

## Lung: Research



## GENERAL THORACIC SURGERY:

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## Comparable Clinical Outcomes Between Segmentectomy and Lobectomy for NSCLC With Unsuspected N1/N2: A Multicenter Real-World Data Study



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## ABSTRACT

**BACKGROUND** Segmentectomy for lung cancer has been increasingly performed. However, evidence regarding the necessity of additional surgical resection after the diagnosis of unsuspected N1 or N2 lymph node metastasis is limited.

**METHODS** We conducted a multicenter, real-world data study of patients with any clinical T and N0 non-small cell lung cancer (NSCLC) who underwent lobectomy or segmentectomy between 2012 and 2021 and who subsequently received a diagnosis of pathologic N1 or N2 lymph node metastasis. Patients were categorized into lobectomy and segmentectomy groups. We analyzed overall survival (OS), recurrence-free survival (RFS), cumulative recurrence rates, and recurrence patterns using both unadjusted and propensity score-adjusted cohorts.

**RESULTS** A total of 736 patients were in the lobectomy group, and 70 were in the segmentectomy group. In the unadjusted cohort, segmentectomy-treated patients were older, had a lower preoperative percentage of vital capacity, had smaller tumors, and received less postoperative adjuvant chemotherapy. The 5-year OS was significantly worse in the segmentectomy group ( $P = .011$ ), with no significant differences in 5-year RFS or cumulative recurrence rates. In the propensity score-adjusted cohort, there were no significant differences in OS, RFS, or recurrence rates; however, the segmentectomy group had a higher rate of local recurrence.

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**CONCLUSIONS** In patients with unsuspected N1 or N2 NSCLC, analysis using a cohort adjusted for patient background with propensity scores revealed no differences in OS, RFS, or cumulative recurrence rates between segmentectomy and lobectomy. This finding suggests that additional resection of the remaining segments may not be necessary for these patients. However, the higher rate of local recurrence in the segmentectomy group warrants careful consideration.

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#### Abbreviations and Acronyms

CALGB = Cancer and Leukemia Group B  
HR = hazard ratio  
JCOG = Japan Clinical Oncology Group  
ND = nodal dissection  
NSCLC = non-small cell lung cancer  
OS = overall survival  
PS = performance status  
RFS = recurrence-free survival  
WJOG = West Japan Oncology Group

Since the 1960s, lobectomy has been the standard surgical approach for lung cancer. Segmentectomy, a form of sublobar resection, was initially viewed unfavorably as a result of higher local recurrence and poorer prognosis.<sup>1</sup> Consequently, it has primarily been reserved for patients unable to tolerate lobectomy because of factors such as impaired pulmonary function, interstitial lung disease, or poor general health. However, 2 randomized trials<sup>2,3</sup> demonstrated the noninferiority of segmentectomy to lobectomy in terms of overall survival (OS) for peripheral, small-sized non-small cell lung cancer (NSCLC), thus leading to the broader acceptance of segmentectomy as a standard surgical option.<sup>4,5</sup> Furthermore, an expansion of its indications is also anticipated.<sup>6-10</sup>

The question whether additional resection is necessary for patients found to have unsuspected lymph node metastasis during or after segmentectomy remains unresolved. In the Japan Clinical Oncology Group (JCOG) 0802/West Japan Oncology Group (WJOG) 4607L trial, lobectomy was performed if lymph node metastasis was detected intraoperatively,<sup>2</sup> whereas the Cancer and Leukemia Group B (CALGB) 140503 trial excluded such patients.<sup>3</sup> Current recommendations suggest thorough mediastinal lymph node dissection and adequate resection margins when metastasis is identified.<sup>11</sup> For patients eligible for lobectomy, conversion to lobectomy or a staged completion lobectomy with mediastinal lymph node dissection is often considered. In patients unable to undergo

lobectomy, mediastinal lymph node dissection alone is typically performed.<sup>11</sup>

To address this issue fundamentally, a direct comparative study between patients who underwent additional resection and patients in the observation group after a diagnosis of pN1 or N2 NSCLC is needed. However, no prospective studies have been reported, and only a few retrospective case series exist.<sup>12</sup> Nomori and colleagues<sup>12</sup> reported the direct comparison of 10 patients who underwent completion lobectomy after segmentectomy for patients with unsuspected N1 or N2 NSCLC vs 5 patients who completed treatment with segmentectomy alone. However, the small number of cases makes it difficult to draw definitive conclusions. Therefore, this study aimed to evaluate the necessity of “additional resection” by comparing the prognosis of patients with unsuspected N1 or N2 NSCLC that was diagnosed after segmentectomy with the prognosis of patients treated with lobectomy. We used real-world data provided by multiple institutions and performed an appropriate comparative analysis using propensity score methods.

#### PATIENTS AND METHODS

**PATIENT SELECTION.** This multicenter retrospective observational study used the real-world database maintained by the Okayama University Thoracic Surgery Study Group, which includes patients who underwent pulmonary resection for primary lung cancer at affiliated institutions, with ongoing updates on survival outcomes. We reviewed this database for 10,084 patients who underwent surgery at 22 institutions (Supplemental Table 1) between January 2012 and December 2021. The T criteria comprised cases of any T status regardless of location with clinical NO NSCLC in patients who underwent lobectomy or segmentectomy and were subsequently found to have pathologically positive N1 or N2 lymph node metastasis. The choice between segmentectomy and lobectomy

for each patient, as well as the extent of lymph node dissection, was left to the discretion of the institutions and surgeons, who made comprehensive decisions on the basis of factors such as tumor size, location, characteristics, the patient's respiratory function, and performance status (PS). Exclusion criteria included neoadjuvant therapy, distant metastasis at surgery, macroscopically positive surgical margins, pneumonectomies, and multiple segmentectomies. Additionally, cases with inadequate pathologic evaluation or significant data loss were also excluded. All lung cancer staging followed the Union for International Cancer Control (UICC) *TNM Classification of Malignant Tumours*, eighth edition. Postoperative adjuvant chemotherapy was recommended according to the guidelines, but the analysis included cases in which it was not administered because of factors such as PS, patient condition, or patient refusal. Local recurrence was defined as recurrence at the resection margin, in regional lymph nodes, or within the ipsilateral thoracic cavity, including the residual lung lobe. The study protocol (No. 2310-039) was approved by the Ethics Committee of Okayama University Hospital (Okayama, Japan), as well as the ethics committees of all participating institutions. Written informed consent was waived, and all methods adhered to relevant guidelines and regulations.

