobar resection (both clinical Stage 1 and T1a tumor). We thought that the imaging characteristics of tumors were selective bias when the surgeon performed operation. For solid tumor, the surgeon tended to do anatomic operation. Further prospective study was necessary to clarify this issue.

Accurate staging can help predict the prognosis for patients with NSCLC. The number of lymph nodes dissected is a key factor because it can help improve both DFS and OS.[17,18] However, the extent of lymph node dissection needed remains controversial.[19] The current staging system for NSCLC is based on the 7th edition of the International Association for the Study of Lung Cancer classification.[20] This focuses on the locations of the involved lymph nodes but not on their number. The role of lymphadenectomy or sampling for early-stage NSCLC is still under debate. In a previous meta-analysis, sublobar resection produced a lower likelihood of having more than three lymph nodes and a significantly lower rate of nodal upstaging.[6] That analysis focused on Stage 1A disease and came to no conclusions on the role of lymph node examination for prognosis. In the present study, there were fewer dissected lymph nodes in the sublobar resection group than in the anatomic resection group. One possible reason was the intraoperative examination of frozen sections of lymph nodes. Attempts at sublobar resection would have been converted to anatomic resection if this proved the presence of lymph node metastasis. The prognosis for the sublobar resection group of patients was no worse than that for the anatomic resection group even though they had fewer dissected lymph nodes. We consider that intraoperative lymph node evaluation is important for the sublobar resection procedure, and the absence of lymph node metastases can reassure the surgeon to proceed in performing anatomic resection. Lymph node sampling did not compromise the prognosis in this situation.

The limitations of this study were in its small sample size and that it was a single-institution retrospective study. More data are needed with a larger number of patients and a longer follow-up. In addition, we did not address the imaging characteristics of the tumor (e.g., "ground-glass" opacity), the classification of adenocarcinomas (preinvasive, minimally invasive, or invasive) in the two groups. Further studies combined with histopathological characteristics of the tumors might provide more convincing results.

CONCLUSIONS

The oncologic outcomes of sublobar resection were fair to those of anatomic resection in these patients with clinical T1a NSCLC. Lymph node sampling might not compromise surgical outcomes in such patients. Further large-scale studies are necessary to clarify the difference in clinical outcome between segmentectomy or wedge resection.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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