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Clinical Research

Long-Term Outcomes in Stage I Lung Cancer After Segmentectomy with a Close Resection Margin

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Background: In general, a 2-cm surgical margin is recommended for limited resection to obtain equivalent oncologic outcomes to lobectomy for lung cancer. This study aimed to examine the patterns of recurrence and prognostic factors for recurrence in patients with a close parenchymal resection margin.

Methods: From January 2009 to April 2017, 156 patients with stage I lung cancer who underwent segmentectomy with a close resection margin (<2 cm) were enrolled. Recurrence-free survival and overall survival were assessed. In addition, predisposing factors for recurrence were evaluated.

Results: The mean tumor size was 1.7±0.8 cm and the parenchymal resection margin was 1.1±0.6 cm. Recurrence developed in 17 (10.7%) of the 156 patients, and the 5-year recurrence-free survival rate was 88.9%. Distant metastasis (7.7%) was the predominant recurrence pattern. The isolated local recurrence rate was 1.9%. Multivariate Cox regression analysis revealed that age, tumor size, mediastinal lymph node dissection, postoperative complications, and histologic type were significant predisposing factors for recurrence. However, parenchymal margin distance did not significantly affect the long-term prognosis.

Conclusion: Segmentectomy with a close resection margin for early-stage lung cancer in selected patients resulted in acceptable recurrence and survival. However, patients with tumors larger than 2 cm, squamous cell carcinoma histology, and insufficient mediastinal evaluation should be carefully followed up for recurrence.

Keywords: Lung neoplasms, Segmentectomy, Resection margin, Recurrence

Introduction

Although lobectomy is a standard surgical approach for lung cancer, segmentectomy with a sufficient surgical resection margin is acceptable for patients who have small tumors or have limited pulmonary function [1,2]. For small (<2 cm) early-stage lung cancer, segmentectomy has shown comparable oncologic outcomes and safety to those of lobectomy [3,4]. In general, a resection margin of at least 2 cm for segmentectomy is recommended to obtain oncologic outcomes equivalent to those of lobectomy for early-stage lung cancer [2,5]. Previous studies reported that the overall recurrence rate was 15%–30% and the local recurrence rate after segmentectomy for lung cancer was 4%–5% [2,6-9]. Meanwhile, factors such as the resection margin and tumor size could impact oncologic outcomes [8,10]. In particular, concerns have been raised regarding the possibility that a close resection margin (≤2 cm) after limited resection may be associated with a poor prognosis and local recurrence [11,12]. However, some studies revealed that the margin distance did not significantly impact the recurrence and survival of patients with small tumors [13]. Segmentectomy is inherently more likely than wedge resection to enable a proper hilar lymph node evaluation and sufficient resection margin. However, accurate intraoperative measurements of the parenchymal resection margin are not usually made during segmentectomy. Furthermore, a discrepancy between the gross-surface margin

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distance and microscopic margin is generated around the parenchymal cutting edge [14]. Completion lobectomy or additive treatment is not recommended with resection margins <2 cm after segmentectomy in all cases. However, the long-term outcomes of patients with an insufficient parenchymal resection margin distance have not yet been clearly evaluated.

Hence, we examined the patterns of recurrence and prognostic factors for recurrence in patients with a close parenchymal resection margin (<2 cm) after curative segmentectomy for stage I non-small cell lung cancer (NSCLC).

Methods

Ethical statement

The study was approved by the Institutional Review Board of Seoul National University Hospital. The requirement for individual consent was waived (approval no., 1907-106-1048).

Patients

We reviewed 486 patients who underwent segmentectomy between January 2010 and April 2017 at our institution. Patients who (1) underwent surgery for metastatic cancer, (2) underwent non-curative surgery, (3) had a history of segmentectomy, or (4) had pathologic stage II–VI cancer were excluded. Finally, we enrolled 156 patients who underwent curative segmentectomy for stage I NSCLC, who had a parenchymal resection margin distance less than 2 cm (Fig. 1).