**VARIABLES.** The extracted data included preoperative patient information, tumor characteristics, surgical details, and postoperative data. Preoperative information comprised age, sex, PS, smoking history, Brinkman Index, history of diabetes and malignant diseases, presence of interstitial pneumonia, need for dialysis, percentage of vital capacity, and the ratio of forced expiratory volume in 1 second to forced vital capacity ratio as predictors. Tumor characteristics included histologic type, overall and solid tumor diameters, clinical T status, computed tomographic features (solid or ground-glass nodule), and tumor location. Surgical details covered approach, type, duration, blood loss, intraoperative complications, lymph node dissection extent, and margins. Postoperative data included complications within 30 days, pathologic staging, and adjuvant chemotherapy status. Lymph node dissection was classified as nodal dissection 1 (ND1) (hilar) or ND2 (mediastinal). Recurrence patterns were based on the first recurrence site, excluding new recurrences during follow-up. Primary outcomes were OS and RFS, with cumulative recurrence rates analyzed using death as a competing risk, along with recurrence patterns.

In counting recurrence patterns, overlapping cases were included in each relevant category.

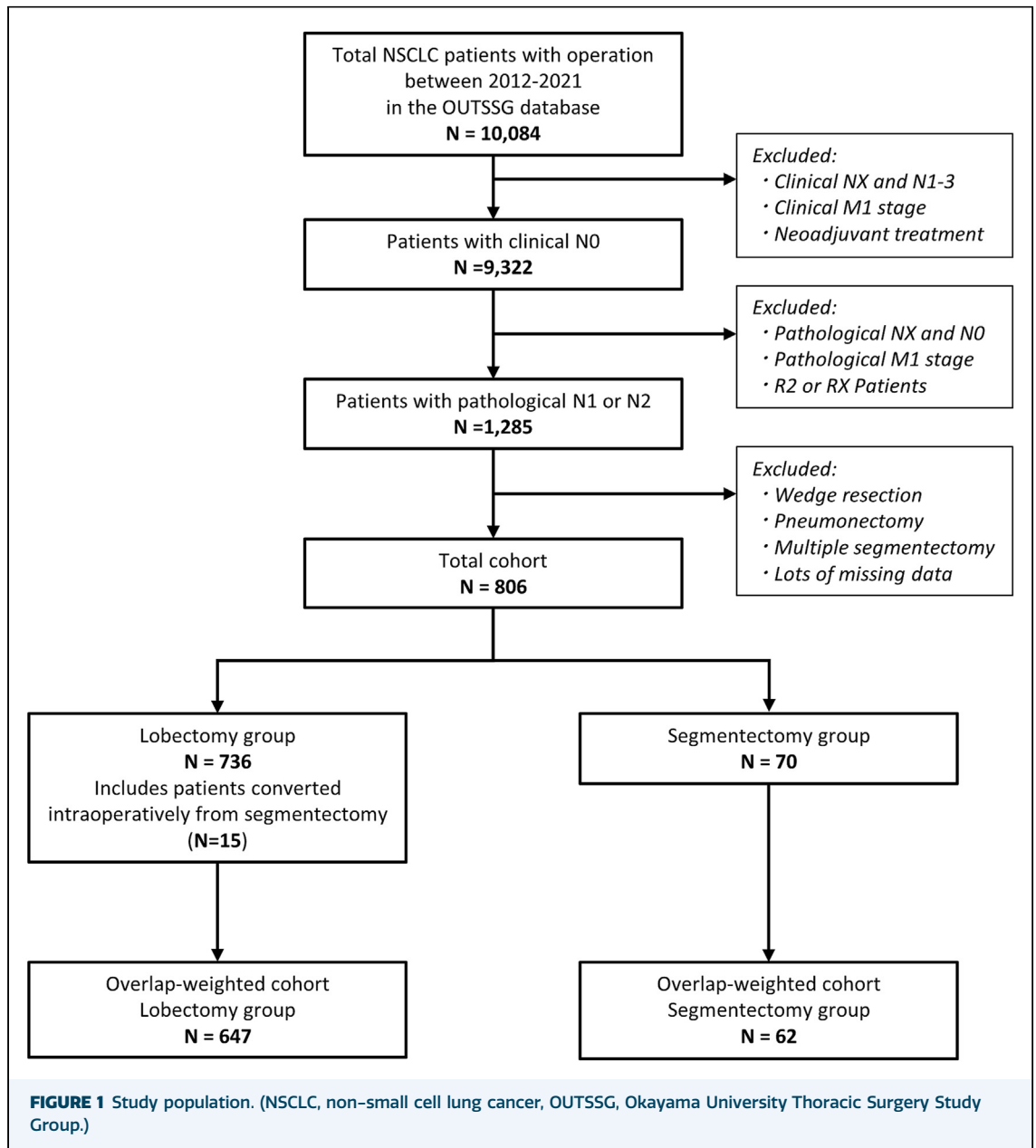
**STATISTICAL ANALYSIS.** Descriptive statistics presented continuous variables as mean (SD) or median (interquartile range) and categorical variables as frequency and percentage. The Welch *t* test was used for continuous variables, whereas the Pearson  $\chi^2$  test was used for categorical variables to assess differences between lobectomy and segmentectomy groups. The standardized mean difference (SMD) was calculated, with an absolute SMD <0.10 indicating adequate covariate balance.<sup>13,14</sup> To adjust for confounding factors, overlap weighting based on propensity scores was used.<sup>15</sup> Confounders were selected according to the modified disjunctive cause criterion<sup>16</sup> and were used in a logistic regression model with surgical procedure (lobectomy or segmentectomy) as the outcome to estimate propensity scores (conditional probabilities). Marginal probabilities were computed using a logistic regression model without explanatory variables. Overlap weights were calculated as follows:

$$\text{For segmentectomy, overlap weight} = \\ (1 - \text{Pr}[X = 1 | \text{Cs}]) / (1 - \text{Pr}[X = 1])$$

$$\text{For lobectomy, overlap weight} = \text{Pr}(X = 1 | \text{Cs}) / \text{Pr}(X = 1)$$

where Pr is probability,  $X = 1$  indicates segmentectomy,  $X = 0$  indicates lobectomy, and Cs represents confounding variables. All weights are presented with rounded values to integers in the result tables.

