**Original
Article**

Extent of Lung Resection in Non-small Lung Cancer with Interlobar Lymph Node Involvement

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Background: Optimal resection type for non-small cell lung cancer (NSCLC) with interlobar lymph node involvement (ILNI) has seldom been reported. To completely resect a NSCLC with ILNI, some surgeons believe that a pneumonectomy is needed.

Methods: We retrospectively studied 151 patients (147 men, 4 women; mean age 58 ± 8 years, range 34–79) with non-small lung cancer without mediastinal or hilar lymph node metastasis who underwent an anatomic lung resection with systematic lymph node dissection between January 1995 and November 2006. All patients had involvement of the surgical-pathologic interlobar (#11) lymph node: 8 patients had a T1 tumor; 95, T2; 39, T3; and 9, T4. We evaluated the effect of resection type (pneumonectomy in 90 patients versus lobectomy in 61) on their prognosis by univariate and multivariate analyses.

Results: The 5-year survival rate of patients was 61% for the lobectomy and 35% for the pneumonectomy ($p = 0.04$). We did not find statistically significant differences in sex, median age, distributions of tumor site, histology and differentiation, complete resection rate, N1 involvement status, morbidity and mortality. Patients who underwent the pneumonectomy had larger tumors and more T3 tumors. The T status, multiple levels N1 involvement and histology did not affect survival in the univariate analysis. Multivariate analysis revealed resection type as a significant prognostic factor.

Conclusions: Pneumonectomy was not necessary in patients with NSCLC and interlobar lymph node involvement that we had discovered intraoperatively.

Key words: non-small cell lung cancer, interlobar lymph node, sump node, pneumonectomy

Introduction

The lymph node stations of the lung have been defined according to the structure of the tracheobronchial tree as

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“main bronchial” (No. 10), “interlobar” (No. 11), “lobar bronchial” (No. 12), “segmental bronchial” (No. 13), and “intrapulmonary” (No. 14).^{1,2} Interlobar nodes have been further divided into No. 11s (superior, between the upper and intermediate bronchi, named “right lymphatic sump” by Borrie) and No. 11i (inferior, between the middle and lower bronchi) on the right side. In the left lung, the most common location of interlobar lymph nodes is at the angle of the left upper lobe bronchus and the lower lobe bronchus (i.e., No. 11) and named “left lymphatic sump.”^{1,3} For patients with operable non-small cell lung cancer (NSCLC), involvement of interlobar “sump” nodes can affect the choice of the lung resection type. It is hard to decide whether one should perform pneumonectomy or just do a sleeve resection, bilobectomy and lobectomy in

Table 1 N1 lymph node involvement in patients with resected non-small cell lung cancer

Lymph Node Station No.	n	%
10 pos, 11, 12, 13, 14 pos/neg	38	10.1
10 neg, 11 pos, 12, 13, 14 pos/neg (Study group)	151	40.2
11 pos, 12, 13, 14 neg	76	50.3
11 pos, 12, 13, 14 pos/neg	75	49.7
11 neg, 12 or 13 or 14 pos	187	49.7
Total	376	100

pos, positive; neg, negative

that case. It depends on the philosophy for interlobar N1 disease. Involvement of these nodes by the tumor implies that tumor cells have entered the lymphatic channels of the adjacent lobe, and consideration should be given to performing a pneumonectomy to obtain a complete resection.^{4,5)} However, there is no any evidence indicating a lower recurrence and higher survival rates in patients who had a pneumonectomy versus those who had a lobectomy.

To determine the impact of pneumonectomy on the survival of patients with NSCLC and interlobar sump nodes involvement, we retrospectively reviewed the records of patients who underwent a lobectomy or pneumonectomy.

Patients and Methods

Between January 1995 and November 2006, our clinical database was searched to find patients with NSCLC who had undergone a lung resection and systematic lymph node dissection. Exclusions were (1) partial resection or segmentectomy, (2) multiple lung tumors; (3) low-grade malignancy, such as bronchial carcinoid tumor; (4) metastatic carcinoma (5) neoadjuvant therapy and (6) lung cancer in the superior sulcus. After applying the exclusion, we found 376 consecutive patients who were pathologically staged as N1 (**Table 1**), and of these, 151 had interlobar sump node metastasis and no hilar lymph node metastasis. The records of 151 patients were studied retrospectively, which did not require institutional review board approval. The database analysis was reviewed and approved by the Scientific Study Committee of Yedikule Teaching Hospital for Chest Diseases and Thoracic Surgery.

