PROGNOSIS OF COMPLETELY RESECTED pN2 NON-SMALL CELL LUNG CARCINOMAS: WHAT IS THE SIGNIFICANT NODE THAT AFFECTS SURVIVAL?

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Objective: We analyzed the effect of the station of mediastinal metastasis with regard to the location of the primary tumor on the prognosis in patients with non-small cell lung cancer. **Methods:** Of 956 consecutive patients who underwent operation for primary lung carcinoma between 1986 and 1996, 760 patients (79.5%) were diagnosed as having non-small cell carcinoma and were subjected to complete removal of hilar and mediastinal lymph nodes together with the primary tumor. **Results:** The status of lymph node involvement was N0 in 480 patients (63.2%), N1 in 139 patients (18.3%), and N2 in 141 patients (18.6%). The 5- and 10-year survival of patients with N2 disease were 26% and 17%, respectively. Neither cell type nor the extent of procedure was a significant survival determinant. Patients having involvement of subcarinal nodes from upper-lobe tumors had a significantly worse prognosis than those patients with metastases only to the upper mediastinal or aortic nodes ($P = .003$). Patients with nodal involvement of the upper mediastinum from lower-lobe tumors had a significantly worse survival than those patients with metastases limited to the lower mediastinum ($P = .039$). Furthermore, patients with involvement of the aortic nodes alone from left upper-lobe tumors had a significantly better survival than those patients with metastasis to the upper or lower mediastinum beyond the aortic region ($P = .044$). **Conclusions:** When mediastinal metastasis is limited to upper nodes from upper-lobe tumor, to lower nodes from lower-lobe tumor, or to aortic nodes from left upper-lobe tumor, acceptable survival could be expected after radical resection. (J Thorac Cardiovasc Surg 1999;118:270-5)

Although resection for non-small cell lung cancer remains the management of choice whenever possible, considerable controversy still exists on interpretation of the prognostic and therapeutic implications of metastases to ipsilateral mediastinal node (N2) disease. Many physicians believe in their inability to control N2 disease by surgical treatment and regard it as a contraindication to thoracotomy, but some of these lesions demonstrate relatively fine prognosis after complete resection.^{1,2} Varying survival associated with the surgical treatment of

N2 disease may be due to differences in the extent and level of metastatic nodes. The station of mediastinal lymph node metastases has not been considered as a prognostic indicator for survival in most publications. Naruke and colleagues³ reported that the prognosis of patients with subcarinal lymph node metastases was lower than that of patients with metastases to lymph nodes in other mediastinal locations after surgical resection, which was not confirmed by Martini and colleagues.⁴ Thus a few studies have evaluated the effect of metastatic spread on the survival of patients with lung cancer, but the results have been controversial and confusing.

We reviewed the clinical records of patients with non-small cell lung cancer, all of whom had been subjected to complete resection of tumors with complete mediastinal dissection. The purposes of this study were to analyze the relationship among the station of mediastinal metastases, to analyze the location of the primary tumor and the overall survival rate, and to understand significant nodes that affect postoperative survival.

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Table I. Relationship between the location of primary tumor and pathologic N factor

N factor	Location of tumor (n)					Total (n)
	Rt-U	Rt-M	Rt-L	Lt-U	Lt-L	
pN0	135	38	92	126	89	480
pN1	38	29	18	29	25	139
pN2	48	16	22	30	25	141
Total	221	83	132	185	139	760

Rt-U, Right upper lobe; Rt-M, right middle lobe; Rt-L, right lower lobe; Lt-U, left upper lobe; Lt-L, left lower lobe.

Patients and methods

Between January 1986 and December 1996, 956 consecutive patients underwent operation for primary lung cancer by the same surgical team. Of these, 760 patients (79.5%) with proven non-small cell carcinoma underwent curative operation, which was defined as complete removal of ipsilateral hilar and mediastinal lymph nodes together with the primary tumor. There were 568 men and 192 women with a mean age of 63 years (range, 30-88 years). Patients who had evidence of residual tumor at the surgical margin, malignant effusion, or N3 disease (verified by intraoperative findings or postoperative pathologic examination) were defined as noncurative operation and were excluded from this study. Tumors with minute satellite nodules that were found incidentally within the same lobe of the resected specimen were not excluded from this study because we were not certain whether these lesions should be considered local tumor spread or not. Tumors with satellite lesions in another lobe were excluded. Resected specimens were examined histopathologically, and histologic typing was done according to the World Health Organization classification.⁵ Patients whose tumors were subsequently classified as small cell carcinoma or low-grade malignant tumor were also excluded. Surgical-pathologic staging was assigned according to the New International Staging System for Lung Cancer.⁶ The lymph node classification schema that has been recommended by the American Joint Committee on Cancer and adapted from Naruke and colleagues³ was used to designate N disease.

