Outcomes of Mediastinoscopy and Surgery with or without Neoadjuvant Therapy in Patients with Non-small Cell Lung Cancer Who are N2 Negative on Positron Emission Tomography and Computed Tomography

Hong Kwan Kim, MD, Yong Soo Choi, MD,* Kwhanmien Kim, MD,* Young Mog Shim, MD,* Keunchil Park, MD,† Yong Chan Ahn, MD,‡ Kyung Soo Lee, MD,§ Joon Young Choi, MD,‖ and Jhingook Kim, MD**

Introduction: The objectives of this study were (1) to assess the results of mediastinoscopy and mediastinal lymphadenectomy and (2) to compare outcomes of surgical treatment with or without neoadjuvant therapy in patients with non-small cell lung cancer who are N2 negative on integrated positron emission tomography and computed tomography (PET/CT).

Methods: This was a retrospective, single-institution review of patients with non-small cell lung cancer who were N2 negative on CT and PET/CT. All patients underwent mediastinoscopy; if N2 positive, patients underwent neoadjuvant therapy followed by pulmonary resection, and if N2 negative, patients underwent pulmonary resection with mediastinal lymphadenectomy.

Results: Between 2003 and 2007, there were 750 patients (547 men). Of these, 51 patients were N2 positive at mediastinoscopy and then underwent neoadjuvant therapy (mediastinoscopy N2 group), and 699 were N2 negative at mediastinoscopy and then underwent mediastinal lymphadenectomy. Mediastinal lymphadenectomy revealed that 635 had N0 or N1 disease (N2-negative group), and 64 had N2 disease (surgery N2 group). Overall 5-year survival was 73% for the N2-negative group, 44% for the surgery N2 group, and 47% for the mediastinoscopy N2 group. Disease-free 5-year survival was 59% for the N2-negative group, 27% for the surgery N2 group, and 29% for the mediastinoscopy N2 group.

Conclusions: We found that there were no significant differences in overall and disease-free survivals between the surgery N2 group and the mediastinoscopy N2 group. The benefit of neoadjuvant therapy in patients with PET/CT-negative but mediastinoscopy-positive N2 disease should be confirmed by randomized studies.

*Department of Thoracic Surgery; †Divisions of Hematology-Oncology, Department of Medicine; ‡Department of Radiation Oncology; §Department of Radiology and Center for Imaging Science; and ‖Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Jhingook Kim, MD, Department of Thoracic Surgery, Samsung Medical Center, 50 Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea. E-mail: jkimsmc@skku.edu

ISSN: 1556-0864/11/0602-0336

Key Words: Non-small cell lung cancer, Mediastinoscopy, Integrated positron emission tomography and computed tomography, Neoadjuvant therapy.

(*J Thorac Oncol.* 2011;6: 336–342)

Integrated positron emission tomography (PET) with [^{18}F] fluorodeoxyglucose (FDG) and computed tomography (CT) has improved the accuracy of mediastinal staging for non-small cell lung cancer (NSCLC).[1,2] PET/CT can detect areas of high FDG metabolic activity consistent with malignancy.[3] Nevertheless, when the FDG uptake within lymph nodes is not increased on PET/CT despite the presence of malignancy, this suggests microscopic lymph node metastasis.[1,2,4] If N2 diseases were detected by mediastinoscopy or mediastinal lymphadenectomy in such patients who had neither enlarged lymph nodes on CT nor FDG uptake on PET/CT, their prognoses would be better than those of patients with N2 diseases demonstrated as bulky mediastinal nodal enlargement on CT or increased FDG uptake on PET/CT.[5,6] Nevertheless, few studies have investigated the role of mediastinoscopy and treatment outcomes in this subgroup of patients with minimal N2 disease, which is silent and not avid for FDG on PET/CT.

Since the introduction of PET/CT, we have routinely performed both PET/CT and mediastinoscopy for patients with NSCLC before curative-intent surgery at our institution. The objectives of this study were (1) to assess the results of mediastinoscopy and mediastinal lymphadenectomy and (2) to compare treatment outcomes of surgery with or without neoadjuvant therapy in patients with NSCLC who are N2 negative on PET/CT.

