Radical sublobar resection for small-sized non–small cell lung cancer: A multicenter study

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Objective: At present, even when early-stage, small-sized non–small cell lung cancers are being increasingly detected, lesser resection has not become the treatment of choice. We sought to compare sublobar resection (segmentectomy or wedge resection) with lobar resection to test which one is the appropriate procedure for such lesions.

Methods: From 1992 to 2001, a nonrandomized study was performed in 3 institutes for patients with a peripheral cT1N0M0 non–small cell lung cancer of 2 cm or less who were able to tolerate a lobectomy. The results of the sublobar resection group enrolled preoperatively (n = 305) were compared with those of the lobar resection group (n = 262).

Results: Except for distribution of tumor location, there were no significant differences in any variable, patient characteristics, curability, pathologic stage, morbidity, or recurrence rate. Median follow-up was more than 5 years. Disease-free and overall survivals were similar in both groups with 5-year survivals of 85.9% and 89.6% for the sublobar resection group and 83.4% and 89.1% for the lobar resection group, respectively. Multivariate analysis confirmed that the recurrence rate and prognosis associated with sublobar resection were not inferior to those obtained with lobar resection. Postoperative lung function was significantly better in patients who underwent sublobar resection.

Conclusions: Sublobar resection should be considered as an alternative for stage IA non–small cell lung cancers 2 cm or less, even in low-risk patients. These results could lay the foundation for starting randomized controlled trials anew, which would bring great changes of lung cancer surgery in this era of early detection of lung cancer.

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In the one and only randomized study to compare lobectomy and sublobar resection for stage IA non–small cell lung cancer (NSCLC) published in 1995, the Lung Cancer Study Group (LCSG) demonstrated a 3-fold increase in the local recurrence rate among patients who underwent sublobar resection,[1] and powerfully supported the indisputable dogma that lobectomy is the standard of care for stage I NSCLC. However, the most broadly referenced report included potentially misleading statements and analyses insufficient to advocate the superiority of lobectomy over sublobar resection as some investigators then and later demonstrated.[2-4]

With the dramatic upsurge in early detection of ever smaller NSCLCs through the development of radiographic tools such as high-resolution computed tomography (CT) and the widespread practice of low-dose helical CT for screening,[5] which is rapidly changing clinical practice, many surgeons have inevitably become concerned over the unified treatment of these small peripheral lesions with whole lobectomy. Generally, patients with a larger tumor have a poorer prognosis and a

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Abbreviations and Acronyms

CT	= computed tomography
FEV_1	= forced expiratory volume in 1 second
FVC	= forced vital capacity
LCSG	= Lung Cancer Study Group
NSCLC	= non–small cell lung cancer

higher frequency of hematogenous and lymphatic metastases, whereas smaller tumors such as bronchioloalveolar carcinoma usually have a more indolent biologic behavior. Is it uniformly required to extirpate the entire lobe for such tiny peripheral lesions when sufficient margins of resection can be achieved with sublobar resection? Removing a relatively large volume of healthy lung tissue may result in a higher frequency of operative morbidity and poorer quality of postoperative life, reducing the chance for further resections because these patients survive long enough to be at risk for a second or even a third NSCLC. The incidence of second primary lung cancers may be approximately 3% per year[6,7]; thus patients who survive 5 or more years after their first resection would face a significant cumulative danger of second cancers. The larger the amount of the initial resection, the more restricted the surgical options for next resections.

Recently, several reports demonstrated that sublobar resection was not inferior to lobectomy regarding the prognosis of patients with small-sized NSCLC,[8-13] but the number of cases evaluated in those studies was relatively small. The present study, in which we compared the outcome of sublobar resection with that of lobectomy in low-risk noncompromised patients with a T1N0 NSCLC 2 cm or less in size, is the largest series published so far on radical sublobar resection and followed for long-term outcome. The rigid consensus on lobectomy for stage I cancers has never permitted us to carry out a randomized study. In such a situation in which it has been difficult even to plan a randomized trial because of ethical reasons, a well-designed observational trial may function as an effective reference for a future randomized trial. This was a nonrandomized study in which the decision on whether to be assigned to the sublobar resection group or the lobar resection group was taken by the patients themselves. Because the 2 groups were well matched for known prognostic variables, a comparison between the 2 groups was considered scientifically valid.

