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Thoracoscopic Surgery Shows Non-Inferiority to Open Surgery for Clinical N0-N2 and Pathologic N2 Non-Small Cell Lung Cancer

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Objectives: Controversy has remained over the primary surgical management for stage IIIA-N2 non–small cell lung cancer. Minimal or non-bulky N2 disease defined as single-station nodal involvement may still be a candidate of radical surgery. The aim of this study was thus to assess the outcome of thoracoscopic surgery in clinical N0-N2 and pathologic N2 disease.

Methods: Seventy-nine cases of pathologic N2 diseases without induction therapy (clinical N0, 27; N1, 13; N2, 39) were operated on between September 2003 and December 2010 in our institute. Forty-seven patients underwent thoracoscopic surgery (group T) and 32 patients underwent standard thoracotomy (group S). Perioperative and oncologic outcomes were compared between the 2 groups.

Results: There were no significant differences between the 2 groups regarding dissected number of lymph nodes, operative time, morbidity, and mortality. However, blood loss in group T was less than in group S (Mean: T, 229 versus S, 534 mL, respectively; $P = 0.0004$). Although disease-free survival in group T did not differ from that in group S, overall survival in group T was better than in group S after propensity score matching to adjust confounding factors including tumor size and T factor ($P = 0.03$). Multivariate analysis showed that multinodal stations was significantly worse prognostic factor [hazard ratio (HR) = 4.79; 95% confidence interval (CI) = (1.6–14.3); $P = 0.005$) in disease-free and overall survivals [HR = 8.21; 95% CI = (1.9–35.4); $P = 0.005$]. Thoracoscopic surgery was favorable

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prognostic factor in overall survivals [HR = 0.13; 95% CI = (0.03–0.6); $P = 0.009$].

Conclusions: Our study demonstrated that thoracoscopic surgery for non-bulky N2 disease was feasible and not inferior to standard thoracotomy in terms of oncologic outcome.

Key words: Lung cancer – N2 – Thoracoscopic

Lung cancer is the leading cause of death worldwide,[1] and 10% of such cases are classified as stage IIIA-N2 disease, which involves ipsilateral mediastinal node metastases. However, N2 diseases are heterogeneous and require different treatment strategies. There are 3 groups according to the American College of Chest Physician (ACCP) guidelines,[2] the first of which is patients showing negative mediastinal node involvement clinically but positive findings intraoperatively or postoperatively. These patients were treated by continuous mediastinal node clearance followed by adjuvant chemotherapy. The second group consists of patients with discrete nodal metastases (single or multiple stations) recognized by pre-thoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan). Multimodality treatment should be applied to this group, but induction chemoradiotherapy followed by surgery or definitive chemoradiotherapy should be recommended. The third group is infiltrative N2 disease with bulky or fixed mediastinal lymph nodes involving a major vessel and/or the trachea. This group should be considered for curative-intent treatment, combination chemoradiotherapy.

Since surgery after induction therapy is feasible on the basis of acceptable postoperative mortality and morbidity, surgical resection for stage IIIA-N2 disease is applied to patients showing downstaging after induction therapy.[3] However, clinical staging under multimodality evaluation including mediastinoscopy, endobronchial ultrasonic–transbronchial needle aspiration (EBUS-TBNA), EUS-FNA, or PET scan is not accurate and it is inadequate that all patients with persistent N2 disease do not receive surgical benefit.[4]

Video-assisted thoracic surgery (VATS) has been widespread in a variety of thoracic operations, including lung cancer. VATS is less invasive and provides benefits due to rapid postoperative recovery and a shorter length of hospital stay[5]; however, VATS is limited to clinical stage I and standard thoracotomy is applied to more advanced diseases. In accordance with our policy, as thoracoscopic surgery is feasible and potentially equally as effective at node clearance as thoracotomy, it has been applied even if the disease is advanced.

The standard treatment for stage IIIA-N2 non–small cell lung cancer is multimodality treatment, and surgery is one of the available options. The purpose of this study was to evaluate the outcome of thoracoscopic surgery compared with standard thoracotomy for pathologic N2 disease.