PATIENTS AND METHODS

Study Population

This was a retrospective, single-institution study of patients meeting the following criteria. Patients had to have histologically proven NSCLC; have both PET/CT and mediastinoscopy performed; and were staged N0 or N1 on both

CT and PET/CT. Patients who were staged N2, N3, or M1 on CT or PET/CT were excluded. Patients who had N3 on mediastinoscopy were excluded. Patients were excluded if neoadjuvant therapy was performed despite a negative mediastinoscopy or if surgery was performed despite a positive mediastinoscopy. Patients with double primary lung cancers or a carcinoid were excluded. The study was reviewed and approved by the Institutional Review Board of Samsung Medical Center.

PET/CT Acquisition

Patients received an intravenous injection of 370 MBq (10 mCi) of FDG. Scans were acquired with a PET/CT device (Discovery LS; GE Healthcare, Milwaukee, WI) consisting of an Advance NXi PET scanner and an eight-section LightSpeed Plus CT scanner. The axes of both systems were mechanically aligned, so that shifting the examination table by 60 cm moved the patient from the CT into the PET gantry. An unenhanced CT was performed from the head to the pelvic floor according to a standardized protocol involving 140 kv, 80 mA, a tube-rotation time of 0.5 second per rotation, a pitch of 6, and a section thickness of 5 mm, which was matched to the PET section thickness. Immediately after CT, PET was performed in the identical transverse field of view. The acquisition time for PET was 5 minutes per table rotation. PET data sets were reconstructed iteratively with an ordered subsets expectation maximization algorithm and segmented attenuation correction (two iterations, 28 subsets) and the CT data. Coregistered scans were displayed by using eNTEGRA software.

CT and PET/CT Image Analysis

Lymph nodes greater than 10 mm in the short-axis diameter on CT scans were considered malignant. Lesions with high FDG uptake (higher than that of the surrounding normal mediastinal structure or with a standardized uptake value of >3.5) and with a distinct margin and a round shape on PET/CT were considered malignant. Lesions with equivocally increased glucose uptake (to a level similar to that of the surrounding normal mediastinal structure) and with a morphologic appearance of lobar or bronchopneumonia at CT were interpreted as benign.

Mediastinoscopy

All patients underwent cervical mediastinoscopy. Mediastinoscopic examinations were done by the standard technique to evaluate the lymph nodes of 2R, 2L, 4R, 4L, and the subcarinal stations. All nodal stations were evaluated and sampled unless no nodal tissue was present at that station. If lymph nodes were identified, biopsies were performed regardless of their appearance.

Treatment Modalities

When patients are confirmed to have N2 disease by staging workup, the treatment policy depends on whether tumors or lymph nodes are resectable. If tumors or lymph nodes are considered unresectable, we usually recommend definitive concurrent chemoradiation. If they are considered potentially resectable, we plan to perform neoadjuvant chemoradiation and then restage them to decide whether they receive surgery. Neoadjuvant therapy included thoracic radiation therapy (TRT) concurrent with chemotherapy. The TRT dose was 45 Gy over 5 weeks (1.8 Gy/fraction/d, 5 fractions/wk) using 10 mV x-rays. The TRT target volume included the known gross and clinical disease plus adequate peripheral margins. The chemotherapy regimens consisted of weekly paclitaxel (50 mg/m^2/wk intravenously [IV]) plus cisplatin (25 mg/m^2/wk IV) or weekly paclitaxel (50 mg/m^2/wk IV) plus carboplatin (area under the curve, 1.5/wk IV) for 5 weeks. The first dose of chemotherapy was to be delivered on the first day of TRT. Restaging procedures with complete clinical and radiologic evaluation including CT scans were performed within 3 weeks after the completion of neoadjuvant therapy. Surgical resection was planned at around 4 weeks after the completion of neoadjuvant therapy.