To compare OS and RFS between surgical groups, Kaplan-Meier curves were plotted, and the log-rank test was used to determine statistical significance. Five-year survival rates were calculated. Proportional hazards were verified, and hazard ratios (HRs) with 95% CIs were estimated using the Cox proportional hazards model. Recurrence rates were also compared between groups. Because death constitutes a competing risk for recurrence, cumulative incidence curves were generated, and statistical significance was assessed using the Pepe-Mori test.<sup>17</sup> Five-year cumulative incidences and subhazard ratios (sub-HRs) with 95% CIs were estimated using the Fine and Gray model, where the "sub" in sub-HR denotes the subdistribution hazard. This approach accounts for competing risks by modeling the cumulative incidence of a specific event type rather than the overall hazard. As a supplementary analysis, cumulative incidence was compared between the lobectomy conversion group and the segmentectomy group, with further comparisons



within the segmentectomy group between single-station and multistation lymph node dissection. Both unadjusted and adjusted models weighted by overlap weight were calculated for all analyses. Analyses were conducted using Stata software version 18/MP4 (StataCorp), with  $P < .05$  considered statistically significant. No adjustments for multiple comparisons were made, given the exploratory nature of this study.<sup>18</sup>

## RESULTS

**CLINICAL CHARACTERISTICS.** Among 10,084 patients who underwent surgery for primary lung cancer, a

total of 806 patients met the inclusion criteria, with 736 undergoing lobectomy and 70 undergoing segmentectomy (Figure 1). Of the 736 patients who underwent lobectomy, 15 had conversion from segmentectomy as a result of intraoperative lymph node positivity on rapid pathologic examination. Table 1 summarizes patient characteristics in the unadjusted cohort. The mean follow-up duration for the lobectomy group was 55.9 months, during which 384 patients (52.2%) experienced disease recurrence and 275 patients (37.4%) died. In the segmentectomy group, the mean follow-up was 47.5 months, with 36 patients (54.1%) experiencing recurrence, and 34 patients (48.6%) died. The

**TABLE 1 Characteristics of the Total Cohort**

Characteristics	Lobectomy (n = 736)	Segmentectomy (n = 70)	P Value	SMD
Age, y, mean (SD)	69.42 (9.43)	72.07 (7.59)	.009	0.280
Sex, male/female	463 (62.9)/273 (37.1)	41 (58.6)/29 (41.4)	.474	0.115
Performance status, 0/≥1	634 (86.1)/102 (13.9)	55 (78.6)/15 (21.4)	.086	0.178
Comorbidities				
Interstitial lung disease	51 (6.9)	7 (10.0)	.342	0.119
Diabetes	145 (19.7)	18 (25.7)	.231	0.160
Renal dysfunction with dialysis	6 (0.8)	2 (2.9)	.100	0.156
History of malignancy	163 (22.1)	21 (30.0)	.135	0.133
Smoking status				
Ever/never	496 (67.4)/240 (32.6)	50 (71.4)/20 (28.6)	.490	0.007
Brinkman Index, median (IQR)	600 (0-1000)	720 (0-1070)	.181	0.186
Respiratory function, median (IQR)				
%VC	99.1 (88.4-109.6)	93.3 (80.1-105.3)	.007	-0.370
FEV <sub>1</sub> /FVC	74.9 (69.1-80.7)	73.5 (67.8-79.1)	.081	-0.232
Whole tumor size, mm, median (IQR)	29.0 (22.0-37.9)	22.5 (16.0-31.2)	<.001	-0.561
Solid part size, mm, median (IQR)	28.0 (21.0-36.0)	22.0 (16.0-27.5)	<.001	-0.723
UICC clinical T stage (8th edition)				
cT0-1	337 (45.8)	48 (68.6)	.001	0.482
cT2	308 (41.8)	18 (25.7)		
cT3-4	91 (12.4)	4 (5.7)		
Tumor character, solid/part solid	632 (85.9)/104 (14.1)	57 (81.4)/13 (18.6)	.313	-0.133
Tumor location, UL or ML/LL	416 (56.5)/320 (43.5)	40 (57.1)/30 (42.9)	.920	0.014
Surgical approach, open/VATS or RATS	119 (16.2)/617 (83.8)	8 (11.4)/62 (88.6)	.298	0.170
Operation time, min, median (IQR)	223 (181-275)	235 (186-284)	.105	0.216
Bleeding, mL, median (IQR)	55 (20-178)	50 (20-100)	.721	0.055
Intraoperative complications	25 (3.4)	3 (4.3)	.698	0.052
Postoperative complications (≤30 days)	176 (23.9)	17 (24.3)	.944	-0.014
Nodal dissection, ND1/ND2	40 (5.4)/696 (94.6)	22 (31.4)/48 (68.6)	<.001	-0.695
Surgical margins, RO/R1	655 (89.0)/81 (11.0)	64 (91.4)/6 (8.6)	.531	-0.073
UICC pathologic classification (8th edition)				
pT1	277 (37.6)	31 (44.3)	.334	0.131
pT2	342 (46.5)	32 (45.7)		
pT3-4	117 (15.9)	7 (10.0)		
pN1/pN2	360 (48.9)/376 (51.1)	42 (60.0)/28 (40.0)	.076	-0.198
pIIB/pIIIA/pIIIB	313 (42.5)/353 (48.0)/70 (9.5)	38 (54.3)/29 (41.4)/3 (4.3)	.104	0.208
Tumor histologic type				
Adenocarcinoma	537 (73.0)	50 (71.4)	.798	-0.019
Squamous	152 (20.7)	15 (21.4)		-0.002
Adenosquamous	17 (2.3)	3 (4.3)		0.116
Large cell carcinoma	8 (1.1)	1 (1.4)		0.034
Others	22 (2.9)	1 (1.4)		
Adjuvant chemotherapy	470 (63.9)	35 (50.0)	.022	-0.253