Methods

Patients

In 3 institutes during a 10-year period, from January 1992 to December 2001, patients were enrolled for entry into this study when they had a clinical T1N0M0 peripheral tumor of 2 cm or less in every dimension located in the outer one third of the lung on CT confirmed to be an NSCLC. Patients included in the study were able to tolerate a lobectomy as evaluated by cardiopulmonary functional tests, had no history of previously treated cancer, and provided his/her informed written consent based on the approved protocol of each institute's review board before registration and surgery. Patients with a tumor located in the right middle lobe were excluded. Radionuclide bone scan and CT examination of the brain, chest, and upper abdomen were routinely required to detect possible metastases. At the time of registration, every patient was assigned to undergo lobectomy or sublobar resection in compliance with his/her decision. In other words, patients were allocated to the sublobar resection group if the patient consented to the sublobar resection, and to the lobectomy group if the patient did not consent to sublobar resection. Patients were invariably scheduled to undergo lobectomy or sublobar resection before the thoracotomy. During the operation, the tumor status was confirmed by the surgeon to be T1N0 on the basis of frozen-section analysis of sampled segmental, lobar, hilar, and mediastinal lymph nodes from the drainage area of the tumor and pleural lavage cytology. In patients assigned to the sublobar resection group, the surgeon cautiously evaluated the appropriateness of a sublobar resection for curative treatment and whether the deliberate procedure would be a segmentectomy or an adequate large wedge resection. Basically, the wedge resection could be used as a sublobar resection for a tumor of 1.5 cm or smaller in diameter and a tumor observed as pure ground-glass opacity by CT, when considered appropriate. Resected specimens were examined histopathologically, and histologic typing was done according to the World Health Organization classification.[14] Surgical–pathologic staging was performed according to the New International Staging System for Lung Cancer.[15]

Surgical Procedure of Segmentectomy

At the hilum, isolation, division, and suture of the suitable segmental bronchus, artery, and vein were required. Intraoperatively, lymph nodes around the hilum and those obtained by mediastinal dissection or sampling were pathologically examined. Surgeons were allowed some latitude regarding the technique to detect and divide the intersegmental plane, including the use of electrocautery, neodymium-yttrium-aluminum garnet laser, or segmental stapling. Because a margin of at least 2 cm of healthy lung tissue was required, the resection line could be placed on the segment adjacent to the affected one or portions of a few adjacent segments or subsegments could be extirpated. After the resection, the surgeon was obliged to corroborate that the tumor and required lymph nodes had been completely removed and proven to be negative for involvement by frozen-section examination. It was specified that when the surgical margin was found to be imperfect or any lymph node was found to be diseased, lobectomy had to be performed instead.

Postoperatively, all complications including minor ones were recorded. Every patient was evaluated at 3-month intervals for the first 2 years, at 6-month intervals for the subsequent 3 years, and yearly thereafter. Follow-up assessment included physical examination, hematologic and biochemical analysis including tumor markers, and chest roentgenograms. Local recurrence was defined as recurrence at the primary site or in lymphatic drainage areas, either hilar or mediastinal within the operated thoracic cavity.

TABLE 1. Base-line characteristics of the patients

Characteristic	Sublobar resection group (n = 305)	Lobar resection group (n = 262)	*P* value
Gender			0.8655
Male	167 (54.8%)	146 (55.7%)	
Female	138 (45.2%)	116 (44.3%)	
Age (years)	35-82	38-84	0.3312
	mean: 63.2	mean: 64.0	
Histology			0.4772
AD	276 (90.5%)	229 (87.4%)	
SQ	27 (8.9%)	30 (11.5%)	
AS	2 (0.7%)	3 (1.1%)	
Size			0.0564
Range	5-20 mm	8-20 mm	
Mean	15.7 mm	16.2 mm	
0-10 mm	36	21	
11-20 mm	269	241	
Location			0.0191
Right upper lobe	101 (33.1%)	112 (42.7%)	
Right lower lobe	54 (17.7%)	54 (20.6%)	
Left upper lobe	106 (34.8%)	63 (24.0%)	
Left lower lobe	44 (14.4%)	33 (12.6%)	

AD, Adenocarcinoma; *SQ*, Squamous cell carcinoma; *AS*, Adenosquamous carcinoma. Fisher's exact test was used to compare categoric variables, and student's *t* test was used for continuous data.