Demographic, clinical, and pathologic results were reviewed. The patients were followed up every 3–6 months. Tumors were staged according to the seventh edition of International Association for the Study of Lung Cancer TNM (tumor-node-metastasis) classification. The median follow-up period was 70 months. We identified the incidence and patterns of recurrence and long-term survival outcomes, including overall survival (OS) and recurrence-free survival (RFS). In addition, clinicopathologic factors related to recurrence and survival were analyzed.

Operation

A thoracoscopic approach was primarily performed. The intersegmental plane was identified with the deflation-inflation technique and divided with a surgical stapler. There were 2 main reasons for segmentectomy: intentional surgery, which included small tumors, tumors with a peripheral location, or multiple lung lesions; and compromised surgery, which included patients with poor pulmonary function, the presence of comorbidities, or a previous history of lung resection surgery. The parenchymal resection margin was confirmed based on pathologic results in the setting of a deflated lung. The parenchymal resection margin was defined as the distance from the tumor edge to the nearest stapled resection margin. The measurement was conducted in the resected and deflated lung after removal of the stapling line. The distances were measured both macroscopically and microscopically. If the resection margins were not included in the specimen slide due to a wide resection margin, only the macroscopic margin distance was recorded. During the follow-up period, recurrence was confirmed by imaging results, such as computed tomography (CT) or positron emission tomography-CT, and pathologic results after biopsy. Local recurrence was defined as tumor recurrence at the surgical resection margin, including the stapling line, bronchial or vascular stumps, and the residual tissue of the same lobe after segmentectomy. Regional recurrence was defined as mediastinal lymph node recurrence. Other patterns of recurrence (N3 lymph nodes, ipsilateral and contralateral pulmonary metastasis in other lobes, pleural/pericardial seeding, or extrathoracic metastasis) were defined as distant metastasis.

Statistical analysis

All data were analyzed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables are expressed as mean values, standard deviations, and inter-

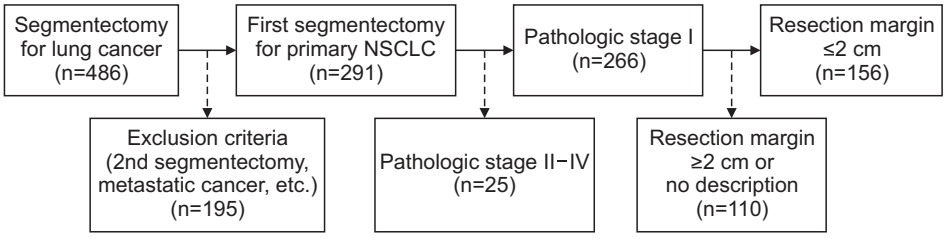

Fig. 1. Flowchart showing the process of patient selection. NSCLC, non-small cell lung cancer.

quartile ranges (IQR) and categorical variables are expressed as absolute numbers and relative frequencies. RFS and OS were analyzed using the Kaplan-Meier method. The Kaplan-Meier curves were compared with the log-rank test. A Cox proportional hazard regression analysis was used to evaluate risk factors associated with OS and RFS. Multiple clinicopathologic variables were evaluated for their association with the time to recurrence using univariate Cox regression analysis. All variables included in the Cox regression analysis were determined a priori due to their clinical significance. The following variables were included: age, sex, smoking history (never smoker versus ever smoker), performance status (Eastern Cooperative Oncology Group [ECOG] performance score 0 or ≥1), reason for segmentectomy (intentional or compromised segmentectomy), nodule type on CT (solid and others), mediastinal lymph node dissection, postoperative complications, pathologic tumor size, parenchymal resection margin, resection margin-to-tumor size ratio, histologic type (squamous cell carcinoma or adenocarcinoma). For the multivariate analysis, factors with a p-value <0.2 in the univariate analysis were included. The variance inflation factor was tested to detect multicollinearity.