Preoperative routine blood tests included hemoglobin, alkaline phosphatase and serum calcium estimations. All

patients underwent posteroanterior and lateral chest radiographs, bronchoscopy, and basic pulmonary function tests with or without DLCO and V/Q scan, and blood gases analysis. Computerized tomography (CT) of the thorax, abdomen (or abdominal ultrasonography), and cranium (or cranial magnetic resonance imaging). All patients had bone scintigraphy or positron emission scans for pretreatment staging. For presurgical mediastinal staging, surgeons sampled stations #2, #4 (both left and right), and #7 in the recent mapping system²⁾ using cervical mediastinoscopy in patients who did not have cT1N0 squamous cell carcinoma. The mediastinal exploration was supplemented by a left anterior mediastinotomy in patients whose tumor lay in the left upper lobe or left main bronchus and in patients with enlarged anterior mediastinal and/or aorticopulmonary lymph nodes (stations #5 and #6) that were visible in the CT. We performed a thoracotomy in patients with no preoperative, mediastinal lymph node metastasis. Appropriate lung resection and systematic lymph node dissection were carried out routinely. After anatomical observation of tumor involvement, the surgeons decided on the type of resection. Interlobar lymph node involvement is not usually included in the indication for an extension of the resection unless the node had invaded the bronchus. To avoid a pneumonectomy, surgeons dissected the involved lymph node from the bronchus, if it was not invaded. Bronchial sleeve lobectomy or standard lobectomy with bronchus plasty procedures were preferred if the node invaded the proximal of the lobar bronchus and standard lobectomy with vascular plasty procedures were done if the node invaded the interlobar pulmonary artery. If the extent of the tumor invasion necessitated it, surgeons performed pneumonectomy, to obtain an anatomically complete resection. The mean number of lymph nodes dissected and examined was 16 per patient, for both N1

and N2 regions. For lymph nodes in N1 regions, the mean number of lymph nodes removed was 8. The specimens (lungs and lymph nodes) were examined histopathologically. All of the histologic slides were evaluated according to the World Health organization classification⁶⁾ and grading for NSCLC. Special attention was paid to N1 and N2 stations according to the uniform lymph node mapping.²⁾ Using information obtained at thoracotomy and supplemented by pathological examination, surgeons staged all patients with the uniform staging protocol in the construction of the final surgical-pathologic stage (pTNM).⁷⁾ In this protocol, complete resection (R0) was defined as “the removal of all detectable disease by the surgeon and histologic confirmation of tumor-free resection margins.” Microscopically incomplete resection (R1) was the assignment to patients who underwent a complete gross resection at thoracotomy and had positive margins in the final pathologic review. Gross residual disease after an attempted resection was R2.

All patients who underwent an incomplete resection later took adjuvant chemotherapy or radiotherapy or both. Those who underwent a complete resection did not usually have adjuvant therapy.

All the patients were followed-up by routine visits, phone or mail. Mean follow-up time was 23 ± 21.8 (6–96) months.

Statistical Analyses

Analyses were performed using SPSS statistical software (version 10.01, SPSS Inc., Chicago, IL). We evaluated the demographic, surgical and pathologic variables of all patients and compared the types of lung resections versus distributions of these variables with the χ^2 and Student's *t* tests. Patient survival was expressed by actuarial analysis according to the Kaplan-Meier method, using time zero as the date of thoracotomy and death as the end point. Patients who had died from operative procedures were excluded from the survival analysis. Prognostic factors were evaluated in the completely resected patients. Prognostic predictors [type of the resection, sex, age, and site, size, histology and differentiation of the tumor, pT classification, N1 involvement status (single or multiple stations involvement) and presence of complication] were studied by univariate (log-rank) analyses. Variables having a *P* value less than 0.2 were included in the multivariate analysis. Cox proportional hazard regression model was used for the multivariate analysis. Results were considered significant if the *p* value was less than 0.05.

Results

There were 147 male and 4 female patients with NSCLC staged as pN1 and having interlobar lymph node involvement. The median age was 58 years (range, 34 to 79 years). Pneumonectomy was performed in 90 (59.6%) and lobectomy in 61 (40.4%, standard lobectomy in 36, bilobectomy in 13, and sleeve lobectomy in 12) patients. Eight patients (5.3%) died postoperatively (in-hospital or within 30 day out-hospital). Postoperative mortality rates were calculated as 6.7% (*n* = 6) and 3.3% (*n* = 2) for pneumonectomy and lobectomy, respectively. Postoperative complication occurred in 21.9% (*n* = 33) of the patients.