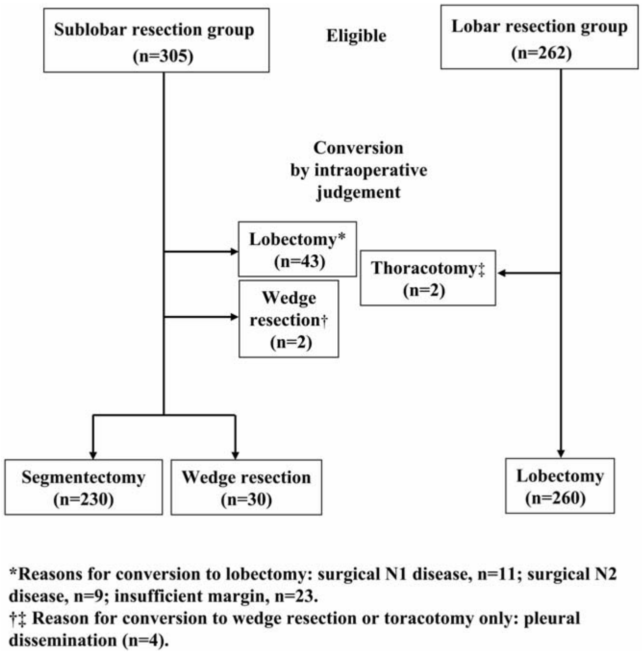

Figure 1. Treatment flow chart.

Distant metastasis was defined as intrapulmonary metastasis or metastasis to other organs. Pulmonary function tests comprising forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), were administered preoperatively and at 2 months after surgery.

Statistical Methods

Fisher's exact test was used for intergroup comparison of categoric variables, and the Student *t* test was used for continuous data. Survivals were estimated by the Kaplan-Meier method,[16] and differences in survival were determined by log-rank analysis. Multivariate analysis with preoperative prognostic stratification variables was done using Cox proportional hazards regression model.[17] Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, non-cancer, or unknown causes for overall survival analysis. Operative mortality defined as a 30-day postoperative death was included in the survival analyses. Disease-free survival was the interval from the date of resection to proven detection of recurrence or metastases. Recurrent disease was defined as the discovery of any new lesion considered to be recurrence of the original lung cancer. All patients were followed until death or study termination, unless lost to follow-up. Analyses of potential survival differences within subgroups and of potential prognostic factors were reported with 2-sided *P* values.

Results

Of the 567 patients preoperatively enrolled, 305 (53.8%) were assigned to the sublobar resection group and 262 (46.2%) were assigned to the lobar resection group. There were no significant differences in gender, age, or histologic type between the 2 groups (Table 1). The mean size of the tumor was a little smaller in the sublobar resection group, although the observed difference was of borderline statistical significance ($P = .0564$). However, location of the tumor was not well balanced ($P = .0191$). Patients with a tumor in the right upper lobe tended to be allocated to the lobar resection group, whereas those with a tumor in the left upper lobe tended to be assigned to the sublobar resection group.

During the operation, the planned procedures were changed for various reasons (Figure 1). Forty-three of the 305 patients in the sublobar resection group underwent lobectomy. Among them, sufficient surgical margins were not obtained in 23 patients, N1 disease was diagnosed in 11 patients, and nodes were judged to be N2 positive intraoperatively in 9 patients. In addition, noncurative wedge resection was carried out in 2 patients because pleural dissemination was found at the time of thoracotomy. Thus, 260 patients in the sublobar resection group underwent operation as planned, 230 patients underwent segmentectomy, and 30 patients underwent curative wedge resection. In contrast, thoracotomy without removal of the tumor was performed in 2 of the 262 patients enrolled in the lobar resection group because of pleural dissemination.