Materials and Methods

Patients

This retrospective study focused on 79 consecutive stage IIIA patients who underwent surgery in our hospital between September 2003 and December 2010. Our institutional ethical committee approved the retrospective study and waived the need for patient consent. Thoracoscopic surgery (group T) was performed for 47 patients and standard thoracotomy (group S) was performed for 32 patients. Both procedures were accompanied by systemic radical lymphadenectomy. The standard preoperative evaluation and procedures were described in our previous report.[6] All patients were evaluated by computed tomography (CT). If hilar or mediastinal lymph node was larger than 1 cm in terms of its short axis, positron emission tomography (PET) was subsequently performed for staging. Mediastinoscopy or endobronchial ultrasonic sonography fine needle aspiration (EBUS-FNA) was not performed in this study. Cases of clinical stage I-IIIA non-small cell lung cancer were eligible for this retrospective analysis. In accordance with our policy, patients with clinical single-station nonbulky N2 disease were candidates for either procedure. Preoperatively, patients with bulky or multistation N2 disease were subjected to induction chemotherapy or chemoradiotherapy and excluded from this analysis.

Postoperative pathologic findings were made by 2 pathologists and the final staging and histology were evaluated according to the seventh edition of the TNM classification.[7] Postoperative adjuvant chemotherapy was recommended for all stage IIIA patients except elderly patients aged over 80 years.

Most patients received platinum-doublet chemotherapy as the treatment of choice. Dose reduction or a delay in the schedule was decided by the attending physicians.

Patients were followed up postoperatively every 3 months by blood tests, and by chest X-ray and CT scan at 6-month intervals. If any finding of relapse was observed, the patients underwent subsequent radiotherapy and/or chemotherapy.

Institutional review board (IRB) was set up in the Fukuoka University Hospital Clinical Research Center. The approval number is 2016M071, which waived the informed consent from individual patients because of it was a retrospective study.

We require every research article submitted to include a statement that the study obtained ethics approval (or a statement that it was not required), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that participants gave informed consent before taking part.

Surgical technique

The surgical approach via thoracotomy was performed in the fourth or fifth intercostal space. The techniques of lung cancer resection were similar in thoracotomy and thoracoscopy. Our surgical technique via thoracoscopy was similar to that in previous reports[8]; essentially, 4 trocars for operator and assistant, and one 12-mm trocar at the 7th intercostal space of the midaxillary line for a thoracoscope at 30° were inserted. All procedures were performed by visualization through a television monitor, so-called complete VATS or total thoracoscopy. The intrathoracic procedure for hilar and intralobar vessel treatment was the same in both procedures. Both procedures were followed by systemic mediastinal lymph node dissection. Selection of approach was due to the patient choice or operator preference and patients with tumors larger than 3 cm tended to be chosen in the thoracotomy group.

Statistical analysis

All statistical analyses were performed using SPSS 14.0 (SPSS Japan Inc., Tokyo, Japan). The different variables were analyzed by χ^2 test or Fisher's exact test.

The propensity scores, which were calculated from the logistic regression models, including the following variables: age, sex, comorbidity, histologic type, T factor, tumor size, clinical staging, procedure and adjuvant chemotherapy, represent the probability of being assigned to either the thoracoscopy or standard thoracotomy groups. In the matching procedure, both groups showed similar distributions of propensity scores, indicating that the differences in covariates between the 2 groups were minimized. We matched propensity scores one by one using nearest neighbor methods, no replacement, and 0.1 caliper width. Finally, 15 matched patients from the thoracoscopy group and 15 from the standard thoracotomy group were included in the analysis. Overall survival was analyzed using the Kaplan-Meier method and evaluated by the log-rank test. The statistical significance of differences was accepted at $P < 0.05$.