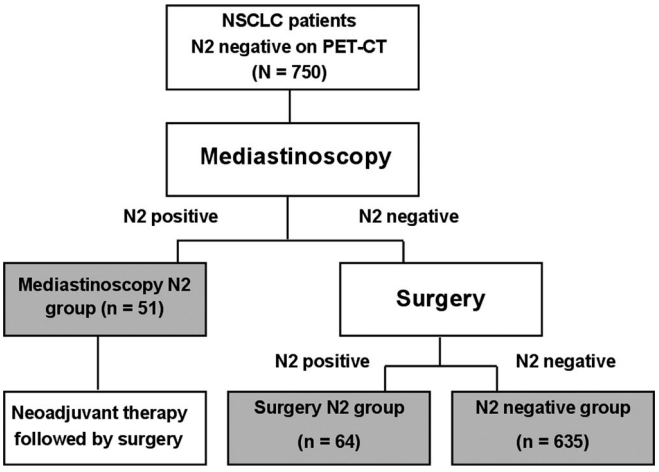

FIGURE 1. Diagram summarizing the study population.

In the absence of N2 or N3 disease at mediastinoscopy, patients immediately underwent pulmonary resection and complete mediastinal lymph node dissection. Operative procedures included lobectomies, bilobectomies, sleeve resections, or pneumonectomies as indicated. Mediastinal lymph node dissection consisted of en bloc resections of all nodes at stations 2R, 4R, 7, 8, 9, and 10R for right-sided tumors and nodes at stations 4L, 5, 6, 7, 8, 9, and 10L for left-sided tumors. We usually performed postoperative radiotherapy in the event of persistent histologically positive N2 lymph node, positive multiple N1 lymph nodes, or positive resection margin at the time of surgery. Patients undergoing surgery were regularly evaluated by CT every 3 months for the first 2 years after surgery and then every 6 months thereafter. In cases lost to follow-up, a telephone interview was conducted to determine the late outcomes.

Statistical Analysis

Descriptive statistics were used to describe the patients' characteristics and outcomes. Student's *t* tests or Mann-Whitney tests, depending on the normality of distribution, and the χ^2 test or Fisher's exact test were used to compare continuous and categorical variables, respectively. One-way analysis of variance was used to compare the continuous variables among three groups. Overall survival (OS) was defined as time from the date of mediastinoscopy to death from any cause. Disease-free sur-

TABLE 1. Baseline Clinical and Pathologic Characteristics ($N = 750$)

	N2-Negative Group ($n = 635$)		Surgery N2 Group ($n = 64$)		Mediastinoscopy N2 Group ($n = 51$)		
Characteristics	**No.**	**Percentage**	**No.**	**Percentage**	**No.**	**Percentage**	p^a
Age, yr (mean)	61.5 (23–90)		59.1 (41–77)		56.2 (30–76)		0.106
Gender							0.355
Male	474	75	43	33	30	59	
Female	161	25	21	67	21	41	
Histology							0.055
SCC	264	42	19	30	9	18	
ADC	304	48	39	61	41	80	
LAC	29	4	2	3	0	0	
Others	38	6	4	6	1	2	
SUVmax of primary tumor (mean)	11.9		13.2		10.9		0.23
Pathologic T stage							0.002
T0	0	0	0	0	5	10	
T1	148	23	9	14	13	25	
T2	405	64	40	62	28	55	
T3	48	8	10	16	0	0	
T4	34	5	5	8	5	10	
Pathologic N stage							0.000
N0	490	77	0	0	16	31	
N1	145	23	0	0	10	20	
N2	0	0	64	100	25	49	
Positive N2 station							0.055
Single	—	—	49	77	46	90	
Multiple	—	—	15	23	5	10	

[a] Comparison was done between the surgery N2 group and mediastinoscopy N2 group.
SCC, squamous cell carcinoma; ADC, adenocarcinoma; LAC, large cell carcinoma; SUVmax, maximum standardized uptake value.

TABLE 2. Results of Neoadjuvant Therapy in the Mediastinoscopy N2 Group

	Patients	
	No.	**Percentage**
Surgery after neoadjuvant therapy	51	100
Response (radiologic)		
Complete response	3	6
Partial response	35	69
Stable disease	13	25
Pathologic complete response	3	6
Pathologic downstaging	26	51
N2–N0	16	31
N2–N1	10	20

vival (DFS) was defined as time from the date of mediastinoscopy to recurrence or death. Survival curves were prepared using the Kaplan-Meier method and compared univariately using the log-rank test. To determine which factors were significantly associated with survival, a multivariate analysis using Cox proportional hazards model was performed. All statistical tests were two-sided, with a significance level set at 0.05 and were performed using Stata software version 10.0 (Stata, College Station, TX).