The median follow-up of living patients in the sublobar and lobar resection groups was 72 months (range, 29-155

TABLE 2. Postoperative findings of the patients

Cheracteristic	Sublobar resection group (n = 305)	Lobar resection group (n = 262)	*P* value
Curability			0.2577
Complete resection	303 (99.3%)	257 (98.1%)	
Incomplete resection	2 (0.7%)	5 (1.9%)	
Pathological stage			0.7819
IA	266 (87.2%)	217 (82.8%)	
IB	7 (2.3%)	10 (3.8%)	
IIA	10 (3.3%)	12 (4.6%)	
IIB	2 (0.7%)	2 (0.8%)	
IIIA	14 (4.6%)	15 (5.7%)	
IIIB	6 (2.0%)	6 (2.3%)	
Postoperative complications	20 (6.6%)	19 (7.3%)	0.7429
Recurrence	43 (14.1%)	45 (17.2%)	0.3524
Distant metastasis	28 (9.2%)	27 (10.3%)	
Local recurrence	15 (4.9%)	18 (6.9%)	

Fisher's exact test was used to compare categoric variables.

months) and 71 months (range, 22-158 months), respectively. There were no significant differences between the 2 groups in curability, pathologic stage, incidence of postoperative complication, and recurrence (Table 2). It is noteworthy that the rate of local recurrence did not differ significantly between the 2 groups. Particularly, the recurrence in the remaining part of the affected lobe that we had intentionally preserved with sublobar resection was our prime concern. Among the 260 patients who underwent curative sublobar resection, recurrence was detected in the residual part in 3 patients (1.2%). One patient who underwent segmentectomy of the left upper division for squamous cell cancer showed recurrence in the surgical margin 5 months after surgery and is alive at 87 months after left completion pneumonectomy. Another patient presented a pulmonary metastasis just in the remaining portion at 49 months after right S2 segmentectomy for adenocarcinoma and is alive at 16 months after completion lobectomy. The third patient with right S3 segmentectomy for papillary adenocarcinoma had occurrence of bronchioloalveolar carcinoma at 40 months postoperatively and is surviving at 38 months after completion lobectomy. All 3 patients are free of disease at the time of this report. There was only 1 operative death in the sublobar resection group. The patient died of acute myocardial infarction 29 days after surgery, although he had been discharged from the hospital after a quick uneventful recovery.

Survival

Figure 2 shows the disease-free and overall survivals of the sublobar resection group and lobar resection group, demonstrating no significant differences between them (P = .2778 and P = .106, respectively). Moreover, multivariate analysis using potential preoperative prognostic determinants revealed that irrespective of gender, age, histologic type, tumor size, and tumor location, the disease-free interval and prognosis in the 2 groups were similar (Table 3; hazard ratio, 1.241, P = .3024 and hazard ratio, 1.363, P = .1537, respectively). Next, we examined the surgical outcome in patients who underwent curative resection for pT1N0M0 disease (Figure 3). Not surprisingly, the survival after curative wedge resection was good because the procedure had been indicated for smaller tumors with possibly indolent biologic behavior. Both the disease-free and overall survivals were comparable in patients in p-stage IA whether treated with segmentectomy or lobectomy.

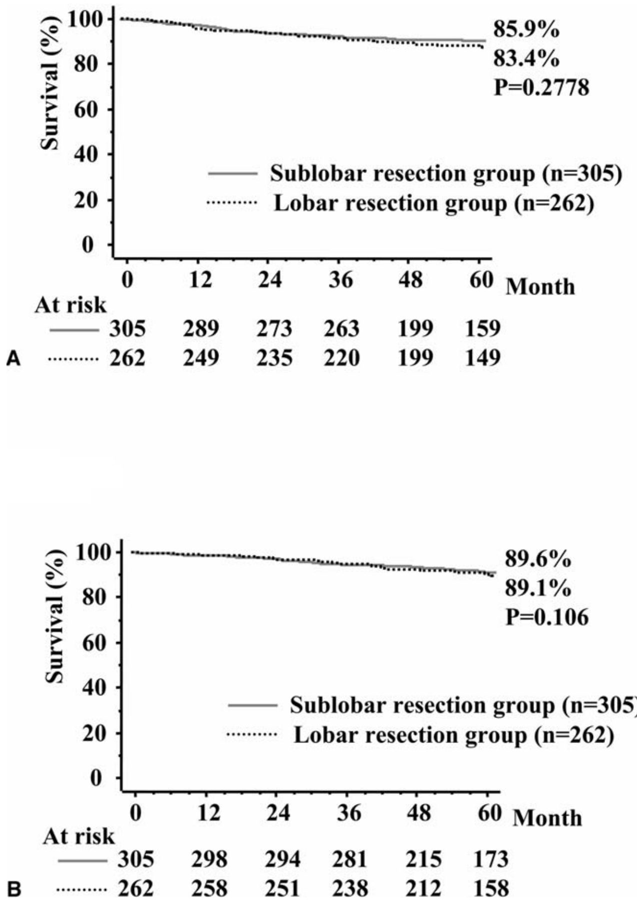

Figure 2. Disease-free survival (A) and overall survival (B). Curves correspond to patients who were initially enrolled for this study (sublobar resection group, *solid line*; lobar resection group, *short-dash line*).