The clinical characteristics of these 151 patients and their tumors according to resection type which had been performed are presented in **Table 2**. There was no significant difference between lobectomy and pneumonectomy group except larger mean tumor size (*p* < 0.001) and higher rate of T3 tumors (*p* < 0.001) in pneumonectomy group.

Five-year survival rates of the patients according to some clinicopathologic parameters are shown in **Table 3**. There was no statistically significant difference in five year survival rates between male and female patients, the right and left-sided, upper and lower lobes located tumors, single and multiple levels N1 involvement and presence or absence of complications. Histology and differentiation of the tumors did not influence the survival. T stage which had not homogeneously distributed between lobectomy and pneumonectomy patients did not influence the survival in resected NSCLC patients with interlobar lymph node involvement (*p* = 0.22). Tumors were classified in four groups according to their sizes as tumors smaller than 30 mm, tumors in size between 31 and 50 mm, 51 and 70 mm and tumors larger than 70 mm. Univariate analysis revealed that, the tumor size has not statistical significant effect on the survival. Only the resection type affected the survival. Five year survival rate was 61% for lobectomy whereas 35% for pneumonectomy patients (*p* = 0.04, **Fig. 1**). The survival of patients who underwent a lobectomy was not statistically different from that of patients who underwent a bilobectomy (*p* = 0.58) but was significantly better than remaining patients who had been performed a pneumonectomy (*p* = 0.02).

When only the patients with T1, T2 and T3 tumor (excluding T4) were analyzed, lobectomy also resulted significantly better survival compared with pneumonectomy (66% versus 43% five year survival rates; *p* = 0.045).

Table 2 Characteristics of patients with non-small cell lung cancer and tumor staged as pN1 due to interlobar lymph node involvement and characteristics of their tumors

	All patients (n = 151)	Lobectomy/bilobectomy/ sleeve lobectomy (n = 61)	Pneumonectomy (n = 90)	p value (lobectomy vs pneumonectomy)
Age [mean $\pm$ SD (range)]	58 $\pm$ 8 (34–79)	59.1 $\pm$ 8 (39–89)	57.7 $\pm$ 9 (34–75)	0.3
Sex				0.3
Male	147	58	89	
Female	4	3	1	
Site				0.14
Right	78 (51.7)	36 (59 %)	42 (46.7 %)	
Left	73 (48.3)	25 (41 %)	48 (53.3 %)	
Tumor size [mean $\pm$ SD]	5 $\pm$ 2.4 cm	4.7 $\pm$ 2 cm	6.2 $\pm$ 2.4 cm	<0.001
pT classification				<0.001
T1	8 (5.2 %)	8 (13.1 %)	0	
T2	95 (62.9 %)	45 (73.8 %)	50 (55.5%)	
T3	39 (25.8 %)	7 (11.5 %)	32 (35.6 %)	
T4	9 (6 %)	1 (1.6 %)	8 (8.9 %)	
Histology				0.69
SCC	110 (72.8 %)	43 (70.5 %)	67 (74.4 %)	
Adenocarcinoma	25 (16.6 %)	12 (19.7 %)	13 (14.4 %)	
Others	16 (10.6 %)	6 (9.8 %)	10 (11.1%)	
Tumor differentiation				0.73
Poor	57 (37.7 %)	21 (34.4 %)	36 (40 %)	
Moderate	88 (58.3%)	37 (60.7 %)	51 (56.7 %)	
Well	6 (4%)	3 (4.9 %)	3 (3.3 %)	
Resection margins				0.17
R0	143 (94.7%)	59 (96.7 %)	82 (91.1 %)	
R1	8 (5.3 %)	2 (3.3 %)	8 (8.9 %)	
Number of involved N1 node				0.57
Single level (#11)	76 (50.3 %)	29 (47.5 %)	47 (52.2 %)	
Multiple level	75 (49.7 %)	32 (52.5 %)	43 (47.8 %)	
Morbidity	33 (21.9 %)	9 (14.8 %)	24 (26.7 %)	0.08
Mortality	8 (5.3 %)	2 (3.3 %)	6 (6.7 %)	0.47

SD, standard deviation; SCC, squamous cell carcinoma

When only the patients with T1 and T2 NSCLC were analyzed, lobectomy showed better survival compared with pneumonectomy (64% versus 52%; $p = 0.27$) but the difference did not reached to statistically significance.

By multivariate analysis, we found that pneumonectomy was an independent prognostic factor, though a weak one, for patients with resected NSCLC and interlobar lymph node involvement.