Results

Patient and tumor characteristics are summarized in Table 1. There were no differences in age, sex, histology, preoperative comorbidity, and the proportion of clinical nodal involvement between the 2 groups. However, tumor size and T factor in group T were significantly less than those in group S. There were no statistically significant differences between the 2 groups regarding dissected number of lymph nodes and operative time, morbidity, and mortality. However, blood loss and length of chest tube drainage or hospital stay in group T were less than in group S (Mean: T, 229 versus S, 534 mL, $P = 0.0004$; Mean: T, 5 versus S, 6 days, $P = 0.04$; and Mean: T, 14 versus S, 16 days, $P = 0.01$, respectively, Table 2).

There was no 30-day mortality in either group. The postoperative morbidity rates were not significantly different between the 2 types of operation. The major complications are shown in Table 3. Two patients in group S suffered a bronchopleural fistula, but they were cured after re-thoracotomy. Characteristics of metastatic N2 stations and recurrences were shown in Table 4. There was no significant difference between the 2 groups with regard to metastatic mediastinal nodal stations. Median follow-up was 23.3 months, and 30 patients (64%) in the thoracoscopy group and 27 (84%) in the thoracotomy group showed recurrence. The pattern of recurrence was as follows: 13 (28%) locoregional, 15 (32%) distant, and 2 both (4%) in the thoracoscopy group. On the other hand, recurrence in the thoracotomy group was 16 (50%) locoregional, 10 (31%) distant, and 1 both (3%).

Table 1 Characteristics of the patients

Characteristics	Thoracoscopy (n = 47)	Thoracotomy (n = 32)	*P*
Age			
Median (range)	67 (49–81)	68 (52–80)	0.59
Sex			
Male, n (%)	31 (66)	23 (72)	0.58
Female, n (%)	16 (34)	9 (28)	
Comorbidity	6	2	0.46
COPD	4	-	
IP	1	-	
Arrythmia	1	-	
DM	-	2	
Histologic type			
Ad, n (%)	32 (68)	17 (53)	0.43
Sq, n (%)	9 (19)	10 (31)	
La, n (%)	4 (9)	2 (7)	
Others, n (%)	2 (4)	3 (9)	
T factor			
T1, n (%)	18 (38)	6 (19)	0.03
T2, n (%)	24 (51)	14 (44)	
T3, n (%)	4 (9)	10 (31)	
T4, n (%)	1 (2)	2 (6)	
Tumor size, mm			
Mean ± SD	29.2 ± 11.6	48.4 ± 26.3	0.0004
Clinical stage			
IA, n (%)	12 (26)	3 (9)	0.16
IB, n (%)	7 (16)	4 (13)	
IIA, n (%)	3 (6)	-	
IIB, n (%)	3 (6)	6 (19)	
IIIA, n (%)	19 (40)	16 (50)	
IIIB, n (%)	3 (6)	3 (9)	
Procedure			
Pneumonectomy, n (%)	1 (2)	2 (6)	0.23
Lobectomy, n (%)	43 (92)	30 (94)	
Segmentectomy, n (%)	3 (6)	-	
Adjuvant chemotherapy, n (%)	28 (60)	18 (56)	0.77

Ad, adenocarcinoma; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IP, interstitial pneumonia; La, large cell carcinoma; Sq, squamous cell carcinoma.

Disease-free survival in group T did not differ from that in group S ($P = 0.1$, Fig. 1A). However, as shown in Fig. 1B, 5-year overall survival in group T (32%) was better than in group S (16%, $P = 0.013$), even for the same adjuvant chemotherapy setting (group T, 60%; group S, 56%) and same population of multistational metastases (group T, 36%; group S, 37%). In Table 5, multivariate Cox proportional hazard model showed that multinodal stations were a significantly worse prognostic factor [hazard ratio (HR) = 2.87; 95% CI = (1.64–5.04); $P < 0.001$], but a thoracoscopic approach revealed a better tendency than thoracotomy [HR = 0.54; 95% CI = (0.29–1.01); $P = 0.055$] in disease-free survivals. Multi nodal stations were a worse prognostic factor in overall survivals [HR = 3.26; 95% CI = (1.7–6.26); $P < 0.001$]. Additionally, thoracoscopic approach was better prognostic factor in overall survivals [HR = 0.37; 95% CI = (0.18–0.75); $P = 0.006$].