Routine systematic dissection of all the hilar and mediastinal nodes was performed in every case, even if the preoperative evaluation was N0 or N1. Every node dissected en bloc (not sampled) was placed into the compartments, with each lymph node level numbered separately during the operation, and was examined by pathologists to be diagnosed as microscopically positive or negative after the operation. The sites of N2 lymph nodes were divided into upper mediastinal (highest mediastinal nodes, paratracheal nodes, pretracheal nodes, anterior mediastinal nodes, posterior mediastinal nodes, and tracheobronchial angle nodes), aortic (Botallo's nodes, para-aortic nodes, and ascending aortic nodes), and lower mediastinal (subcarinal nodes, paraesophageal nodes, and pulmonary ligament nodes) lymph nodes.^{3,4} Operative mortality rates implied a 30-day postoperative mortality plus intraoper-

Fig 1. Cumulative survival curves of patients who underwent complete resection for non-small cell lung cancer according to surgical-pathologic status of ipsilateral mediastinal lymph nodes. Patients with N0 disease had a significantly better survival than those patients with N1 disease ($P = .0009$), and patients with N1 disease had a significantly better survival than those patients with N2 disease ($P = .0001$).

ative mortality. Survival was estimated by the Kaplan-Meier method,⁷ and differences in survival were determined by log-rank analysis. A multivariate analysis of various independent prognostic factors was assessed by Cox's proportional hazards regression model.⁸ Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancer, or unknown cause. Operative death was included.

Results

Overall follow-up ranged from 18 to 150 months, with a median of 61 months. The operative mortality rate was 0.3% (2/760 patients). One patient died of hemorrhage during completion pneumonectomy. The cause of death in the remaining patient was acute myocardial infarction. The relationship between the location of the primary tumor and the pathologic N factor is shown in Table I. The status of lymph node involvement was N0 in 480 of the 760 patients (63.2%), N1 in 139 patients (18.3%), and N2 in 141 patients (18.5%). A significant difference in survival according to the absence or presence of N1 or N2 nodes is shown in Fig 1. The 5-year survival of patients with N0, N1, and N2 disease was 77%, 58%, and 26%, respectively (N0 vs N1, $P = .0009$; N1 vs N2, $P =$

Fig 2. Cumulative survival curves of patients with an upper-lobe tumor according to the absence or presence of subcarinal node metastases. Patients having involvement of subcarinal nodes had a significantly worse prognosis than those patients with metastasis only to the upper mediastinal or aortic nodes ($P = .003$).

Fig 3. Cumulative survival curves of patients with a lower-lobe tumor according to the absence or presence of upper mediastinal metastases. Patients with nodal involvement of the upper mediastinum had a significantly worse survival than those patients with metastasis only to the lower mediastinum ($P = .039$).

.0001). In addition, 70% of patients with N0 disease, 52% of patients with N1 disease, and 17% of patients with N2 disease were expected to survive 10 years or more after operation.

In the 141 patients with N2 disease, the histologic cell types were 98 adenocarcinoma, 40 squamous cell carcinoma, 2 adenosquamous carcinoma, and 1 large cell carcinoma. Histologic classification was not a sig-

Fig 4. Cumulative survival curves of patients with a left upper-lobe tumor according to the absence or presence of aortic node metastases. Patients with involvement of only the aortic nodes had a significantly better survival than those patients with metastasis to the upper or lower mediastinum over the aortic region ($P = .044$).

nificant survival determinant (adenocarcinoma versus squamous cell carcinoma, $P = .76$). Lobectomy was by far the most common procedure and was performed in 123 patients, including 21 combined sleeve resections of the bronchus. Fourteen pneumonectomies including 2 sleeve techniques for the tracheobronchus and 4 segmentectomies were performed. Because we followed the policy that lung-saving procedures such as bronchoplasty must always be kept in mind,⁹ we performed very few pneumonectomy procedures. The extent of procedure did not significantly affect survival (lobectomy versus pneumonectomy, $P = .98$).