Results

Demographics and clinical characteristics

The demographic results are presented in Table 1. Most patients had no performance limitation with an ECOG performance score of 0 (n=122) and exhibited normal pulmonary function (forced expiratory volume in 1 second: 100.2%±23.4% [IQR, 87.0%–115.0%]) and diffusing capacity for carbon monoxide (95.2%±17.5% [IQR, 83.0%–107.7%]). In total, 112 patients had comorbidities at the time of surgery. Common comorbidities were hypertension (40.4%), diabetes mellitus (17.9%), and chronic obstructive pulmonary disease (9.0%). The location of the tumor was evenly distributed. Pure ground-glass (GGN), part-solid (PSN), and solid nodules accounted for 36 (23.1%), 73 (46.8%), and 47 (30.1%) cases, respectively.

Video-assisted thoracoscopic surgery was predominantly performed (n=149, 95.5%). Intentional segmentectomy (n=107, 68.6%) was performed more frequently than compromised segmentectomy (n=49, 31.4%) (Table 2). Most patients underwent systematic mediastinal lymph node dissection (n=144, 92.3%). The mean number of dissected lymph nodes was 20.8±10.2. There were no cases of postoperative mortality, and the postoperative morbidity rate was 10.9% (n=17). Postoperative complications included pneumonia (n=4), atrial fibrillation (n=5), and prolonged

Table 1. Preoperative demographics

Characteristic	Value
Age (yr)	63.6±9.2
Sex (male)	76 (48.7)
History of smoking	64 (41.0)
ECOG PS ≥1	34 (21.8)
Comorbidities	
Hypertension	63 (40.4)
Diabetes mellitus	28 (17.9)
Chronic obstructive pulmonary disease	19 (12.2)
History of tuberculosis	15 (9.6)
Cardiovascular disease	10 (6.4)
History of cerebrovascular disease	8 (5.1)
Chronic kidney disease	7 (4.5)
Liver disease	8 (5.1)
History of previous cancer	48 (30.8)

Values are presented as mean±standard deviation or number (%).
ECOG PS, Eastern Cooperative Oncology Group performance score.

Table 2. Perioperative clinical characteristics

Variable	Value
Size, radiologic (cm)	1.7±0.8
Type of nodule	
Part-solid nodule	109 (66.9)
Solid nodule	47 (30.1)
C/T ratio	0.3±0.3
Surgical approaches	
Video-assisted thoracoscopic surgery	149 (95.5)
Open surgery	7 (4.5)
Reasons for segmentectomy	
Intentional	107 (68.6)
Compromised	46 (31.4)
No. of resected segments	
1	73 (46.8)
2	27 (17.3)
3	46 (29.5)
4	10 (6.4)
Location of tumor	
Right upper lobe	20 (12.8)
Right lower lobe	45 (28.8)
Left upper lobe	56 (35.9)
Left lower lobe	35 (22.4)
Postoperative complication	17 (10.8)
Pneumonia	4 (2.6)
Prolonged air leakage	3 (1.9)
Atrial fibrillation	5 (3.2)
Others	5 (3.2)
Postoperative mortality	0

Values are presented as mean±standard deviation or number (%).
C/T ratio, consolidation-to-tumor ratio of part-solid nodules.

air leakage (n=3).

The pathologic tumor size was 1.6±0.8 cm (IQR, 1.0–2.0 cm) with a mean parenchymal resection margin distance of 1.1±0.6 cm (IQR, 0.7–1.5 cm). The resection margin/tumor size ratio (MTR) was 0.8±0.6 (IQR, 0.4–1.2). In total, 110 patients (70.5%) had a close resection margin that was smaller than the tumor size. The pathologic stage was pIA in 133 patients (85.3%) and pIB in 23 patients (14.7%). Adenocarcinoma (n=145, 92.9%) was the predominant histologic subtype. In adenocarcinoma, most pathologic reports described the morphologic appearance; in those results, lepidic (33.8%) and acinar (31.7%) patterns were frequently observed (Table 3).