Propensity score matching was performed and matched 15 patients from the thoracoscopy group and 15 patients from the standard thoracotomy group were included in the analysis. The distribution of baseline patient characteristics including T factor ($P = 0.99$) and tumor size (Mean: group T, 31.8 mm; group S, 32.5 mm, $P = 0.94$) was well balanced between the 2 groups after propensity score matching.

Disease-free survival in group T did not differ from that in group S ($P = 0.18$, Fig. 2A). However, overall survival in group T was better than in group S ($P = 0.03$, Fig. 2B). In Table 6, multivariate Cox proportional hazard model showed that multinodal stations were a significantly worse prognostic factor [HR = 4.79; 95% CI = (1.6–14.3); $P = 0.005$] in disease-free survivals. Multinodal stations [HR = 8.21; 95% CI = (1.9–35.4); $P = 0.005$] and male sex [HR = 9.3; 95% CI = (1.93–44.6); $P = 0.005$] were worse prognostic factors and thoracoscopic surgery was a favorable prognostic factor in overall survivals [HR = 0.13; 95% CI = (0.03–0.6); $P = 0.009$].

Discussion

Preoperative assessment for lung cancer staging is a critical issue for making the decision to treat. Because of limitations for invasive and noninvasive assessment of nodal involvement, clinical staging remains uncertain.[4] Inevitable upstaging by postoperative nodal involvement sometimes occurs in clinical N0 patients. It was previously reported that

Table 2 Perioperative outcome

	Thoracoscopy mean ± SD	Thoracotomy mean ± SD	*P*
Number of dissected lymph nodes	29 ± 15	30 ± 13	0.83
Blood loss, mL	229 ± 248	534 ± 468	0.0004
Operating time, min	291 ± 99	316 ± 94	0.13
Duration of chest tube drainage, d	5 ± 3	6 ± 3	0.04

Table 3 Morbidity and mortality

	Thoracocopy (n = 47)	Thoracotomy (n = 32)	*P*
Pneumonia	2	1	
Prolonged drainage of effusion[a]	2	3	
Bronchofistula	0	2	
Chylothorax	1	0	
Hoarseness	3	0	
Atrial fibrillation	1	1	
Phrenic nerve palsy	1	0	
Total morbidity, n (%)	10 (21)	7 (22)	0.94
30-Day mortality	0	0	

[a]Prolonged drainage of effusion were defined as drainage needed for longer than 7 days.

Table 4 Metastatic N2 stations and recurrences

	Thoracocopy (n = 47)	Thoracotomy (n = 32)	*P*
Stations			
Single station, n (%)	30 (64)	20 (63)	0.9
Multistation, n (%)	17 (36)	12 (37)	
Recurrence	30 (64)	27 (84)	0.47
Locoregional, n (%)	13 (28)	16 (50)	
Distant, n (%)	15 (32)	10 (31)	
Both, n (%)	2 (4)	1 (3)	

about 10% of clinical N0 patients revealed a pathologic N2 stage after operation.[9] On the other hand, some clinical N2 patients show pathologic N0 postoperatively. Patients with clinical N2 constitute a heterogeneous population with different types of behavior and prognosis.[2] Some selected patients with pathologic N2 disease are candidates for operation with curative intent; namely, patients with clinical N0 by CT and pathologic N2 by operation were still operative indications. These patients showed a favorable prognosis following adjuvant chemotherapy, even if VATS lobectomy was performed.[10] However, operation for patients with clinical single-station nonbulky N2 disease remains controversial. In our study, we performed a retrospective review of thoracoscopic surgery for patients with pathologic N2 and clinical N0-2 disease.