RESULTS

Patient Characteristics

Between June 2003 and December 2007, there were 750 patients (547 men and 203 women). Of these, 51 patients (7%) were N2 positive at mediastinoscopy and then underwent neoadjuvant therapy (mediastinoscopy N2 group). The remaining 699 patients (93%) who were N2 negative at mediastinoscopy underwent pulmonary resection and mediastinal lymph node dissection. Of the 699 patients who underwent surgery, 635 patients had N0 ($n = 490$) or N1 ($n = 145$) disease (N2-negative group), and 64 patients had N2 disease (surgery N2 group) (Figure 1). As a result, the negative predictive value of PET/CT and mediastinoscopy was 84.7% and 91.5%, respectively. Patient characteristics are summarized in Table 1. There was no significant difference in clinical and pathologic features between the surgery N2 group and mediastinoscopy N2 group, except in pathologic T stage and N stage.

In the mediastinoscopy N2 group, all the patients completed the neoadjuvant therapy and then underwent surgery. The overall response rate was 75%, including three patients with complete response, 35 with partial response, and 13 with stable disease (Table 2). Overall, 322 patients (43%) underwent adjuvant treatment after surgery, and there was no difference in the frequency of adjuvant therapy between the

TABLE 3. Summary of Treatment Modalities

	N2-Negative Group (n = 635)		Surgery N2 Group (n = 64)		Mediastinoscopy N2 Group (n = 51)		
	No.	Percentage	No.	Percentage	No.	Percentage	p^a
Extent of resection							0.059
Lobectomy (VATS[b])	476 (97)	75	43 (10)	67	45 (0)	88	
Bilobectomy	42	7	7	11	3	6	
Pneumonectomy	52	8	8	13	2	4	
Sleeve lobectomy	64	10	6	9	1	2	
Others	1	0.2	0	0	0	0	
Completeness of resection							0.775
R0	620	98	61	95	48	94	
R1	15	2	3	5	3	6	
R2	0	0	0	0	0	0	
Adjuvant treatment							0.498
Chemotherapy	170	27	13	31	10	20	
Radiotherapy	63	10	14	20	24	47	
Chemoradiation	7	1	17	22	4	8	
Not done	395	62	20	27	13	25	

[a] Comparison was done between the surgery N2 group and mediastinoscopy N2 group.
[b] The number of VATS lobectomy cases was expressed.
R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; VATS, video-assisted thoracic surgery.

surgery N2 group and mediastinoscopy N2 group. Details about the extent of surgery and adjuvant treatment are presented in Table 3.

Treatment-Related Morbidity and Mortality

No unexpected toxicities or deaths were noted during neoadjuvant therapy in the mediastinoscopy N2 group. Twelve patients (2%), one patient (2%), and two patients (4%) died during the postoperative period in the N2-negative group, the surgery N2 group, and the mediastinoscopy N2 group, respectively. The cause of death included acute respiratory distress syndrome in seven patients, pneumonia in seven, and empyema in one (Table 4). Major postoperative complications occurred in 104 patients (16%) of the N2-negative group, in 15 (23%) of the surgery N2 group, and in six (12%) of the mediastinoscopy N2 group (Table 4). There was no significant difference in the treatment-related morbidity ($p = 0.91$) or mortality rate ($p = 0.43$) among the three groups.