Survival and recurrence

Among the 156 patients, 17 patients (10.9%) developed recurrence. Of the 17 patients who developed recurrence, distant metastasis (n=12) was more common than locoregional recurrence (n=5) (Table 4). Fourteen of the 17 patients underwent chemotherapy and/or radiotherapy. No completion lobectomy was performed for local recurrence. The 5-year OS and RFS rates were 95.3% and 88.9%, respectively (Fig. 2). There was no significant difference in OS and RFS based on the parenchymal resection margin between the <1 cm and 1–2 cm groups (p=0.39 and p=0.11 for OS and RFS, respectively). In an analysis depending on the MTR, OS showed no statistical difference (p=0.27) and the RFS was significantly different between the MTR ≤1 and MTR >1 groups (p=0.024). Multivariate Cox regression analysis revealed that old age, the absence of systematic mediastinal lymph node dissection, the presence of postoperative complications, tumor size >2 cm, and the squamous cell carcinoma histologic type were unfavorable factors for RFS (Table 5). Compromised segmentectomy and postoperative complications were poor prognostic factors for OS (Table 6). The parenchymal resection margin did not significantly influence RFS or OS.

Table 3. Pathologic results

Variable	Value
Stage (seventh-edition TNM)	
IA	133 (85.3)
IB	23 (14.7)
Size, pathologic (cm)	1.6±0.8
Parenchymal margin (cm)	1.1±0.6
Bronchial margin (cm)	2.5±1.4
Visceral pleural invasion	16 (10.3)
Vascular invasion	2 (1.3)
Lymphatic invasion	18 (11.5)
Histologic type	
Adenocarcinoma	145 (92.9)
Lepidic	49 (33.8)
Acinar	46 (31.7)
Papillary	19 (13.1)
Micropapillary	1 (0.7)
Solid	3 (2.1)
Mucinous	6 (4.1)
Squamous cell carcinoma	11 (7.1)

Values are presented as mean±standard deviation or number (%).
TNM, tumor-node-metastasis.

Discussion

The present study demonstrated patterns of recurrence and risk factors for recurrence after segmentectomy with close parenchymal resection. The recurrence rate was acceptable, with only rare cases of local recurrence along the stapling line or resected lobes. The parenchymal resection margin did not significantly affect RFS or OS.

As the early detection of lung cancer increases due to lung cancer screening campaigns, the size of diagnosed tumors tends to be smaller [15]. It has been established that segmentectomy has a favorable prognosis for lung cancer under specific conditions based on the total size and the consolidation-to-tumor ratio [16]. Moreover, the number of patients with lung cancer with limited pulmonary function is increasing because many patients are older and have complicated underlying medical conditions. In these patients, segmentectomy, which has the benefits of limited resection, is more acceptable than lobectomy [1]. Addition-

Table 4. Patterns of recurrence (N=17)

Variable	No. (%)
Isolated local recurrence	
Bronchial stump	1 (0.6)
Lung, staple line	1 (0.6)
Lung, residual lobe	1 (0.6)
Isolated regional recurrence	
Mediastinal LNs	1 (0.6)
Distant recurrence	
Lung, ipsilateral	2 (1.3)
Lung, contralateral	4 (2.6)
Bone	2 (1.3)
Pleural seeding	2 (1.3)
Brain	0
Combined recurrence	
Lung, residual lobe+mediastinal LNs	1 (0.6)
Lung, staple line+contralateral lung	1 (0.6)
Lung, ipsilateral+mediastinal LNs	1 (0.6)

LN, lymph node.