We analyzed the perioperative and oncologic outcomes of thoracoscopic surgery in patients with pathologic stage IIIA NSCLC. Although the operating time did not show a difference between procedures, blood loss, duration of chest tube drainage, and hospital stay in the thoracoscopic surgery group were better than those with thoracotomy. These results may be due to the less tumor size and T factor in thoracoscopic group. Our favorable outcomes with a short hospital stay, short chest tube drainage, and less blood loss in the thoracoscopy group are supported by previous reports.[11,12] However, morbidity rates did not differ between the 2 procedures. Thoracoscopy may be safe and feasible, even for advanced-stage cases. Although we did not evaluate the postoperative

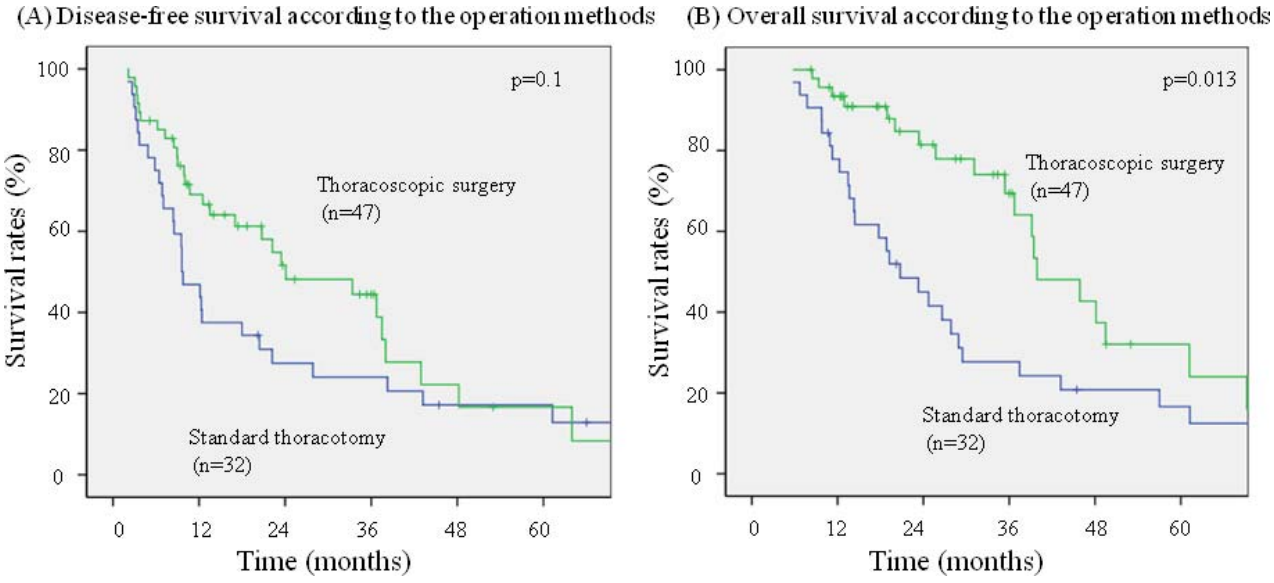

Fig. 1 (A) Kaplan-Meier estimate shows disease-free survivals according to the operation methods in unmatched cases. Five-year disease-free survival in group T (17%) was not different from group S (16%, $P = 0.1$). (B) Overall survival curve according to the operation methods. Five-year overall survival in group T (32%) was better than in group S (16%, $P = 0.013$).

Table 5 Multivariate analyses of disease-free and overall survivals (unmatched cases)

Characteristics	Disease-free survivals			Overall survivals		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (female versus male)	1.52	0.76–3.03	0.23	2.2	0.95–5.08	0.07
Age (<70 versus ≥70)	0.63	0.35–1.13	0.12	0.63	0.33–1.2	0.16
T factor (T1 versus T2-4)	0.64	0.32–1.28	0.21	0.69	0.32–1.48	0.34
Histologic subtype (Ad versus non-Ad)	1.19	0.62–2.27	0.61	1.8	0.85–3.83	0.13
Nodal stations (single versus multiple)	2.87	1.64–5.04	<0.001	3.26	1.7–6.26	<0.001
Operation approach (thoracotomy versus thoracoscopy)	0.54	0.29–1.01	0.055	0.37	0.18–0.75	0.006

pain and lung function, these results may show at least noninferiority of thoracoscopic surgery.[11]