Pulmonary Function

Because lung function tests were not mandatory for this study, information regarding the testing completed pre-

TABLE 3. Proportional hazard model

	Disease-free survival		Overall survival	
Variables	Relative risk	*P* value	Relative risk	*P* value
Gender				
Male (vs Female)	1.761	0.0105	1.568	0.0531
Age				
Older	1.012	0.2761	1.030	0.0168
Histology				
Non-AD (vs AD)	0.526	0.0909	1.149	0.6360
Size				
Larger	1.098	0.0058	1.022	0.4994
Side				
Left (vs Right)	1.307	0.2004	1.200	0.3976
Lobe				
Upper (vs Lower)	1.483	0.1041	1.576	0.0667
Enrolled group				
Lobar (vs Sublobar)	1.241	0.3024	1.363	0.1537

AD, Adenocarcinoma. Continuous data for age and size, and categories for gender, histology, side, lobe, and enrolled group.

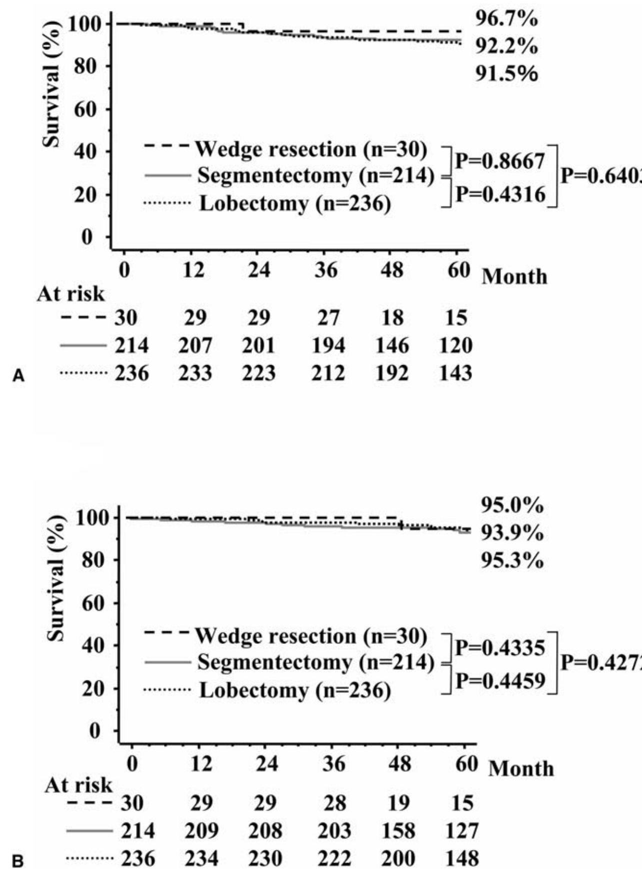

Figure 3. Disease-free survival (A) and overall survival (B). Curves correspond to patients who underwent curative resection for pT1N0M0 tumor (wedge resection, *long-dash line*; segmentectomy, *solid line*; lobectomy, *short-dash line*).

operatively and postoperatively was available on 354 patients (62.4%). We analyzed the data according to the procedure actually executed. Preoperative functional values were similar among the groups who underwent wedge resection (n = 18), segmentectomy (n = 168), and lobectomy (n = 168), confirming that patients in the sublobar resection group could have functionally tolerated a lobectomy (Table 4). In regard to both FVC and FEV_1, the extent of resection seemed to correlate with the reduction of lung function. Next, we directly compared functional changes between the 3 groups. Figure 4 clearly demonstrates that the greater the resected amount of tissue, the more reduced the postoperative pulmonary function. Statistically significant differences in the ratio of postoperative to preoperative FVC and FEV_1 were observed among the 3 groups, although a marginal difference in FVC was seen between the segmentectomy group and the wedge resection group.

