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Long Term Survival of Patients with Unsuspected N2 Disease in Non-Small Cell Lung Cancer

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Background: The aim of this study was to determine the survival rate of patients with non-small cell lung cancer (NSCLC) who were preoperatively diagnosed with a negative N2 lymph node, but postoperatively confirmed as a positive N2 node based on a pathological evaluation. ***Materials and Methods:*** The hospital records of 248 patients from 1994 to 2009 with resected primary NSCLC who were preoperatively diagnosed with negative N2 lymph node, were retrospectively reviewed. Of these, after surgery, there were 148 (59.7%) patients with pathological N0, 54 (21.8%) with pathological N1 and 46 (18.5%) with pathological N2. ***Results:*** The median follow-up period was 24 months (range, 1 to 132 months). The 5-year disease free survival rates were 60% in pN0, 44% in pN1, and 29% in pN2. The 5-year overall survival rates were 63.1% in pN0, 51.9% in pN1, and 33.5% in pN2. There were no statistically significant differences between pN1 and pN2 (p=0.326 and p=0.106, respectively). Thirty-three (71.7%) of the 46 pN2 patients had single-zone metastasis, and 13 patients (28.3%) had multiple-zone metastases over the two nodal zone metastasis. There were no statistical differences in the 5-year disease free survival rate and the 5-year overall survival rates between the two groups. ***Conclusion:*** The 5-year disease free survival and the overall survival rate of the patients with unsuspected N2 disease were statistically similar with that of the patients with pathological N1 disease. There was no statistically significant difference between the patients with a single-zone metastasis and a multiple zone metastasis.

Key words: 1. Carcinoma, non-small-cell lung
2. Lymph nodes
3. Neoplasm staging

INTRODUCTION

Mediastinal nodal involvement is generally considered to be one of the most important prognostic factors in patients with non-small cell lung cancer (NSCLC). In patients with N2 disease, identified preoperatively, pulmonary resection is not recommended by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [1]. However, the optimal treatment approach for clinical stage IIIA has been controversial, because N2 disease is defined just as the presence of metastasis in the ipsilateral mediastinal lymph node by the 7th American Joint Committee on Cancer tumor-node-metastasis (AJCC/TNM) staging for lung cancer [2]. Stage IIIA NSCLC, especially N2 disease, shows a broad spectrum of the disease. Several published reports have suggested that there were significant variabilities of the long

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term outcomes, according to the heterogeneity of N2 disease, such as a single N2 disease versus a multiple N2 disease, skip metastasis (negative N1 and positive N2 disease), the number of positive N2 disease, and unsuspected, occult or incidental N2 disease [3-11].

Recently, the nodal zone concept was proposed as a new descriptor of the intrathoracic lymph node by International Association for the Study of Lung Cancer (IASLC) [12]. The lymph node maps, which have been widely used for several decades, were classified by Mountain and Dressler [13], Naruke [14], and Naruke et al. [15]. However, there are several discrepancies in the definition of the nomenclature between the two classifications. The nodal zone concept was proposed as able to achieve uniformity, an accurate assessment of lymph node involvement, and to promote future analyses of a planned prospective international database.

The purpose of this study is to investigate the long term outcomes for patients with unsuspected N2 (negative N2 disease on the preoperative diagnosis, but positive N2 disease on the postoperative pathologic diagnosis) disease, and to identify the effects of the 'nodal zone' relationship to the long-term outcomes of unsuspected N2 disease.