TABLE 4. Summary of Postoperative Morbidity and Mortality

	No. (%)			
	N2-Negative Group (n = 635)	Surgery N2 Group (n = 64)	Mediastinoscopy N2 Group (n = 51)	p^a
Overall in-hospital mortality	12 (1.9)	1 (1.6)	2 (3.9)	0.43
ARDS	5 (0.8)	1 (1.6)	1 (2)	
Pneumonia	6 (0.9)	—	1 (2)	
Empyema	1 (0.2)	—	—	
Overall morbidity	104 (16)	15 (23)	6 (12)	0.91
ALI or ARDS	26 (4.1)	2 (3.1)	1 (2)	
Pneumonia	5 (0.8)	2 (3.1)	2 (3.9)	
Empyema ± BPF	6 (0.9)	—	—	
Atrial fibrillation	28 (4.4)	3 (4.7)	4 (7.8)	
Prolonged air leak	21 (3.3)	5 (7.8)	3 (5.9)	
Chylothorax	11 (1.7)	1 (1.6)	—	
Vocal cord palsy	13 (2)	2 (3.1)	1 (2)	
Bleeding	2 (0.3)	1 (1.6)	—	

[a] Comparison was done between the three groups.
ARDS, acute respiratory distress syndrome; ALI, acute lung injury; BPF, bronchopleural fistula.

OS and DFS

The median follow-up time was 40 months (range, 1–79 months), and 17 patients (2.3%) were lost to follow-up. No significant differences were found in the follow-up duration ($p = 0.09$) and follow-up loss rate ($p = 0.61$) among the three groups. At the end of follow-up, 556 patients were alive (491 in the N2-negative group, 34 in the surgery N2 group, and 31 in the mediastinoscopy N2 group). Median OS time was not reached for the N2-negative group, whereas it was 45 months (95% confidence interval [CI], 30–60 months) for the surgery N2 group and 59 months (95% CI, 43–75 months) for the mediastinoscopy N2 group. Overall 5-year survival rate was 73% for the N2-negative group, 44% for the surgery N2 group, and 47% for the mediastinoscopy N2 group (Figure 2*A*). There was no significant difference in OS between the surgery N2 group and the mediastinoscopy N2 group ($p = 0.49$). Among the mediastinoscopy N2 group, overall 5-year survival rate was 42% for patients who achieved mediastinal clearance and 20% for those who have persistent lymph node involvement after neoadjuvant therapy. Among the surgery N2 group, there was no significant difference in overall 5-year survival between patients with right-sided lesions

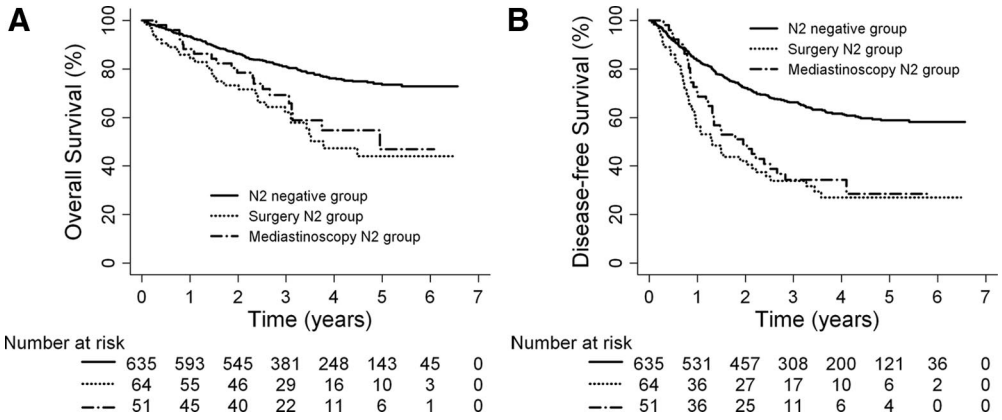

FIGURE 2. *A,* Overall survival according to subgroups. *B,* Disease-free survival according to subgroups.

TABLE 5. Summary of Recurrence Pattern

	No. (%)			
	N2-Negative Group (n = 635)	**Surgery N2 Group (n = 64)**	**Mediastinoscopy N2 Group (n = 51)**	p^a
Overall recurrence	190 (29.9)	38 (59.4)	29 (56.9)	0.79
Locoregional	53 (8.4)	17 (26.6)	8 (15.7)	0.16
Distant	114 (20)	19 (29.7)	16 (31.4)	0.85
Locoregional + distant	23 (3.6)	2 (3.1)	5 (9.8)	0.24

[a] Comparison was done between the surgery N2 group and mediastinoscopy N2 group.

(25%) and those with left-sided lesions (31%). Also, there was no significant difference in the site of first recurrence between the two groups.