The locations and levels of involved nodes affected survival. Patients having involvement of subcarinal nodes from either right or left upper-lobe tumors ($n = 8$) were not expected to survive 3 years after operation and had a significantly worse prognosis than those patients with metastases only to the upper mediastinal or aortic nodes ($n = 70$; $P = .003$). The 5-year survival for these patients was 0% and 37%, respectively (Fig 2). Table II shows a multivariate analysis of independent prognostic factors among patients with an upper-lobe tumor. Involvement of subcarinal nodes was a statistically significant factor ($P = .023$). On the other hand, patients with nodal involvement of the upper mediastinum from either right or left lower-lobe tumors ($n = 28$) had a significantly worse survival than those with metastases limited to the lower mediastinum ($n = 19$; $P = .039$). The survival in these patients was 8% and 49% at 5 years, respectively (Fig 3). As a result of a multivariate

Table II. Multivariable analysis of prognostic factors among patients with an upper-lobe tumor ($n = 78$)

Factors	Characteristics		Risk ratio	95% CI	P value
	Unfavorable	Favorable			
Sex	Male	Female	1.570	0.701-3.514	.27
Age (y)	<70	70≤	1.586	0.665-3.785	.30
Side of tumor	Right	Left	1.154	0.604-2.205	.66
Histologic type	AD	SQ	2.276	0.951-5.451	.064
Extent of involved nodes	Subcarinal*	Upper or aortic†	2.840	1.158-6.966	.023

CI, Confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma.

*Involvement of subcarinal nodes.

†Involvement of only upper mediastinal or aortic nodes.

Table III. Multivariable analysis of prognostic factors among patients with a lower-lobe tumor ($n = 47$)

Factors	Characteristics		Risk ratio	95% CI	P value
	Unfavorable	Favorable			
Sex	Female	Male	1.191	0.495-2.864	.70
Age (y)	70≤	<70	1.084	0.481-2.440	.85
Side of tumor	Left	Right	1.492	0.690-3.230	.31
Histologic type	SQ	AD	2.053	0.807-5.221	.13
Extent of involved nodes	Upper*	Lower†	2.358	1.022-5.439	.044

CI, Confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma.

*Involvement of upper mediastinal nodes.

†Involvement of only lower mediastinal nodes.

Table IV. Multivariable analysis of prognostic factors among patients with a left upper-lobe tumor ($n = 30$)

Factors	Characteristics		Risk ratio	95% CI	P value
	Unfavorable	Favorable			
Sex	Male	Female	2.409	0.595-9.752	.22
Age (y)	70≤	<70	1.481	0.082-26.693	.79
Histologic type	AD	SQ	4.858	0.268-88.052	.28
Extent of involved nodes	Upper or lower*	Aortic†	3.923	1.022-15.061	.046

CI, Confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma.

*Involvement of upper or lower mediastinal nodes.

†Involvement of only aortic nodes.

analysis among patients with a lower-lobe tumor (Table III), involvement of upper mediastinal nodes was identified to be an independent prognostic factor ($P = .044$). Furthermore, patients with involvement of the aortic nodes alone from left upper-lobe tumors ($n = 12$) had a significantly better survival than those patients with metastasis to the upper or lower mediastinum beyond the aortic region ($n = 18$; $P = .044$). The 5-year survival for these patients was 57% and 36%, respectively (Fig 4). According to a multivariate analysis among patients with a left upper-lobe tumor (Table IV), involvement of upper or lower mediastinal nodes over aortic nodes was an independent prognostic factor ($P = .046$). We also evaluated the effect of the number of stations of

involved N2 lymph nodes on patients' survival. Patients with involvement of the single station ($n = 84$) had a significantly better survival than those patients with involvement of the multiple stations ($n = 57$; $P = .0001$). The 5-year survival for these patients was 39% and 11%, respectively.

Discussion

The presence of mediastinal lymph node metastases in patients with lung cancer is a significant prognostic factor and may profoundly influence therapeutic decisions. The actuarial 5-year survival of patients with N2 non-small cell lung cancer having complete resection reported in the literature vary between 19.2% and

30%.¹⁰⁻¹³ However, selection of patients and methods for reporting survival figures vary widely, thereby making comparisons between reported series difficult, if not impossible. It must be kept in mind that this series included both macroscopically apparent N2 disease and microscopic N2 disease but excluded incomplete resection. The study was retrospective analysis, but the number of missing data was too small; follow-up was obtained in all patients. Because we always keep lung-saving procedures in mind,⁸ pneumonectomy was performed infrequently and much less than sleeve lobectomy. In consequence, we had fewer postoperative complications such as pneumonia, pulmonary infarction, or pulmonary edema; and curative resection could be done with low operative mortality rates. Because we always perform routine systematic dissection of all the hilar and mediastinal nodes, we have many patients who were sliding from advanced N1 disease to early N2 disease at postoperative pathologic examination; that is, they had no macroscopically apparent N2 disease but microscopic N2 disease, and we had more patients with single station of involved N2 nodes than those with multiple stations of involved N2 nodes. In our series, therefore, N2 disease could be considered to achieve relatively good survival.