MATERIALS AND METHODS

The hospital records of 485 patients with primary NSCLC who underwent pulmonary resection and mediastinal lymphadenectomy in Keimyung University Dongsan Medical Center from May 1994 to December 2009, were retrospectively reviewed. The preoperative work-up included the following: standard chest posteroanterior radiography, chest computed tomography (CT), fiberoptic bronchoscopy, whole body bone scan, and brain magnetic resonance imaging (MRI). Positron emission tomography-CT (PET-CT) scans have been part of the preoperative work-up at Keimyung University Dongsan Medical Center since March 2007. Preoperative mediastinoscopic biopsy was also performed in selected patients. In this study, we included any patients 1) who had primary NSCLC, 2) who underwent anatomical resection, and 3) who were negative for malignancy of a mediastinal lymph node by mediastinoscopic biopsy among selected patients. We excluded any patients 1) who had mediastinal lymph nodes, which were over 1 cm of short axis diameter on CT, 2) who had mediastinal lymph nodes, which showed a maximum standardized uptake value of over 2.5 on PET-CT scan, 3) who had metastasis of mediastinal lymph node confirmed by preoperative mediastinoscopic biopsy, 4) who had received neoadjuvant chemotherapy or radiotherapy, 5) who had multiple primary lung cancer, 6) who were diagnosed with T4 staging by postoperative pathologically evaluation, or 7) who underwent minor resection or incomplete pulmonary resection, or 8) who had died within 30 days due to postoperative morbidity. We retrospectively reviewed the hospital records of 248 patients who met the inclusion and exclusion criteria.

Surgery was performed using posterolateral thoracotomy. Anatomical resection and complete mediastinal lymph node dissection or mediastinal lymph node sampling were performed in the enrolled patients. The lymph node description used in this study was 'The Lymph Node Classification of Mountain and Dressler' [13]. Involved mediastinal lymph nodes (N2) were reclassified with 'four nodal zone,' which was recently proposed by the IASLC [12]. The 1 to 4 station of the mediastinal lymph node, according to 'The Lymph Node Classification of Mountain and Dressler,' were united with the upper zone, the 5 and 6 station with the aortopulmonary zone, the 7 station with the subcarinal zone, and the 8 and 9 station with the lower zone. All of the patients were surgically staged, according to the 7th AJCC/TNM staging classification of lung cancer [2].

The patients were followed up every 3 months for the first 2 years after surgery, and every 6 months thereafter. The chest radiographs were obtained during every follow-up, and CT was obtained every 6 months for the first two years, and annually thereafter. Other specific studies, such as a PET-CT scan, brain MRI, a whole body bone scan, or bronchoscopy were performed for selected patients during the follow-up period.

All statistical analyses were carried out with the statistical software SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as the mean and standard deviation, and the discrete data were presented as a number and percentage. The association between the data was analyzed using the independent t-test or the Mann-Whitney U-test for continuous variables, and the Pearson's χ^2 test or Fisher's exact test was used for the discrete variables. The disease free survival was defined as the period of staying free from

Table 1. Characteristics of the study population

Variable		Value
Age (yr)		62.3±9.4
Gender	Male/female	175 (70.6)/73 (29.4)
Type of surgery	Lobectomy	209 (84.3)
	Bilobectomy	14 (5.6)
	Pneumonectomy	25 (10.1)
Histology	Squamous cell carcinoma	117 (47.2)
	Adenocarcinoma	96 (38.7)
	Others	35 (14.1)
Location of tumor	Right upper lobe	62 (25.0)
	Right middle lobe	13 (5.2)
	Right lower lobe	72 (29.0)
	Left upper lobe	56 (22.6)
	Left lower lobe	45 (18.1)
Pathologic T stage	T1a	37 (14.9)
	T1b	55 (22.2)
	T2a	102 (41.1)
	T2b	22 (8.9)
	T3	32 (12.9)
Pathologic N stage	N0	148 (59.7)
	N1	54 (21.8)
	N2	46 (18.5)
Pathologic TNM stage	IA	62 (25.0)
	IB	59 (23.8)
	IIA	50 (20.2)
	IIB	22 (8.9)
	IIIA	55 (22.2)

Values are presented as mean±standard deviation or number (%). TNM, tumor-node-metastasis.

Table 2. Location of the nodal zone according to the tumor location in the patients with a single-zone metastasis

Tumor location (patients)	No. of patients			
	U	AP	Sub	L
Right upper lobe (9)	7	0	2	0
Right middle lobe (3)	1	0	2	0
Right lower lobe (6)	1	0	5	0
Left upper lobe (8)	1	6	0	1
Left lower lobe (7)	0	0	4	3

U, upper zone; AP, aortopulmonary zone; Sub, subcarinal zone; L, lower zone.