Values are n (%) unless stated otherwise. FEV<sub>1</sub>/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity; IQR, interquartile range; LL, lower lobe; ML, middle lobe; ND, nodal dissection; RATS, robotic-assisted thoracoscopic surgery; SMD, standardized mean difference; UICC, Union for International Cancer Control; UL, upper lobe; VATS, video-assisted thoracoscopic surgery; %VC, percentage of vital capacity.

patients who underwent segmentectomy were significantly older (72.1 years vs 69.4 years;  $P = .009$ ) than those with lobectomy, although this extent of age difference may not have significant clinical relevance. Segmentectomy-treated patients also had a lower preoperative percentage of vital capacity (93.3% vs 99.1%;  $P = .007$ ), smaller total and solid tumor sizes (22.5 mm vs 29.0 mm;  $P < .001$ ; 22.0 mm vs 28.0 mm;  $P < .001$ , respectively),

and less extensive lymph node dissection (ND1, 31.4% vs 5.4%; ND2, 68.6% vs 94.6%;  $P < .001$ ) compared with lobectomy-treated patients. In addition, fewer patients in the segmentectomy group received adjuvant chemotherapy than in the lobectomy group (50.0% vs 63.9%;  $P = .022$ ). In the cohort adjusted using overlap weighting with propensity scores, 647 (91.3%) patients were in the lobectomy group and 62 (8.7%) were in the

**TABLE 2** Characteristics of the Adjusted Cohort

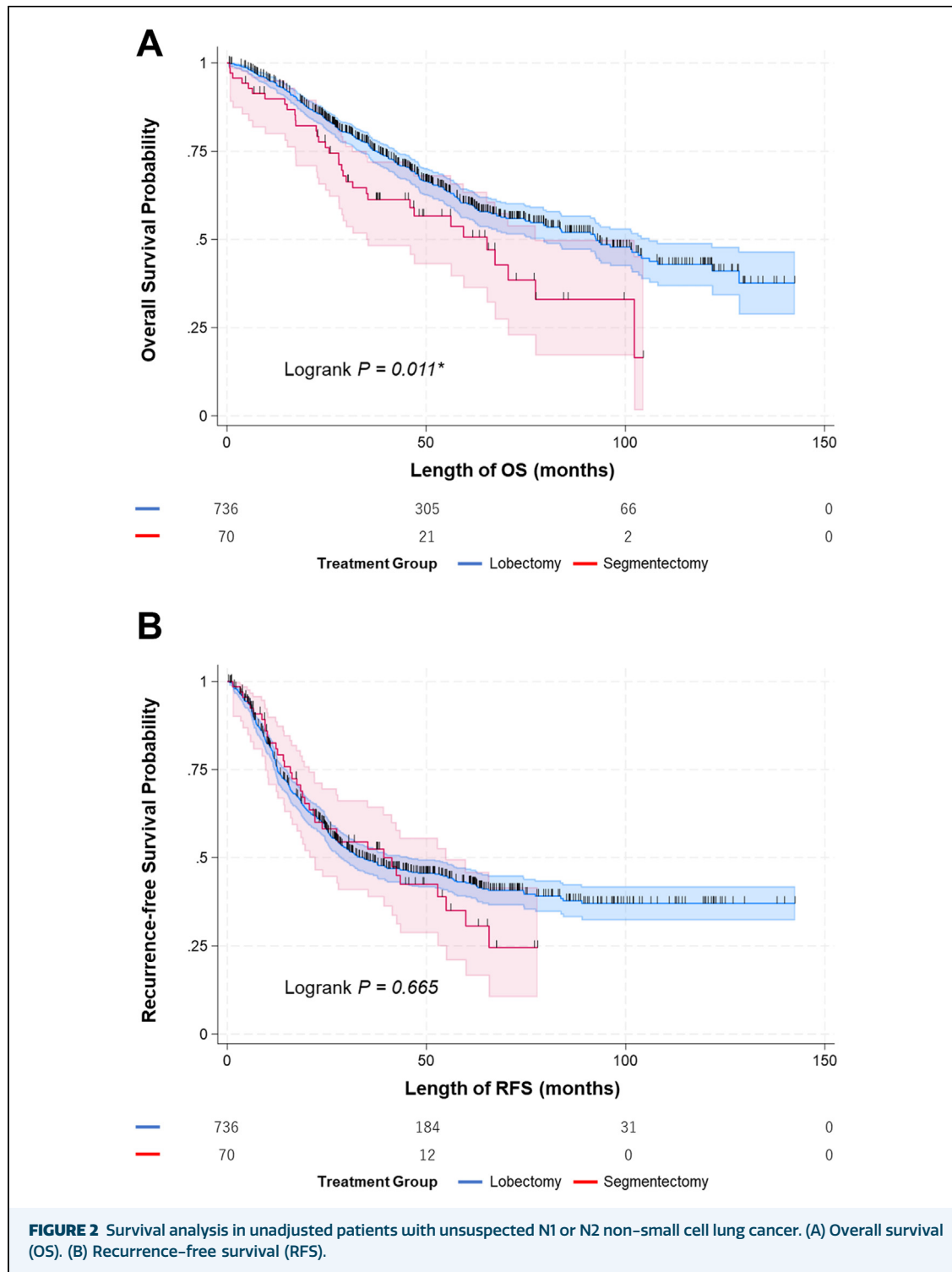
Characteristics	Lobectomy (n = 647)	Segmentectomy (n = 62)	P Value	SMD
Age, y, mean (SD)	71.78 (8.23)	71.78 (7.58)	>.999	0.000
Sex, male/female	382 (59.0)/265 (41.0)	36 (59.0)/25 (41.0)	>.999	0.000
Performance status, 0/≥1	512 (79.1)/135 (20.9)	49 (79.1)/13 (20.9)	>.999	0.000
Comorbidities				
Interstitial lung disease	67 (10.4)	6 (10.4)	>.999	0.000
Diabetes	169 (26.1)	16 (26.1)	>.999	0.000
Renal dysfunction with dialysis	15 (2.4)	1 (2.4)	>.999	0.000
History of malignancy	173 (26.7)	16 (26.7)	>.999	0.000