Discussion

The hypothesis behind our study was that, since interlobar lymph nodes are located in intersections in the way through the lymphatic sump, we expected there to be a risk of tumoral cells entering lymphatic channels of the adjacent lobe. Therefore, we wondered if interlobar lymph node involvement necessitated a pneumonectomy. We found that, lobectomy, not pneumonectomy, provided

improved survival in NSCLC patients with interlobar lymph node involvement (though it was statistically borderline, $p = 0.05$, multivariate analysis). The improved survival of the lobectomy group could not have been caused by the postoperative mortality rate in pneumonectomy group since we excluded patients who had died due to operative reasons. The pneumonectomy group included more patients with T3 and T4 tumors than did the lobectomy group; however, T status did not affect survival though the survival rate seemed to be better when patients with T1 and T2 tumors were included in the analysis. Patients who underwent pneumonectomy had significantly larger tumors. This finding was expected since the decision for resection type was made according to the anatomical involvement of the tumor. However, we did not find tumor size to be a significant prognostic factor in the univariate analysis, though multivariate analysis revealed the independent role of interlobar lymph node

Table 3 Evaluation of prognostic factors by univariate and multivariate statistical analyses in patients with pathologic pN1 (interlobar lymph node involvement) non-small cell carcinoma of the lung

	Median survival	5-year survival rate (%)	Univariate <i>p</i> value	Multivariate <i>p</i> value	Hazard ratio (95 % CI)
Sex			0.78	NIA	
Site					
Right	30	36	0.08	0.07	
Left	-	55			
Tumor size					
<30 mm (n = 25)		71	0.33	NIA	
31–50 mm (n = 58)		54			
51–70 mm (n = 34)		56			
>70 mm (n = 34)		34			
pT classification			0.20	0.18	
T1 (n = 12)		74			
T2 (n = 91)	63	55			
T3 (n = 39)	36	21			
T4 (n = 9)	26	-			
Histology			0.35	NIA	
SCC	-	61			
Non-SCC	30	36			
Tumor differentiation			0.31	NIA	
Poor	36	42			
Moderate	60	47			
Well					
Surgical procedure			0.04	0.05	
Lobectomy	-	61			
Pneumonectomy	32	35			2.0 (1.0–4.1)
Resection margins			0.48	NIA	
R0	63	51			
R1	26	-			
N1 involvement status			0.71	NIA	
Single station	-	58			
Multiple level	60	34			
Morbidity			0.76	NIA	
Present	28				
Absent	63	47			

CI, confidence interval; SCC, squamous cell carcinoma; NIA, not included in analysis

Fig. 1 Survival curves of pN1 (interlobar lymph node involvement) of patients with NSCLC who underwent either lobectomy or pneumonectomy. NSCLC, non-small cell lung cancer

involvement. The lobectomy seems sufficient for the tumor resection in NSCLC patients with NSCLC and interlobar lymph node involvement.

No studies have focused on the impact of pulmonary resection type in patients with NSCLC and interlobar lymph node metastasis. However, for patients with N1 involvement, there are a number of studies that have reported a favorable or at least not worse survival for the lobectomy than for the pneumonectomy.⁸⁻¹⁰ Similar results had been reported in the comparison between pneumonectomy and sleeve lobectomy.¹¹⁻¹⁵ Subgroup analysis had been done in only one study: Luzzi et al. reported that no significant survival difference between pneumonectomy and lobectomy for patients with N1 stage NSCLC and level 11 lymph node involvement.¹⁶ On the other hand, a pneumonectomy, especially a right one, includes a higher occurrence of postoperative complications compared to the lobectomy: poorer quality of life, cardiopulmonary dysfunction, and long-term complications.¹⁷⁻²¹ So we think that, lobectomy could be the surgery of choice when interlobar lymph node is involved (including the involvement of more distal lymph nodes). Maximum efforts should be spent to avoid pneumonectomy. In the retrospective analysis reported here, 8 of 90 patients who underwent pneumonectomy could have had a lobectomy instead.

In conclusion, the survival of patients with interlobar lymph node involvement undergoing pneumonectomy is significantly shorter than of those undergoing lobectomy or bilobectomy. In patients to test positive for an interlobar lymph node, we recommend a lobectomy over pneumonectomy for oncologically complete therapy, when the resection area is small and an anatomically complete resection is possible.

However, the limitations of the present study should also be addressed. We were unable to analyze recurrence pattern in pneumonectomy and lobectomy groups. It was also not possible to collect adjuvant therapy information in all patients. Finally, our study was not prospectively designed because the pneumonectomy group comprised patients with a tumor type that necessitated the pneumonectomy because of anatomic reasons. So, new studies should be planned to clarify the optimum resection type in patients with NSCLC and interlobar lymph node involvement.

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