Table 3. Location of the nodal zone according to the tumor location in the patients with a multiple-zone metastasis

Tumor location (patients)	Location of nodal zone	No. of patients
Right upper lobe (1)	U and Sub	1
Right middle lobe (2)	U and Sub	1
	Sub and L	1
Right lower lobe (4)	U and Sub	2
	U and L	1
	Sub and L	1
Left upper lobe (4)	U and AP	1
	AP and L	1
	AP, Sub, and L	1
	Sub and L	1
Left lower lobe (2)	Sub and L	2

U, upper zone; Sub, subcarinal zone; AP, aortopulmonary zone; L, lower zone.

disease after surgery. The confirmed loco-regional recurrences, distant metastases, and deaths were used as the specific events for disease free survival. The overall survival was defined as the duration from the operation to death from any cause. The survival rates were derived using the Kaplan-Meier method, and the differences between the subgroups were assessed using the log-rank test. The multivariate analysis of the survival influence was performed using a Cox proportional hazards model. A statistically significant difference was defined as a p-value of less than two-sided 0.05. The institutional review board of the University of Keimyung in South Korea approved this study.

RESULTS

There were 248 patients who met the inclusion and exclusion criteria of this study. There were 175 males (70.6%) and 73 females (29.4%), with a mean age of 62.3±9.4 years. The median follow-up period was 24 months (range, 1 to 132 months). Lobectomy was performed in 209 patients (84.3%), bilobectomy in 14 (5.6%), and pneumonectomy in 25 (10.1%). The patients' characteristics are described in Table 1. The most common histology was squamous cell carcinoma (117 patients, 47.2%). There were 96 patients (38.7%) with adenocarcinoma, and 35 other patients (14.1%) presented with different histologies.

A total of 148 (59.7%) patients presented with pathological N0 (pN0) disease, 54 (21.8%) with pathological N1 (pN1), and 46 (18.5%) with pathological N2 (pN2), after surgery. Thirty-three (71.7%) of the 46 pN2 patients had single-zone metastasis, and 13 patients (28.3%) had multiple-zone metastases over two nodal zone metastasis. The patterns of meta-

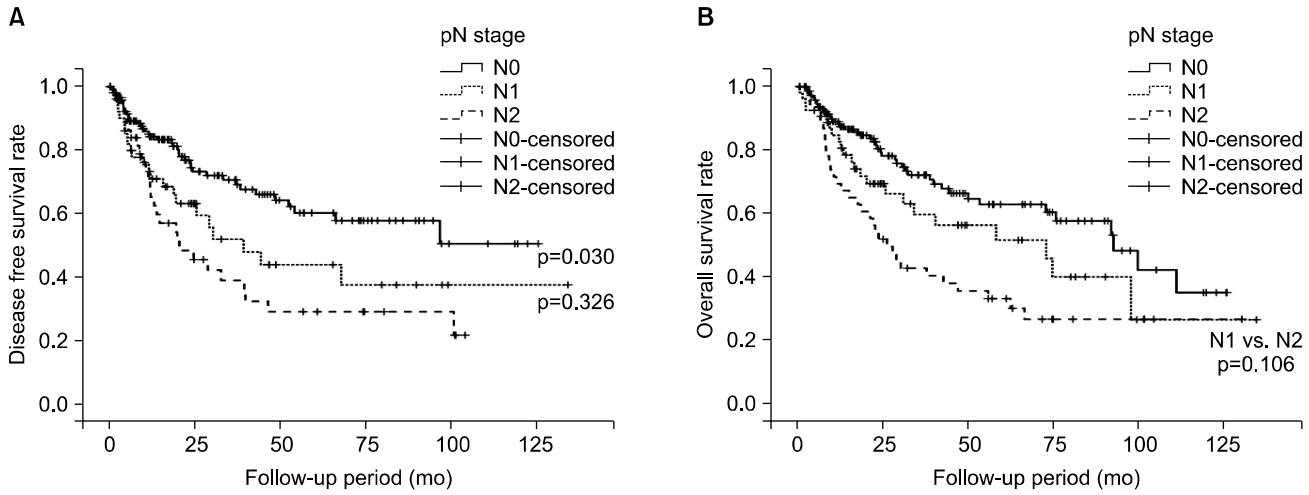

Fig. 1. (A) The disease free survival rate and (B) overall survival rate among the patients with N0, N1, and N2 disease. pN, pathologic node.

stasis of N2 disease are shown in Tables 2, 3. There were 109 patients (43.9%) that received adjuvant therapy, according to the local protocol for NSCLC. Adjuvant chemotherapy was administered to 66 patients (26.6%), radiotherapy to 16 (6.4%), and concurrent chemo-radiotherapy to 27 patients (10.8%).