Smoking status				
Ever/never	460 (71.1)/187 (28.9)	44 (71.1)/18 (28.9)	>.999	0.000
Brinkman Index, median (IQR)	720 (0.00-1160)	740 (0.00-1080)	>.999	0.000
Respiratory function, median (IQR)				
%VC	94.4 (83.7-104.3)	93.4 (80.8-105.5)	>.999	0.000
FEV <sub>1</sub> /FVC	73.5 (65.6-79.8)	73.1 (67.8-79.1)	>.999	0.000
Whole tumor size, mm, median (IQR)	23.0 (17.2-31.0)	24.0 (17.0-32.0)	>.999	0.000
Solid part size, mm, median (IQR)	21.0 (16.0-28.0)	22.0 (16.0-28.0)	>.999	0.000
UICC clinical T stage (8th edition)				
cT0-1	432 (66.7)	41 (66.7)	>.999	0.000
cT2	175 (27.0)	17 (27.0)		0.000
cT3-4	41 (6.3)	4 (6.3)		
Tumor character, solid/part solid	516 (79.7)/131 (20.3)	49 (79.7)/12 (20.3)	>.999	0.000
Tumor location, UL or ML/LL	361 (55.8)/286 (44.2)	34 (55.8)/27 (44.2)	>.999	0.000
Surgical approach, open/VATS or RATS	72 (11.1)/575 (88.9)	7 (10.6)/55 (89.4)	.903	0.016
Operation time, min, median (IQR)	219 (179-266)	236 (195-284)	.040	0.300
Bleeding, ml, median (IQR)	50 (20-115)	50 (20-100)	.504	0.115
Intraoperative complications	23 (3.6)	3 (4.7)	.684	0.054
Postoperative complications (≤30 days)	171 (26.4)	15 (24.2)	.707	-0.051
Nodal dissection, ND1/ND2	63 (9.7)/584 (90.3)	19 (30.1)/43 (69.9)	<.001	-0.525
Surgical margins, RO/R1	579 (89.4)/69 (10.6)	57 (92.0)/5 (8.0)	.509	-0.089
UICC pathologic classification (8th edition)				
pT1	314 (48.5)	27 (43.8)	.552	-0.093
pT2	254 (39.2)	28 (46.2)		0.141
pT3-4	80 (12.3)	6 (10.0)		
pN1/pN2	325 (50.2)/322 (49.8)	36 (59.2)/25 (40.8)	.178	-0.181
pIIB/pIIIA/pIIIB	299 (46.2)/295 (45.6)/54 (8.3)	33 (53.5)/26 (42.3)/3 (4.2)	.376	0.146
Tumor histologic type				
Adenocarcinoma	470 (72.6)	44 (70.9)	.929	-0.038
Squamous	132 (20.4)	13 (21.3)		0.023
Adenosquamous	21 (3.2)	3 (4.9)		0.087
Large cell carcinoma	6 (1.0)	1 (1.3)		0.027
Others	18 (2.8)	1 (1.6)		
Adjuvant chemotherapy	340 (52.5)	32 (52.5)	>.999	0.000