During follow-up, 257 patients developed recurrence, and there was no significant difference in the incidence of recurrence between the surgery N2 group and mediastinoscopy N2 group ($p = 0.79$). Data regarding recurrence pattern are summarized in Table 5. Median DFS time was not reached for the N2-negative group, whereas it was 16 months (95% CI, 9–22 months) for the surgery N2 group and 24 months (95% CI, 13–34 months) for the mediastinoscopy N2 group. Disease-free 5-year survival rate was 59% for the N2-negative group, 27% for the surgery N2 group, and 29% for the mediastinoscopy N2 group (Figure 2*B*). There was no significant difference in DFS between the surgery N2 group and the mediastinoscopy N2 group ($p = 0.39$).

Multivariate Analysis for Mediastinoscopy N2 and Surgery N2 Groups

For patients with pathologic N2 disease (Surgery N2 + mediastinoscopy N2 groups), multivariate analysis were performed and listed in Table 6. Histology other than adenocarcinoma or squamous cell carcinoma and pneumonectomy were independent predictive factors associated with both OS and DFS. Adjuvant treatment was also associated with increased OS. Comparison of the survival curves according to pneumonectomy and adjuvant therapy were depicted in Figures 3*A*, *B*, respectively.

DISCUSSION

In this retrospective study of patients who underwent both PET/CT scans and mediastinoscopy for staging of NSCLC, we excluded patients with bulky mediastinal lymph nodes on CT and those with increased FDG uptake in the mediastinum on PET/CT. This suggests that even if patients with N2 disease detected at mediastinoscopy or mediastinal lymphadenectomy were included, this study population represents patients with minimal N2 disease. There was no significant difference in OS and DFS between patients who underwent neoadjuvant therapy and those who did not undergo neoadjuvant therapy.

These findings can be interpreted in two different ways, depending on whether both the mediastinoscopy N2 group and surgery N2 group represent the same population in terms of mediastinal nodal status. If two groups represent the same population, our results suggest that there might be no survival benefit of neoadjuvant therapy in this subset of patients with "PET/CT-negative" N2 disease. In other words, even if N2 is unexpectedly detected at primary surgery, the outcomes might be comparable with neoadjuvant therapy plus surgery in this group. Several authors showed the favorable outcomes of primary surgery for minimal N2 disease.[6–12] Andre et al.[6] reported a 5-year survival of 34% for 244 patients with single-level minimal N2 disease who underwent primary surgery. Ichinose et al.[7] reported a 5-year survival of 43% for 209 patients who had not received neoadjuvant therapy and were found to have single-level N2 disease. Presumably, chemotherapy is mainly active on distant micrometastases rather than locoregional lymphatic spread. The probability of distant micrometastases in patients with minimal N2 disease is likely to be low compared with clinical N2 disease. Therefore, the role of neoadjuvant chemotherapy may have been less obvious in patients with minimal N2 disease.

Nevertheless, if two groups represent different patient populations, the absence of differences in survival could be related to the therapeutic benefit of neoadjuvant treatment. The fact that N2 disease was detected by mediastinoscopy in the mediastinoscopy N2 group and not in the surgery N2 group implies that the mediastinoscopy N2 group might have more extensive mediastinal nodal involvement than the surgery N2 group. If it is true, comparable survivals of the

TABLE 6. Multivariate Association between Clinicopathologic Factors and Overall Survival or Disease-Free Survival in the Mediastinoscopy N2 and Surgery N2 groups ($N = 115$)