Discussion

It is of utmost importance to adequately resolve a controversial issue concerning the choice of resection for peripheral small early-stage NSCLCs, because the detection rate of these lesions potentially amenable to effective treatment with lesser resection has dramatically increased in recent years. In 1995, the LCSG reported 1 randomized study concluding that lobectomy was the standard of care for stage IA NSCLCs,[1] which made a great impact on the following advance of lesser resection, although most recent studies comparing lesser resection with lobectomy for stage IA NSCLC demonstrated equivalent survival.[8-13] Patel and colleagues[4] raised several doubts about the analysis and interpretation of the results of the LCSG study. Their review of the LCSG trial outcome suggested that patients with lesser resections may be at a higher risk of developing local recurrence, lower rate of perioperative lung morbidity, similar cancer-related mortality rate, and better preservation of lung function compared with lobectomy for stage IA NSCLC. Table 5 shows a review of the literature regarding the survivals after resection of stage IA (T1N0M0) NSCLC.[1,8,9,12,18,19]

The LCSG study showed a high incidence of local recurrence after sublobar resection, which we did not find in our series, although the methods of follow-up such as serial CT have been rapidly evolved year after year to identify local recurrence. We are focusing on the high rate of wedge resection in the sublobar resection group (32.8%), although the LCSG study involved stage IA cancers including tumors up to 3 cm in diameter. The predominance of wedge resection might affect the frequency of local recurrence. In our

TABLE 4. Changes of lung function

Procedure	Preoperative values	→	Postoperative values
Wedge resection (n = 18)			
FVC (L)	3.30 ± 0.81	→	3.10 ± 0.69
FEV1.0 (L)	2.29 ± 0.59	→	2.21 ± 0.84
FEV1.0/FVC (%)	70.2 ± 12.1	→	71.9 ± 11.5
Segmentectomy (n = 168)			
FVC (L)	3.16 ± 0.84	→	2.83 ± 0.80
FEV1.0 (L)	2.32 ± 0.64	→	2.10 ± 0.62
FEV1.0/FVC (%)	73.7 ± 9.2	→	74.8 ± 10.0
Lobectomy (n = 168)			
FVC (L)	3.19 ± 0.80	→	2.68 ± 0.77
FEV1.0 (L)	2.32 ± 0.58	→	1.93 ± 0.58
FEV1.0/FVC (%)	73.2 ± 8.3	→	72.5 ± 10.2

FVC, forced volume capacity; *FEV1.0*, forced expiratory volume in 1 second.

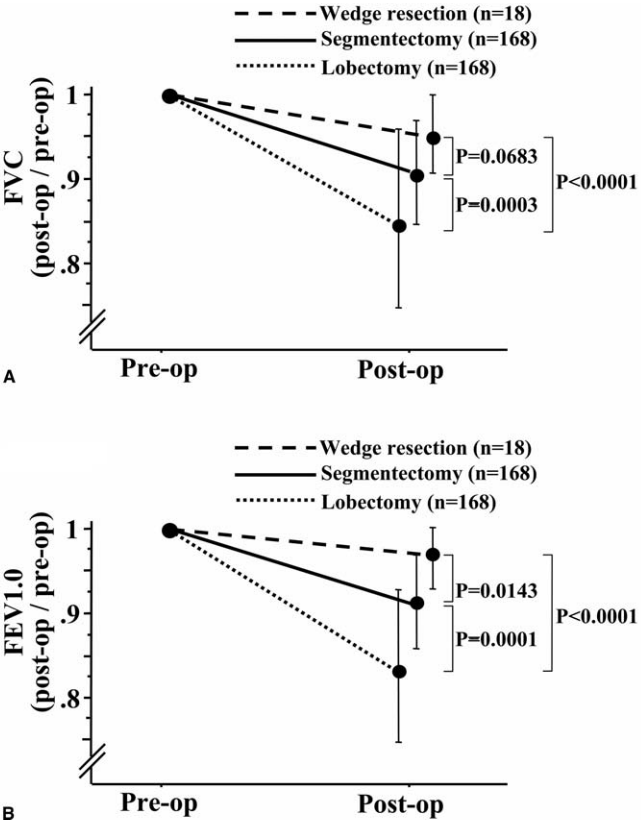

Figure 4. FVC (A) and FEV_1 (B) measured preoperatively and postoperatively (wedge resection, *long-dash line*; segmentectomy, *solid line*; lobectomy, *short-dash line*). Y-axis shows the ratio of the postoperative value to the preoperative one. Values are presented as the mean ± standard error. *FVC*, Forced vital capacity; *FEV_1*, forced expiratory volume in 1 second.