Values are n (%) unless stated otherwise. For clarity in the table, the adjusted values using overlap weights have been rounded to the nearest whole number, which may result in discrepancies between whole numbers and percentage values. FEV<sub>1</sub>/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity; IQR, interquartile range; LL, lower lobe; ML, middle lobe; ND, nodal dissection; RATS, robotic-assisted thoracoscopic surgery; SMD, standardized mean difference; UICC, Union for International Cancer Control; UL, upper lobe; VATS, video-assisted thoracoscopic surgery; %VC, percentage of vital capacity.

segmentectomy group (Table 2). Confounding bias was adequately reduced, except for operative time, which was longer in the segmentectomy group (236 minutes vs 219 minutes;  $P = .040$ ), although this was not considered to affect the results significantly.

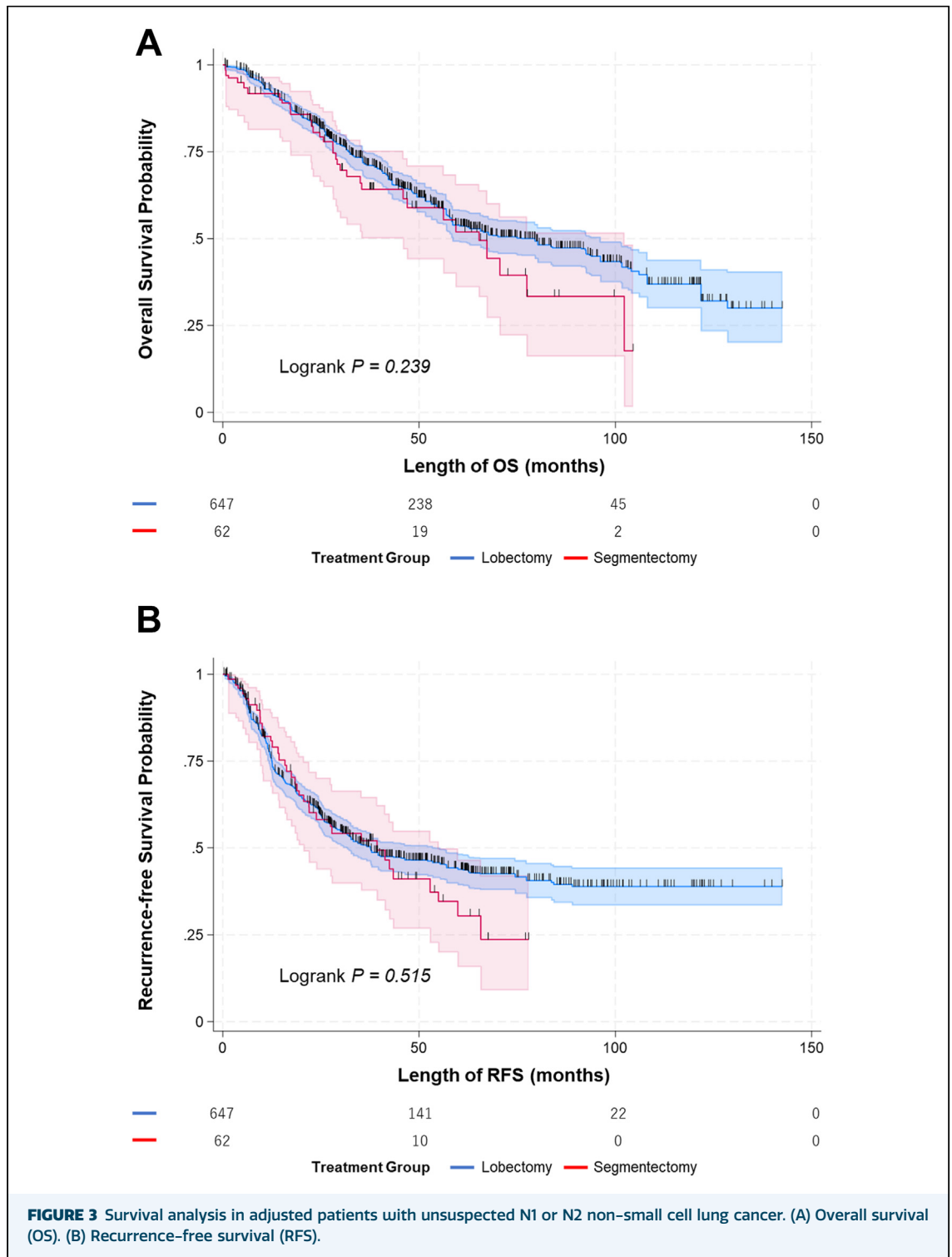
**SURVIVAL ANALYSES.** In the unadjusted cohort, Kaplan-Meier analysis with the log-rank test

showed that the 5-year OS of the segmentectomy group was significantly inferior compared with that of the lobectomy group (0.51 [95% CI, 0.36-0.63] vs 0.60 [95% CI, 0.56-0.64];  $P = .011$ ), but there was no difference in 5-year RFS (0.31 [95% CI, 0.17-0.46] vs 0.43 [95% CI, 0.39-0.47];  $P = .665$ ) (Figure 2). After adjusting for background factors using overlap weighting with propensity



scores, there were no significant differences in 5-year OS (0.52 [95% CI, 0.36-0.66] vs 0.54 [95% CI, 0.49-0.58];  $P = .239$ ) or RFS (0.30 [95% CI, 0.16-0.47] vs 0.44 [95% CI, 0.39-0.48];  $P = .515$ ) (Figure 3). Cancer-specific mortality rates showed no significant difference between the groups

regardless of adjustment (Table 3, Supplemental Table 2). The cumulative incidence of recurrence, accounting for death as a competing risk, showed no significant difference in the 5-year recurrence rate between the lobectomy and segmentectomy groups in both the unadjusted cohort (0.60 [95%



CI, 0.45-0.72] vs 0.55 [95% CI, 0.51-0.59];  $P = .560$ ) and the adjusted cohort (0.63 [95% CI, 0.46-0.75] vs 0.53 [95% CI, 0.48-0.57];  $P = .948$ ) (Figure 4). Cumulative recurrence rates were also analyzed in the segmentectomy group and did not differ on the basis of the extent of lymph node dissection

(ND1 vs ND2) (Supplemental Figure 1) or cT status (T1 vs  $\geq$  T2) (Supplemental Figure 2).

In the Cox proportional hazards model, segmentectomy was associated with significantly poorer OS compared with lobectomy in the unadjusted cohort, although this difference was not observed in the

adjusted cohort (Supplemental Table 3). No significant difference in RFS was found before or after adjustment (Supplemental Table 3). The sub-HR for cumulative recurrence rates between segmentectomy and lobectomy showed no significant difference in both unadjusted and adjusted analyses (Supplemental Table 3).

**RECURRENCE PATTERN.** No significant difference was seen in total recurrence events between the groups (Table 3, Supplemental Table 2). However, local recurrence was significantly higher in the segmentectomy group (unadjusted, 34.3% vs 19.6%;  $P = .004$ ; adjusted: 35.5% vs 21.4%;  $P = .013$ ), with notable differences in ipsilateral lung lobe (unadjusted,  $P < .001$ ; adjusted,  $P < .001$ ) and stump recurrence (unadjusted,  $P = .006$ ; adjusted,  $P = .022$ ). There were no significant differences in regional lymph node recurrence or distant recurrence rates between the groups.

**SURGICAL OUTCOME IN PATIENTS WITH INTRAOPERATIVE CONVERSION TO LOBECTOMY.** Although the number of cases is limited, we analyzed the prognosis and recurrence patterns of the cases that were converted from segmentectomy to lobectomy during surgery. In the comparison between the 15 converted cases and the 70 segmentectomy cases, Kaplan-Meier analysis of the adjusted cohort revealed no significant differences in OS (log-rank  $P = .199$ ), RFS (log-rank  $P = .699$ ), or cumulative recurrence rate (Pepe-Mori  $P = .566$ ) (Supplemental Figure 3). Similarly, no significant differences in recurrence patterns were observed between the 2 groups in either cohort (Supplemental Table 4).