There have been some reports that have shown that patients with involvement of multiple N2 stations have a worse prognosis than those patients with involvement of only a single N2 station.^{13,14} These reports were compatible with our present study. However, the station of mediastinal lymph node metastases in relation to the location of the primary tumor has not been considered a prognostic indicator for survival in most publications. Also, the results on the importance of the involved station are conflicting in the literature. A few reports^{11,15} found that the level of the nodal station involved had only a minor effect on the potential for long-term survival and that the survival differences between the various levels of involvement appeared not to be of statistical significance. Riquet and colleagues¹⁶ reported that the distribution of the metastatic mediastinal lymph nodes was not important for the prognosis.

Miller and colleagues¹⁴ revealed that the survival in patients with involvement of upper mediastinum was improved compared with those patients with involvement of the lower mediastinum, regardless of the location of the primary tumor. Kirsh and Sloan¹⁷ reported better survival for patients with metastases in the upper mediastinum alone. This result was in agreement with ours in case of upper-lobe tumors.

Naruke and colleagues³ reported the survival of patients with subcarinal node involvement to be 9.1%,

as opposed to a 29% 5-year survival for patients with N2 disease without involvement of the node. In addition, Patterson and colleagues¹ and Kirsh and Sloan¹⁷ reported a poor survival in patients with subcarinal involvement. We speculated that subcarinal nodes were significant as a cross-road where lymphatic channels from the various organs in the thorax meet directly or by means of lymphoid relays.¹⁸ Our own studies would confirm the importance of the subcarinal nodes and the poor prognostic implications when they are involved by upper-lobe cancer. This may have been because nodal involvement of subcarina tends to be more widely scattered. Nohl¹⁹ stated that, in upper-lobe cancers, subcarinal lymph node metastases usually occurred secondary to involvement of nodes around the main bronchus and noted that subcarinal involvement was infrequent. From these results, involvement of subcarinal lymph nodes from upper-lobe cancer is considered as more advanced disease.

Patterson and colleagues¹ reported that patients with metastasis to subaortic lymph nodes alone had a comparatively good prognosis after complete resection and a 5-year survival of 42%. Martini and Flehinger¹¹ demonstrated a 35% 5-year survival rate in patients with similar nodal involvement. In the present study, patients with involvement of only the aortic nodes from left upper-lobe tumors had a significantly better survival than those patients with metastasis to the upper or lower mediastinum. The subaortic nodes constitute an important pathway of lymph drainage for left upper lobe and may be equivalent to the hilar lymph nodes, unlike the other mediastinal lymph nodes. In contrast, Miller and colleagues¹⁴ found no difference in 5-year survival between patients with positive disease and negative disease in aortic nodes.

We regarded the location of the primary tumor, which was not under consideration in most of the past literature, very important in analyzing the relationship between the level of involved nodes and the prognosis.

Vansteenkiste and colleagues²⁰ found that right upper- and middle-lobe tumors had pathways of lymphatic metastases to the right upper-mediastinal nodes, right lower-lobe tumors to the lower ones, and left upper-lobe tumors to the aortic ones. These findings were compatible with our preceding study.¹⁸ A usual pattern of lymphatic spread not following the findings mentioned earlier was considered a poor prognostic sign (eg, there were no 3-year survivors in patients with metastases to subcarinal nodes from an upper-lobe tumor).

From the results of the present study, it appears that the relationship between the station of mediastinal lymph node metastases and the location of the primary

tumor is important when planning therapy for patients with N2 non-small cell lung cancer. When metastasis limited to upper mediastinal or aortic nodes from upper-lobe tumor, to lower mediastinal nodes from lower-lobe tumor, or to aortic nodes from left upper-lobe tumor, the patient should undergo as complete a resection as possible because acceptable survival can be expected after radical resection.

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