The rates of perioperative morbidity were similar between thoracoscopy (21%) and thoracotomy (22%). We found 3 cases of recurrent nerve palsy and 1 of phrenic nerve palsy in the thoracoscopic group; however, these were not specific to this procedure as they were also seen in the thoracotomy group. Therefore, the magnified view of thoracoscopy may provide both advantages and disadvantages. The obtained morbidity rates are comparable to those in previous reports, in which the mean morbidity rates were 17.6% to 31.3% in VATS lobectomy and 15.3% to 31% in open lobectomy.[8,13–15] The 30-day mortality rates were zero in both groups. Taken together, these results show the safety and feasibility of thoracoscopic surgery, even in cases of advanced NSCLC.

In terms of the oncologic findings, our results showed no differences in dissected lymph nodes number. Sugi[16] and D'Amico *et al*[17] reported that the total numbers of stations of lymph node resected for the 2 groups were similar and there was equivalent efficacy of mediastinal lymph node dissection. Our results are in agreement with these previous findings. However, a contradictory report by Denlinger *et al*[18] showed that VATS lobectomy was associated with less lymph node dissection than open lobectomy. Their lymph node numbers for the 2 procedures were 7.4 and 8.9, respectively, and these numbers were lower than our data owing to the quality of maneuvering for dissection. The advantage of our technique is the use of a 5-port method, which enables easier and more precise dissection of lymph nodes than 2- or 3-port methods because both operator and assistant can use 2 hands in a similar fashion to that in thoracotomy. There-

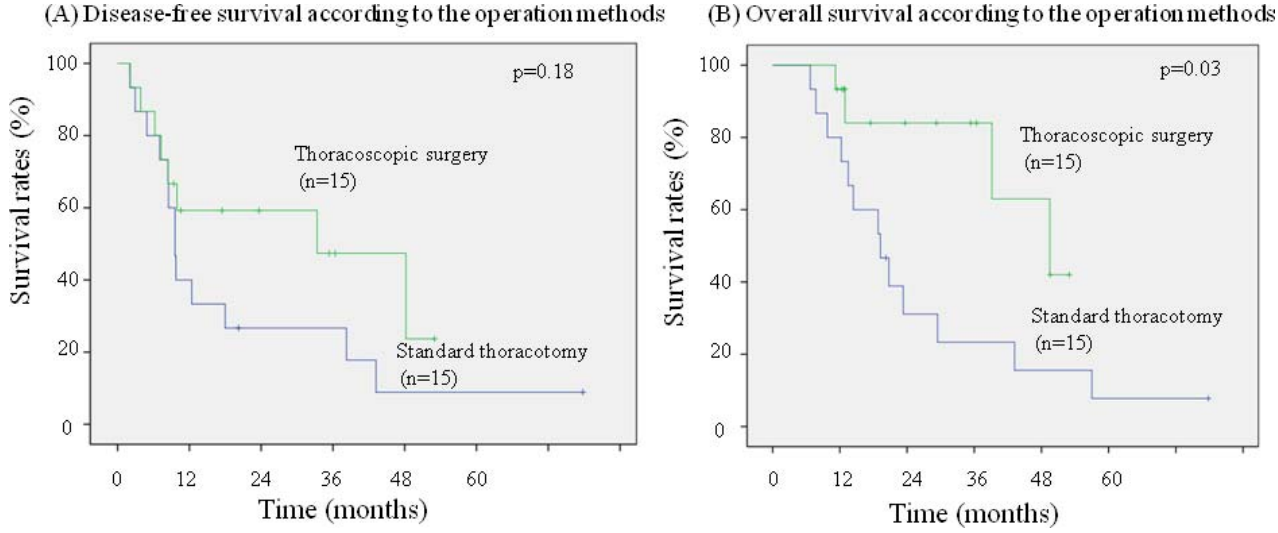

Fig. 2 After propensity score matching, 15 patients from the thoracoscopy group and 15 patients from the standard thoracotomy group were included in the analysis. (A) Kaplan-Meier estimate shows disease-free survivals according to the operation methods. Disease-free survival in group T was not different from in group S ($P = 0.18$). (B) Overall survival curve according to the operation methods. Overall survival in group T was better than in group S ($P = 0.03$).