The 5-year disease free survival rates were 60.4% in the pN0 group, 44.1% in the pN1 group, and 29.4% in the pN2 group. The disease free survival rate was significantly better in the pN0 group than in that of the pN1 or pN2 group (p=0.030 and p=0.000, respectively). However, there was no statistically significant differences between the pN1 and pN2 groups (p=0.326). The 5-year overall survival rates were 63.1% in the pN0 group, 51.9% in the pN1 group, and 33.5% in the pN2 group. The overall survival was significantly better in the pN0 group than in that of the pN2 group ($p < 0.000$). However, there was no statistically significant differences between the pN0 and pN1 group (p=0.088), and between the pN1 and pN2 groups (p=0.106) (Fig. 1).

The 5-year disease free survival rates were 29.5% in the single-zone metastasis group and 28.0% in the multiple-zone metastasis group (p=0.635). The 5-year overall survival rates were 35.1% in the single-zone metastasis group and 30.8% in the multiple-zone metastasis group (p=0.857). There were no statistical differences between the two groups.

There were recurrences in 91 patients (36.7%). Of these, 46 patients (18.5%) had loco-regional recurrence and 45 patients (18.1%) had distant recurrence. Loco-regional recurrence was most common in the postoperative pN1 group (20 [37.0%] of the 54 patients), and distant recurrence was most common in postoperative pN2 group (22 [47.8%] of the 46 patients).

The significant risk factors associated with disease free survival and overall survival based on the univariate analysis were pathologic N staging (p=0.001) in disease free survival and pathologic T staging (p=0.001) and pathologic N staging (p=0.001) in the overall survival. Table 4 shows that the pathologic N stage was the independent predictor in disease free survival, and pathologic T stage and pathologic N stage were the independent predictors in the overall survival on multivariate analyses.

DISCUSSION

Surgery is recommended for patients with early stage NSCLC (stage I and II) or surgery with adjuvant chemotherapy or radiotherapy; it is widely considered to result in a better chance for a patient's long-term survival. However, the role of surgery for N2 disease is controversial. Most physicians agree that patients with mediastinal lymph node metastasis have a poor long-term outcome, and surgery should not

Table 4. Multivariate analyses for disease free survival and overall survival with a Cox proportional hazards model

Variable	Disease free survival		Overall survival	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Age (<60 vs. ≥60)	0.447	1.185 (0.765-1.836)	0.153	1.367 (0.890-2.100)
Gender (male/female)	0.709	1.093 (0.685-1.745)	0.594	1.133 (0.717-1.790)
Operation (L/P)	0.840	0.966 (0.691-1.351)	0.119	1.259 (0.942-1.684)
Location (U/ML)	0.120	1.410 (0.915-2.172)	0.058	1.514 (0.987-2.322)
Side (left/right)	0.689	1.094 (0.705-1.695)	0.077	0.684 (0.449-1.042)
Pathologic pT stage	0.112		0.003[a)]	
pT1 vs. pT2	0.532	0.789 (0.375-1.660)	0.002[a)]	0.356 (0.186-0.682)
pT2 vs. pT3	0.468	1.296 (0.643-2.615)	0.251	0.714 (0.401-1.270)
Pathologic pN stage	0.003[a)]		0.031[a)]	
pN0 vs. pN1	0.001[a)]	0.407 (0.241-0.687)	0.008[a)]	0.500 (0.299-0.838)
pN1 vs. pN2	0.251	0.717 (0.406-1.266)	0.148	0.665 (0.383-1.156)

HR, hazard ratio; CI, confidence interval; L, lobectomy; P, pneumonectomy; U, upper lobe; ML, middle and lower lobe; pT, pathological tumor; pN, pathological node.
[a)]p-value≤0.05.

be performed as an initial treatment.