**COMMENT**

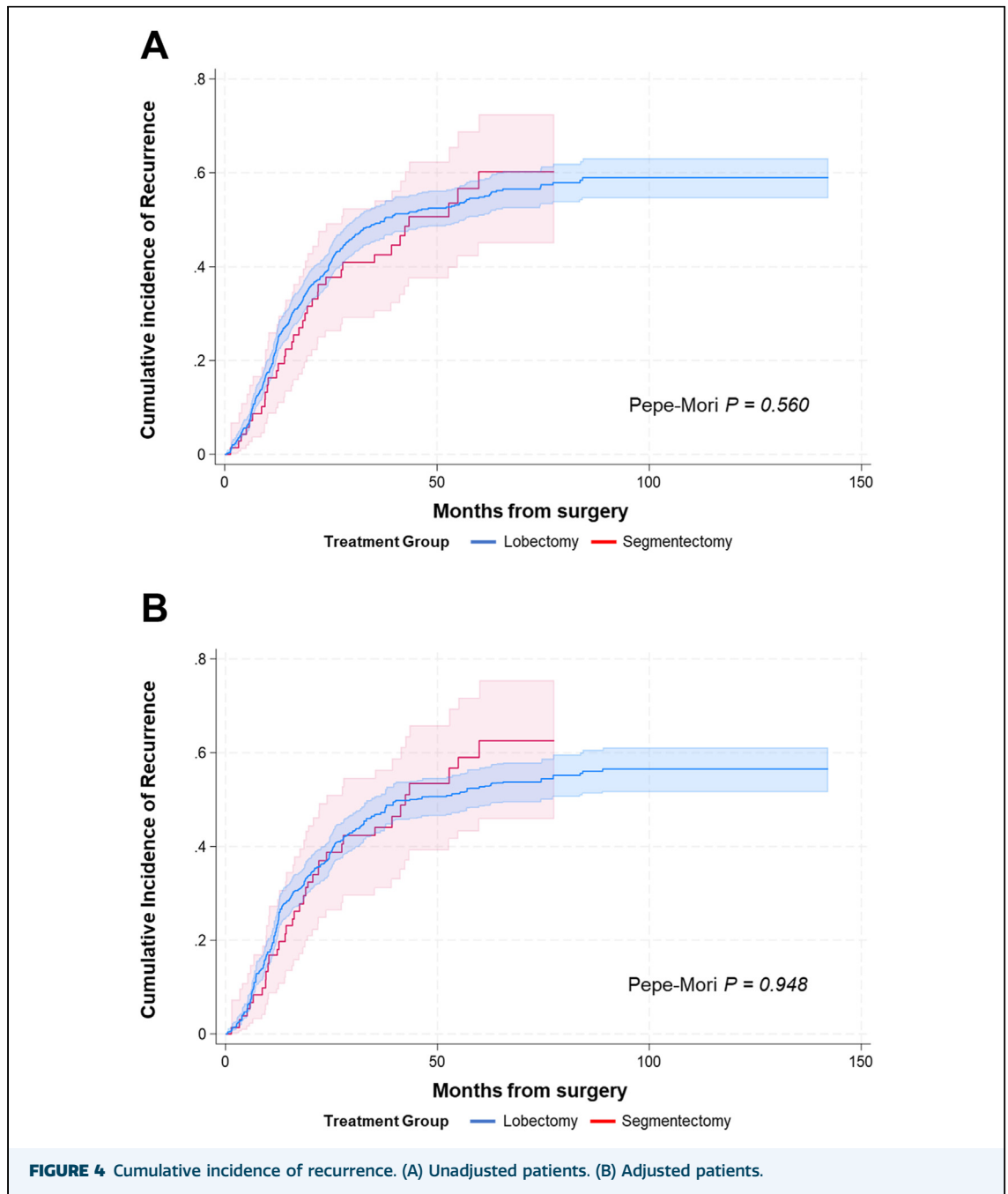
Considering the results of large-scale randomized comparative trials from Japan and the United States (JCOG0802/WJOG4607L and CALGB140508),<sup>2,3</sup> which demonstrated the noninferiority of segmentectomy compared with lobectomy for patients with early-stage lung cancer,<sup>4,5</sup> the adoption of segmentectomy has been increasing and may continue to expand in the future.<sup>6-9</sup> However, the occurrence of unsuspected lymph node metastasis in clinically N0 patients is not uncommon. In fact, the JCOG0802/WJOG4607L trial reported unsuspected N1 or N2 disease in 34 of 552 cases (6.2%) in the segmentectomy group,<sup>2</sup> and a German trial by Stamatis and colleagues<sup>19</sup> found 4 of 53 cases (7.6%) with unsuspected N1 or N2 involvement. Similarly, in our study, 70 of 1284 cases (5.5%) in the segmentectomy group were observed with unsuspected N1 or N2 disease. It is

Characteristics	Adjusted Cohort		P Value
	Lobectomy (n = 647)	Segmentectomy (n = 62)	
Recurrence	320 (49.4)	33 (53.0)	.597
Local recurrence	139 (21.4)	22 (35.5)	.013
Surgical margin	14 (2.2)	5 (7.6)	.022
Within the remaining lung lobe	0 (0.0)	2 (3.0)	<.001
Regional lymph node recurrence	128 (19.8)	17 (27.7)	.148
Hilar and interpulmonary	64 (9.9)	9 (15.3)	.201
Mediastinum	108 (16.8)	13 (21.3)	.362
Distant metastatic recurrence	271 (41.8)	22 (35.1)	.304
Intrapulmonary	70 (10.8)	4 (5.8)	.207
Bone	66 (10.1)	4 (6.3)	.327
Brain	42 (6.5)	7 (11.9)	.12
Liver	27 (4.2)	5 (8.9)	.112
Adrenal	10 (1.6)	2 (3.3)	.348
Pleural dissemination	46 (7.2)	6 (9.0)	.611
Malignant pleural effusion	29 (4.5)	1 (2.3)	.363
Others	11 (1.6)	0 (0.0)	.268
Cause of death			
Lung cancer death	155 (58.6)	17 (58.5)	.730
Other death	81 (30.8)	10 (35.3)	...
Unknown	28 (10.6)	2 (6.2)	...