	Overall Survival			Disease-Free Survival		
Factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***p***
Histology						
ADC ($n = 80$)	1		0.0001	1		0.0001
SCC ($n = 28$)	0.37	0.13–1.03	0.056	0.43	0.2–0.93	0.032
Others ($n = 7$)[a]	8.63	2.81–26.5	0.0001	5.01	1.83–13.8	0.002
Pathologic T stage						
T0[b] ($n = 5$)	1		0.002	1		0.23
T1 ($n = 22$)	2.42	0.44–13.5	0.31	1.1	0.27–4.41	0.9
T2 ($n = 68$)	0.94	0.19–4.71	0.94	1.03	0.28–3.79	0.97
T3 ($n = 10$)	4.7	0.74–29.9	0.1	2.16	0.47–9.99	0.32
T4 ($n = 10$)	4.6	0.75–28.7	0.1	2.17	0.49–9.6	0.3
Pathologic N stage						
N0 ($n = 16$)	1		0.41			0.06
N1 ($n = 10$)	0.93	0.21–4.13	0.93	3.67	1.2–11.1	0.02
N2 ($n = 89$)	2.0	0.58–6.88	0.27	1.75	0.63–4.86	0.29
Pneumonectomy						
No ($n = 105$)	1		0.0001	1		0.0001
Yes ($n = 10$)	9.32	3.07–28.3		5.08	2.1–12.2	
Neoadjuvant therapy						
Not done ($n = 64$)	1		0.239	1		0.84
Done ($n = 51$)	1.73	0.69–4.32		0.93	0.46–1.87	
Adjuvant therapy						
Not done ($n = 33$)	1		0.006	1		0.1
Done ($n = 82$)	0.37	0.18–0.76		0.64	0.37–1.1	

[a] Others included large cell carcinoma in three patients, sarcomatoid carcinoma in three patients, and adenosquamous cell carcinoma in two patients.
[b] Pathologic complete response after neoadjuvant therapy.
HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

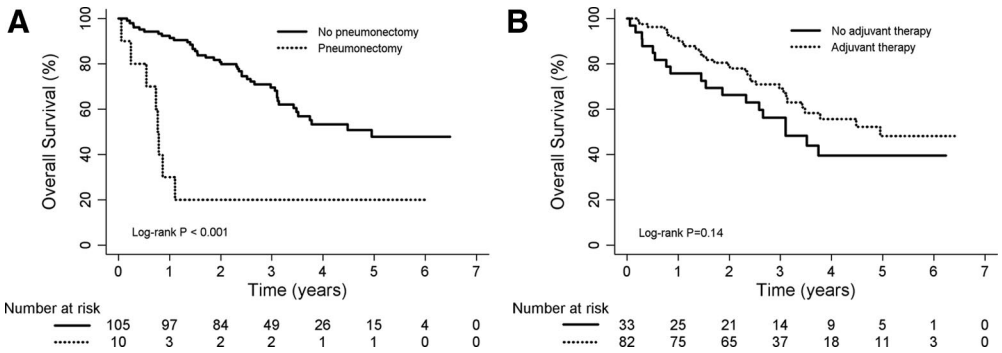

FIGURE 3. *A,* Overall survival according to the extent of resection in patients who had pathologic N2 disease. *B,* Overall survival according to adjuvant therapy in patients who had pathologic N2 disease.

mediastinoscopy N2 group with the surgery N2 group can be attributed to the benefit of neoadjuvant therapy. Unfortunately, however, it is nearly impossible to verify whether there is truly a difference in the extent of mediastinal nodal involvement or the probability of distant metastasis between the two groups. Because the mediastinoscopy N2 group already went through neoadjuvant therapy and their mediastinal nodes responded to the therapy, it would be inappropriate to simply compare the findings obtained at mediastinal nodal dissection between the two groups. Therefore, only a randomized controlled trial where patients with PET/CT-negative but mediastinoscopy-positive N2 disease would be randomized to neoadjuvant therapy could really answer the question about the role of neoadjuvant therapy in this subset of patients.

As clearance of mediastinal node involvement is a major prognostic factor, it is important to predict and identify patients who experienced pathologic downstaging after neoadjuvant therapy. Nevertheless, whether restaging tests accurately predict responders and which restaging test is best are

still unclear.[13] Although, the most commonly used method of restaging is the radiographic response by CT or PET/CT, they have relatively high false-negative and false-positive rates. Remediastinoscopy could be reliable in terms of restaging techniques, but it needs experienced surgeons to be feasible, especially for patients who underwent neoadjuvant chemoradiation and initial mediastinoscopy. Endobronchial ultrasound or endoscopic ultrasound tests are gradually becoming more widely available, and these modalities seem to be promising for restaging in recent studies. Although we cannot definitely answer what modality would be the best in terms of restaging, it is still important to perform surgery in selected patients who undergo downstaging after neoadjuvant treatment.