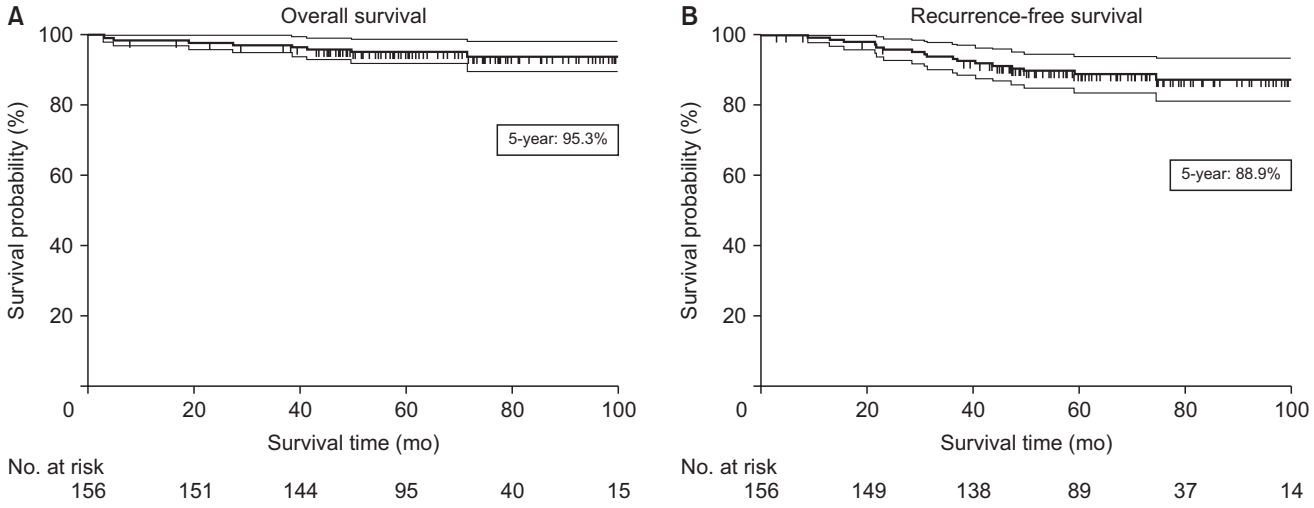

Fig. 2. Kaplan-Meier curve for overall survival (A) and recurrence-free survival (B). Thin lines: 95% confidence limits.

Table 5. Cox regression analysis for recurrence-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65 yr	4.15 (1.35–12.74)	0.013	5.95 (1.48–23.86)	0.012
Male	9.33 (2.13–40.84)	0.003		
Smoking history	4.18 (1.47–11.89)	0.007		
ECOG PS ≥1	2.37 (0.90–6.25)	0.080	3.24 (0.99–10.56)	0.050
Compromised surgery	6.10 (2.14–17.33)	0.001	1.59 (0.39–6.39)	0.217
Solid nodule on computed tomography	7.29 (2.55–20.86)	<0.001		
Mediastinal lymph node dissection	0.58 (0.13–2.55)	0.473	0.13 (0.02–0.85)	0.034
Complication	5.87 (2.16–15.90)	0.000	10.27 (2.98–35.37)	0.000
Size >2 cm	9.02 (3.17–25.65)	<0.001	9.16 (2.89–29.04)	<0.001
Parenchymal resection margin >1 cm	2.25 (0.79–6.40)	0.127	2.82 (0.91–8.70)	0.071
Margin/tumor ratio >1	0.13 (0.01–1.03)	0.054	0.60 (0.06–5.9)	0.663
Histologic type		<0.001		0.001
Squamous cell carcinoma	9.02 (3.17–25.65)		7.45 (2.21–25.10)	
Adenocarcinoma	1 (Reference)		1 (Reference)	

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score.

ally, a meta-analysis revealed that segmentectomy (anatomical lung resection), had better oncologic outcomes than wedge resection, another sublobar lung resection technique [17]. When segmentectomy can provide favorable oncologic outcomes comparable to lobectomy, it could be a better surgical option for many patients with early-stage cancer or poor pulmonary function [18,19]. Two randomized studies demonstrated that segmentectomy may achieve similar oncologic outcomes to those of lobectomy [20,21]. Our study also showed a lower than reported in previous studies [2,6,9]. Intentional segmentectomy for pure GGNs or PSNs accounted for more than 60% of the patients. Furthermore, adenocarcinoma accounted for 92% of cases, the majority of which showed low-grade histology, with acinar or lepidic patterns, which are associated with a lower recurrence rate and favorable prognosis [22]. These selection criteria may have contributed to the low recurrence rate. The follow-up duration might have been insufficient to detect late recurrence after the resection of small PSNs. Late recurrence, even 5 years after resection, was occasionally found after complete resection of GGNs [23]. In addition, the adenocarcinoma recurrence hazard ratio did not dramatically decrease after 40 months postoperatively [24]. However, most cases of recurrence develop around 2 years after curative resection for stage I lung cancer [25]. Therefore, a follow-up duration of 70 months is sufficient