Values are n (%).

anticipated that the number of patients undergoing segmentectomy with unsuspected N1 or N2 involvement will increase, thus making it imperative to discuss whether additional resections, such as intraoperative conversion to lobectomy or secondary completion lobectomy postoperatively, are necessary. The present study indicated that, after adjusting for background factors, there was no significant difference in 5-year OS, RFS, and cumulative recurrence rates between the 2 groups, a finding suggesting that additional lobectomy may not contribute to extending prognosis or improving cumulative recurrence rates in our study population.

Although not a direct comparison of additional lung resection and nonresection, studies using large-scale databases in the United States have retrospectively compared lobectomy and segmentectomy for patients with unsuspected N1 or N2 involvement and have shown no difference in OS, similar to our study.<sup>20,21</sup> The study by Razi and colleagues<sup>20</sup> did not include detailed preoperative patient background analysis, cumulative recurrence rates, or recurrence patterns. Our study was able to perform these analyses by collecting rare cases from multiple facilities. Furthermore, whereas previous reports focused on clinical stage IA, our study also included clinical stage IB and higher,



thereby allowing analysis in a cohort with a higher risk of recurrence.<sup>22</sup>

We expected that the segmentectomy group could have a higher recurrence rate in the remaining regional lymph nodes because intrapulmonary lymph nodes could not be completely resected, and this cohort included patients with advanced stages. Unexpectedly, there was no significant difference in regional lymph node recurrence between the groups, before and after propensity score adjustment. However, stump recurrence was significantly

higher in the segmentectomy group than in the lobectomy group, both before and after adjustment. Furthermore, in line with many previous reports,<sup>2,23</sup> whereas overall local recurrence was more frequent in the segmentectomy group, the difference in local recurrence did not affect the difference in prognosis between segmentectomy and lobectomy, a finding suggesting that the presence of distant metastases in patients with unsuspected N1 or N2 disease may have a greater impact on prognosis than the extent of lung resection.<sup>24</sup>

One interesting finding was that, despite the narrower range of lymph node dissection in the segmentectomy group, there was no significant difference in cumulative recurrence rates compared with the lobectomy group. Because lymph node dissection acts as an intermediate variable between the surgical procedure and prognosis, it was excluded from the propensity score calculation, to prevent bias.<sup>25</sup> Therefore, a significant difference in the extent of lymph node dissection remained in the background-adjusted cohort. This finding suggests that the segmentectomy group may have included cases staged earlier than their actual stage, considering the possibility of unsuspected N2; however, interestingly, this did not result in an increased recurrence rate. Furthermore, there was no significant difference in cumulative recurrence rates between N1 and N2 dissections within the segmentectomy group (Supplemental Figure 1). Although the efficacy of mediastinal lymph node dissection for NSCLC was debated previously,<sup>26-29</sup> the present study suggested that additional mediastinal lymph node dissection after the diagnosis of unsuspected N1 or N2 disease may not provide significant benefits, especially because it can increase the risk of complications such as bleeding, chyle leak, and nerve injury.

In this study, we also compared the cumulative recurrence rate and recurrence outcomes between 15 patients who underwent conversion to lobectomy during segmentectomy and 70 patients who completed segmentectomy alone. There was no significant difference in recurrence rates, local recurrence patterns, or any form of distant recurrence, excluding multiple lung metastasis recurrences, and no significant difference in cumulative recurrence rates (Supplemental Figure 3, Supplemental Table 4). These results also suggested that additional resection may not offer benefits in recurrence outcomes, but the sample size limits the ability to make definitive conclusions,

and further large-scale direct comparison studies are needed.

**STUDY LIMITATIONS.** As a retrospective study using real-world data, it is prone to biases from data selection, confounding variables, and missing data. Unmeasured variables in the propensity score may have affected the results. We used the overlap weight method to reduce confounding bias and ensure a fair comparison within a well-balanced subset of patients. However, it limits the analysis to the propensity score overlapped population, which may reduce generalizability to the broader patient population. Additionally, current guidelines recommend curative segmentectomy only for peripheral lung cancers smaller than 2 cm, but our study included cases beyond this criterion. Even for lesions larger than 2 cm or not in the periphery, lobectomy may not be feasible as a result of poor pulmonary function or poor PS. Nevertheless, demonstrating segmentectomy's potential efficacy in cases where lobectomy is difficult adds value to the analysis.

**CONCLUSION.** In patients with NSCLC harboring unsuspected N1 or N2 involvement, the analysis adjusted for patient backgrounds showed no difference in OS, RFS, or cumulative recurrence rates between segmentectomy and lobectomy. These findings may suggest that additional completion lobectomy may not be necessary for these patients, although the higher local recurrence rate with segmentectomy warrants further attention.

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#### DISCLOSURES

The authors have no conflicts of interest to disclose.

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## An Unresolved Surgical Conundrum: How to Manage Unsuspected Nodal Involvement in Early-stage Lung Cancer



### INVITED COMMENTARY:

The recent Japanese (Japan Clinical Oncology Group/West Japan Oncology Group [JCOG/WJOG]<sup>1</sup> and Cancer and Leukemia Group B<sup>2</sup>) randomized clinical trials established sublobar resection as standard surgical management for select clinical T1a or T1b N0 M0 non-small cell lung cancers (NSCLCs) but did not address several important questions. In a retrospective, multicenter study reported in this issue of *The Annals of Thoracic Surgery*, Ryuko and colleagues<sup>3</sup> address the conundrum of whether the finding of unsuspected

N1 or N2 lymph node involvement should lead to conversion from segmentectomy to completion lobectomy. Analyzing a cohort adjusted for patient background by propensity scores, Ryuko and colleagues<sup>3</sup> found no differences in overall survival, recurrence-free survival, or cumulative recurrence rates between segmentectomy and lobectomy but identified a higher rate of local recurrence in the segmentectomy group. Other retrospective studies have reported similar findings,<sup>4,5</sup> but completion lobectomy was mandated in the Japanese trial and is often considered in routine practice. How should we interpret these results?

One issue that merits attention is the definition of local recurrence, considered in the study by Ryuko and colleagues<sup>3</sup> to include recurrence at the resection margin, in regional lymph nodes, or