series, which included tumors up to 2 cm, the ratio of wedge resection was 9.8%. The frequency of local recurrence after sublobar resection could have been lower if the indication had been limited to tumors of 2 cm or smaller. In addition, the reasons for the differences in the occurrence of local recurrence may be associated with our preference to favor extended segmentectomy, which can improve the treated margin.[8,9,12,13] The intraoperative lavage cytology of surgical margins may be useful to check whether resection was complete.[20] On the other hand, frequent application of wedge resection can result in less-extensive intraoperative nodal surveillance, leading to a potential understaging of patients, in contrast with segmentectomy, which allows the assessment of nodal status. We are convinced that nodal assessment is obligatory for tumors larger than 2 cm.[21] We, under strict policy, especially when planning a sublobar resection, must resist the great temptation to perform an easier operation such as wedge resection. Many proficient surgeons have emphasized that segmentectomy must be essential and should not be forgotten by current-generation thoracic surgeons.[22-26]

The LCSG also reported that respiratory failure developed in 6 patients requiring postoperative ventilation for more than 24 hours in the lobectomy group, whereas no patient in the sublobar resection group required ventilatory assistance.[1] Longer ago, the LCSG found that the operative mortality was 6.2% after pneumonectomy, 2.9% after lobectomy, and 1.4% after sublobar resections in a universe of 2220 resections for lung cancer.[27] Preserving lung parenchyma can contribute to a lower occurrence of lung dysfunction, complications, and operative deaths, which suggests that perioperative morbidity and mortality rates would be improved with a lesser resection.

An important positive result overlooked in the LCSG trial is the advantage of sublobar resection concerning pulmonary function.[1] The FVC, FEV_1, and maximum voluntary ventilation were all significantly better in patients who underwent sublobar resection at 6 months after surgery. At 12 months the FEV_1 was still significantly better. Recent studies have shown superior lung function after lesser resection,[10-12] and more recently Harada and colleagues[28] demonstrated that the extent of removed lung parenchyma by the segment affected that of postoperative functional loss even at 6 months after segmentectomy or lobectomy for lung cancer. Our series revealed that sublobar resection provided better preservation of both FVC and FEV_1 compared with lobar resection at 2 months after surgery. These findings support that sublobar resection obviously offers a functional merit and constitute a more compelling reason to consider sublobar resection as identification of small cancers increases.

Possibly, not only a diseased margin but also intrapulmonary metastases or involved intralobar nodes might develop in the intentionally preserved lobe after sublobar resection. Under careful follow-up, in our series we identi-

TABLE 5. Summary of literature in prognosis following sublobar and lobar resection for stage IA(T1N0M0)NSCLC

	Sublobar resection		Lobar resection	
Author	Number	5-year survival (%)	Number	5-year survival (%)
Read et al., 1990[18]	113	84	131	74
LCSG 1995[1]	122	44*	125	65*
Kodama et al., 1997[8]	46	93	77	88
Landreneau et al., 1997[19]	102	62	117	70
Okada et al., 2001[12]	68	87	104	87
Koike et al., 2003[9]	74	89	159	90
The present study	305	89.6	262	89.1

NSCLC, non–small cell lung cancer. *statistically significant.

fied 3 patients with local recurrence in the remaining part of the diseased lobe after segmentectomy. At the time of this report all these patients are alive without disease after completion lobectomy (n = 2) or pneumonectomy (n = 1). In our study, as a result of careful selection of patients and strict procedures, sublobar resection offered no survival demerit over lobectomy. Despite the nonrandomized nature of our study, our data force us to suggest that sublobar resection with sufficient margin and nodal assessment should provide appropriate treatment for stage I NSCLC of 2 cm or smaller in lieu of lobectomy in this era of increasing early discovery of small-sized lung cancer. We hereafter might consider the correlation between CT findings and bronchioloalveolar carcinoma component in the selection of patients for radical sublobar resection.[29] At present, the time is ripe for a large randomized trial, which would greatly change the standards of surgical treatment for lung cancer in the near future.

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