The N stage is defined based only on the presence of involved lymph nodes according to the AJCC/TNM staging system. However, the N stage has various heterogeneous ranges according to minimal N2 and bulky N2, single N2 and multiple N2, and the number of involved lymph nodes. Although ipsilateral mediastinal lymph node metastasis has been considered by most physicians to have a poor long-term prognosis, it has been reported that the long-term prognosis of N2 disease varies depending on the extent of mediastinal lymph node metastasis.

In the present study, we did not principally perform a surgical resection in N2 disease suspected preoperatively. However, the incidence of unsuspected N2 disease after surgical resection was 18.5%. The patients' 5-years survival rate and 5-year disease free survival rate were 33.5% and 29.4%, respectively.

De Leyn et al. [16] reported that the incidence of unsuspected N2 disease was 14.5% in the patients who underwent surgery for NSCLC, and the 5-year survival rate of the patients with unsuspected N2 disease was 22%. Cerfolio and Bryant [8] reported that the 5-year survival rate was 35% in the patients with unsuspected N2 disease who underwent complete resection and adjuvant therapy. Ohta et al. [7] reported that the 5-year and 10-year survival rates were 27% and 12%, respectively, in 94 patients with NSCLC and single-level N2 disease who underwent an initial operation. Misthos et al. [10] suggested that patients with one-station mediastinal lymph node metastasis, who undergo surgery, have a good prognosis.

The wide extent of lymph node involvement tends to have a worse prognosis than the limited extent of nodal metastasis [3,4,9,17,18]. It is necessary to accurately designate each nodal station for an exact nodal assessment. However, strict pre- or intra-operative mapping of the nodal station might have been difficult and confusing. The two different lymph node classifications of Mountain and Dressler [13], Naruke [14], and Naruke et al. [15] have been widely used for the past three decades in Western and Asian countries. There have been some mediastinal lymph nodes mapping discrepancies between the two nodal classifications. In addition, it might be difficult or equivocal that the nodal station was decided exactly because of the continuity of each nodal station, especially in the cases of subcarinal lymph nodes and hilar lymph nodes, or upper paratracheal nodes and lower paratracheal nodes. To resolve these matters, a new concept named 'nodal zone' was recently proposed by IASLC [12].

In this study, single nodal zone metastasis occurred in two-thirds of the patients with unsuspected N2 disease, and multiple nodal zone metastasis occurred in one-third of the patients. There were no statistical differences in the overall survival rate and disease-free survival rate between the two

groups. However, the number of patients with N2 disease may have been too small to conclude statistical significance in our study. Further analysis with a larger population will be needed for a reliable conclusion on the long-term survival between these two groups. Kim et al. [19] analyzed the survival data of 217 patients with ipsilateral mediastinal metastasis of their 1,186 patients with NSCLC, who underwent curative surgical resection. They reported that patients with single nodal zone metastasis showed favorable outcomes compared with that of the group with multiple nodal zone metastases [19]. Takamochi et al. [20] reported that there were statistically significant differences between a single station N2 and a multiple station N2, but there was no statistical significance between a single zone N2 and a multiple zone N2. They also suggested that the survival differences between the different zones were not statistically significant within each pathological N stage [20].

This study has some limitations. First, an unrecognized selection bias might be present because this study is a retrospective analysis. Second, the population of the study is relatively small, especially the population of unsuspected N2 disease (n=46), which may reduce the statistical power for detecting the difference of the overall survival rate and disease free survival rate. Finally, the study period was relatively long (15 years). There have been many changes during the study period such as in the preoperative diagnostic principle and the perioperative and postoperative techniques. The accuracy of the preoperative diagnosis might be different because the PET-CT scan was only applied in the last 3 years of the study period.

CONCLUSION

In conclusion, although the statistical power is weak because of the small number of each subgroup, we may conclude the following: the 5-year disease free survival and overall survival rate of patients with unsuspected N2 disease, who underwent complete resection, was statistically similar with that of pN1 disease in this study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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