Table 6. Cox regression analysis for overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65 yr	1.21 (0.30–4.85)	0.784		
Male	3.54 (0.71–17.57)	0.122		
Smoking history	5.01 (1.00–24.93)	0.049		
ECOG PS ≥1	1.09 (0.21–5.44)	0.914		
Compromised surgery	3.97 (0.95–16.66)	0.059	4.81 (1.11–20.86)	0.036
Solid nodule on computed tomography	1.43 (0.34–6.01)	0.620		
Mediastinal lymph node dissection	0.23 (0.04–1.18)	0.079		
Complication	9.43 (2.35–37.86)	0.002	11.04 (2.63–46.27)	0.001
Size >2 cm	2.05 (0.49–8.61)	0.323		
Parenchymal resection margin >1 cm	0.54 (0.12–2.26)	0.402		
Margin/tumor ratio >1	0.32 (0.04–2.66)	0.297		
Histologic type				
Squamous cell carcinoma	2.16 (0.26–17.69)	0.471		
Adenocarcinoma	1 (Reference)		1 (Reference)	

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score.

to prove long-term oncologic outcomes in lung cancer.

For local control of recurrence, completion lobectomy could be an appropriate surgical option in selected cases. Owing to severe adhesions around the hilar structure, completion lobectomy after segmentectomy is considered technically demanding. Takahashi et al. [26] reported that completion lobectomy for local recurrence could be performed without fatal complications, but open thoracotomy was required in half of the cases. Most of all, additional resection is not possible in most cases of compromised segmentectomy. Other interventions should be considered in such cases.

The parenchymal distance between the tumor and stapling line was not a risk factor for recurrence after segmentectomy in the present study, although several studies have reported that the parenchymal margin distance was associated with poor survival [11,27,28]. However, the parenchymal margin distance does not influence recurrence or survival outcomes when complete resection is conducted [13]. The impact of the parenchymal resection margin in segmentectomy varies because of the lack of uniform methods for measuring the distance from the tumor edge to the resection margin. Furthermore, several factors such as the removal of staplers, whether the lung is deflated or inflated, discrepancies in macroscopic and microscopic measurements, and discrepancies in radiologic and pathologic measurements of the distance impact the accuracy of resection margin measurements [14]. Importantly, tumor biology and surgical techniques are both highly relevant factors for recurrence. According to this study, squamous cell carcinoma had a poorer prognosis than adenocarcinoma, as expected. Clinical features, such as age and postoperative complications, were also associated with recurrence. Therefore, patients with a tumor larger than 2 cm, squamous cell carcinoma histology, insufficient mediastinal evaluation, and the presence of postoperative complications had a high probability of recurrence and should be carefully monitored for recurrence during the follow-up period. Segmentectomy with a close resection margin had a tendency for favorable oncologic results in this study. However, for lung cancer with poor prognostic factors, such as large tumor size and squamous cell carcinoma histology, tolerable oncologic outcomes can be expected only when the resection margin is sufficient.

As a retrospective study conducted at a single institution, this study was subject to selection bias for candidates for limited lung resection. In fact, patients were carefully selected for limited lung resection and most patients had favorable factors (i.e., PSN or GGN and small tumors treated with intentional segmentectomy). Therefore, the oncologic outcomes might have been overestimated, and the number of cases of recurrence was relatively small compared to previous reports in the literature. As with other patients of lung cancer, a sufficient parenchymal resection margin is still important for oncologic soundness. In addition, we did not have information on spread through air spaces, which is a well-known risk factor for recurrence after limited resection. However, this study was conducted with a sufficient follow-up period and can provide comprehensive insights for surgeons when encountering a close resection margin after segmentectomy, particularly considering the increasing frequency of the procedure. The upcoming re-

sults from the Japan Clinical Oncology Group (JCOG) 0802 will provide solid evidence for selecting patients for segmentectomy.

In conclusion, segmentectomy with close resection for early stage lung cancer resulted in acceptable recurrence and survival rates in selected patients. However, patients with tumors larger than 2 cm, squamous cell carcinoma histology, and an insufficient mediastinal evaluation should be carefully followed up for recurrence.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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