In our series, the locoregional failure rate was 11% higher in the surgery N2 group than in the mediastinoscopy N2 group. This may be related to the difference in tumor characteristics between the two groups. Although not statistically significant, more patients had squamous cell carcinoma in the surgery N2 group than in the mediastinoscopy N2 group, which implies that patients of the surgery N2 group were more likely to have centrally extensive tumor than those of the mediastinoscopy N2 group. This is also related to the fact that patients from the surgery N2 group more frequently received pneumonectomy, sleeve lobectomy, or bilobectomy than the mediastinoscopy N2 group, although not statistically significant. We suspect that these findings can explain the reason why the locoregional failure rate was rather higher in the surgery N2 group than in the mediastinoscopy N2 group.

Our study has several limitations. First, this is a retrospective study which has many intrinsic drawbacks. Second, despite the fact that all the patients were N2 negative on PET/CT, the study population consists of a heterogeneous group of patients. Although statistically insignificant, the methods of adjuvant treatment were not evenly distributed in the study population. Also, the perioperative management might have been changed during the study period. There was significant difference in pathologic T and N stages between the mediastinoscopy N2 group and surgery N2 group, even though it is attributed to the effect of neoadjuvant therapy in the mediastinoscopy N2 group. These limitations can be overcome by prospective randomized trial. Third, we combined the patients with N0 and N1 disease into the same group, which might have influenced our results.

In conclusion, we retrospectively reviewed the outcomes of patients with NSCLC who were N2 negative on PET/CT. We compared the survival between patients who underwent neoadjuvant therapy due to a positive mediastinoscopy and those who did not receive neoadjuvant therapy based on a negative mediastinoscopy and were found to have unexpected N2 disease at surgery. We found that there was no significant difference in the OS and DFS between the two groups. If two groups represent the same population, our results suggest that there might be no survival benefit of neoadjuvant therapy in this subset of patients with "PET/CT-negative" N2 disease. Nevertheless, if two groups represent different patient populations, comparable survivals between two groups can be attributed to the benefit of neoadjuvant therapy. Therefore, our results should be confirmed by randomized prospective studies.

REFERENCES

1. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;348:2500–2507.
2. Shim SS, Lee KS, Kim BT, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. *Radiology* 2005;236:1011–1019.
3. Gupta NC, Tamim WJ, Graeber GG, et al. Mediastinal lymph node sampling following positron emission tomography with fluorodeoxyglucose imaging in lung cancer staging. *Chest* 2001;120:521–527.
4. Kim BT, Lee KS, Shim SS, et al. Stage T1 non-small cell lung cancer: preoperative mediastinal nodal staging with integrated FDG PET/CT—a prospective study. *Radiology* 2006;241:501–509.
5. Vansteenkiste JF, De Leyn PR, Deneffe GJ, et al. Clinical prognostic factors in surgical treated stage IIIA-N2 non-small cell lung cancer: analysis of the literature. *Lung Cancer* 1998;19:3–13.
6. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol* 2000;18:2981–2989.
7. Ichinose Y, Kato H, Koike T, et al. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. *J Thorac Cardiovasc Surg* 2001;122:803–808.
8. Martini N, Flehinger BJ, Zaman MB, et al. Results of resection in non-oat cell carcinoma of the lung with mediastinal lymph node metastases. *Ann Surg* 1983;198:386–397.
9. De Leyn P, Schoonooghe P, Deneffe G, et al. Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease). *Eur J Cardiothorac Surg* 1996;10:649–654.
10. Inoue M, Sawabata N, Takeda S, et al. Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe. *J Thorac Cardiovasc Surg* 2004;127:1100–1106.
11. Keller SM, Vangel MG, Wagner H, et al. Prolonged survival in patients with resected non-small cell lung cancer and single-level N2 disease. *J Thorac Cardiovasc Surg* 2004;128:130–137.
12. Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. *Ann Thorac Surg* 2008;86:362–366; discussion 366–367.
13. de Cabanyes Candela S, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. *J Thorac Oncol* 2010;5:389–398.