Table 6 Multivariate analyses of disease-free and overall survivals (matched cases)

	Disease-free survivals			Overall survivals		
Characteristics	HR	95% CI	*P*	HR	95% CI	*P*
Sex(female versus male)	1.98	0.71–5.54	0.19	9.3	1.93–44.6	0.005
Age (<70 versus ≥70)	1.61	0.55–4.72	0.38	4.26	0.86–21.1	0.08
T factor (T1 versus T2-4)	0.5	0.15–1.61	0.24	0.77	0.03–2.86	0.7
Histological subtype (Ad versus non-Ad)	1.52	0.48–4.81	0.48	3.3	0.79–13.9	0.1
Nodal stations (single versus multiple)	4.79	1.6–14.3	0.005	8.21	1.9–35.4	0.005
Operation approach (thoracotomy versus thoracoscopy)	0.53	0.21–1.38	0.19	0.13	0.03-0.6	0.009

fore, the same number of dissected lymph nodes by thoracoscopy suggests quality similar to that of the open procedure.

Significant differences between thoracoscopy and thoracotomy were not found in the rates of locoregional or distant recurrence, or both. However, the locoregional recurrence rate of 28% in thoracoscopy showed a tendency to be lower than in thoracotomy (50%). Many factors influencing the outcome of survival and local recurrence with N2 disease have been proposed, such as adjuvant chemotherapy, the number of involved lymph node stations, and the surgical margin from the tumor.[19,20] Petersen *et al*[11] showed the advantages of thoracoscopic surgery in terms of completeness and early administration of postoperative chemotherapy because of good performance status. In our study, there were no differences between the two groups in these regards. All pathologic specimens showed a free surgical margin from the tumor. However, larger tumor size in thoracotomy group may lead to higher locoregional recurrence rate in our results. As previously reported, patients with single-station N2 disease revealed better survival than those with multistation disease.[21] In the single-station N2 subgroup, there was no significant difference in survival between thoracoscopy and thoracotomy. However, thoracoscopic surgery showed better survival than thoracotomy in multistation N2 disease. This benefit in a subgroup with multistation N2 disease by thoracoscopy may have contributed to the better survival in the entire population. The reasons why thoracoscopy showed a survival advantage in multistation N2 were not clear; however, it is speculated that less immunologic disadvantage by thoracoscopy may provide a better response to adjuvant chemotherapy.[22] Otherwise, more precise and meticulous mediastinal dissection by thoracoscopy may contribute to this, despite the same number of dissected nodes.

Although patient distribution in the thoracotomy group included more advanced T stage and large tumor size compared with the thoracoscopy group, a thoracoscopic approach showed better overall survivals but only a better tendency of disease-free survivals in multivariate Cox regression analysis. However, overall survivals showed similar outcome even if T factor and tumor size distribution between the 2 groups was minimized after propensity score matching. These findings may support nodal stations and less invasive approach as more important prognostic factors.

Since the limitations of our study include its retrospective nature and that it was a single-institution study, this work cannot provide definitive evidence compared with randomized studies and should be interpreted with caution. Thoracoscopic surgery might be performed for selected patients with favorable characteristics such as patients with smaller tumor size. Another limitation is the relatively short period of follow-up to observe differences in local recurrence and overall survival between the 2 methods. A longer follow-up and an increased number of patients in both groups may lead to further confirmation of the results.

Conclusions

The standard treatment for stage IIIA-N2 non–small cell lung cancer is multimodality treatment, and surgery is one of the available options. However, our study demonstrated that thoracoscopic surgery for clinical N0-N2 and pathologic N2 disease including nonbulky N2 have at least noninferiority to standard thoracotomy in terms of oncologic outcome. Thoracoscopic resection may be the treatment of choice for nonbulky N2 disease.

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