Border between N1 and N2 stations in lung carcinoma: Lessons from lymph node metastatic patterns of lower lobe tumors

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Objective: Distinction of lymph node stations is one of the most crucial topics still not entirely resolved by many lung cancer surgeons. The nodes around the junction of the hilum and mediastinum are key points at issue. We examined the spread pattern of lymph node metastases, investigated the prognosis according to the level of the involved nodes, and conclusively analyzed the border between N1 and N2 stations.

Methods: We reviewed the records of 604 consecutive patients who underwent complete resection for non-small cell lung carcinoma of the lower lobe.

Results: There were 390 patients (64.6%) with N0 disease, 127 (21.0%) with N1, and 87 (14.4%) with N2. Whereas 11.3% of patients with right N2 disease had skip metastases limited to the subcarinal nodes, 32.6% of patients with left N2 disease had skip metastases, of which 64.2% had involvement of N2 station nodes, except the subcarinal ones. The overall 5-year survivals of patients with N0, N1, and N2 disease were 71.0%, 50.8%, and 16.7%, respectively (N0 vs N1 $P = .0001$, N1 vs N2, $P < .0001$). Although there were no significant differences in survival according to the side of the tumor among patients with N0 or N1 disease, patients with a left N2 tumor had a worse prognosis than those with a right N2 tumor ($P = .0387$). The overall 5-year survivals of patients with N0, intralobar N1, hilar N1, lower mediastinal N2, and upper mediastinal N2 disease were 71.0%, 60.1%, 38.8%, 24.8%, and 0%, respectively. Significant differences were observed between intralobar N1 and hilar N1 disease ($P = .0489$), hilar N1 and lower mediastinal N2 disease ($P = .0158$), and lower and upper mediastinal N2 disease ($P = .0446$). Also, the 5-year survivals of patients with involvement up to station 11, up to station 10, and up to station 7 were 41.4%, 37.9% and 37.7%, respectively (difference not significant).

Conclusions: N1 and N2 diseases appeared as a combination of subgroups: intralobar N1 disease, hilar N1 disease, lower mediastinal N2 disease, and upper mediastinal N2 disease. Interestingly, the survivals of patients with involvement up to interlobar nodes (station 11), main bronchus nodes (station 10), and subcarinal nodes (station 7) were identical. These data constitute the basis for a larger investigation to develop a lymph node map in lung cancer.

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Received for publication March 19, 2004; revisions received April 23, 2004; accepted for publication June 1, 2004.

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J Thorac Cardiovasc Surg 2005;129:825-30
0022-5223/\$30.00

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doi:10.1016/j.jtcvs.2004.06.016

In non-small cell lung cancer, metastasis to lymph nodes, the N factor, is one of the most important determinants of prognosis.¹⁻⁵ Accurate lymph node staging is therefore imperative to select therapeutic strategies. Currently some variations of the lymph node map can be found, and thus considerable discordance exists regarding the designation of sites among doctors in the United States, Europe, and Japan,⁶ which has been causing confusion. Understandably, the survival of patients with N1 disease is between that

TABLE 1. Pattern of N2

	Right lung	Left lung
Total	44	43
Only lower mediastinum	29	33
Skip of N1, station 7	5	5
Skip of N1, station 8	0	3
Skip of N1, station 9	0	2
Skip of N1, stations 7 and 8	0	2
Skip of N1, stations 7 and 9	0	1
N1 and station 7	15	10
N1 and station 8	1	2
N1 and station 9	0	2
N1 and stations 7 and 8	4	5
N1 and stations 7 and 9	0	1
N1 and stations 8 and 9	1	0
N1 and stations 7, 8, and 9	3	0
Upper mediastinum	15	10
Skip of N1, Botallo's node	0	1
N1 and upper mediastinum	2	4
N1, station 7, and upper mediastinum	13	5

Data represent numbers of patients.

of those with N0 and N2 disease if only the N factor is considered, because N1 lymph nodes are anatomically positioned upstream from N2 nodes. However, both N1 and N2 disease represent heterogeneous groups with variable survivals.^{7,8} In each case, the involved nodal levels could probably have different influences on patients' survival. One of the most significant problems concerning lymph node involvement under debate among thoracic oncologists is the definition of the borderline between N1 and N2 stations, which must be absolutely clarified, because otherwise discordance could distort stages reported in different studies. More importantly, in the clinical setting, the potential therapeutic strategies for patients with N1 and N2 disease differ remarkably. In other words, it is difficult to deal with interface nodes at the junction of the hilum and mediastinum, which are around the main bronchus. We should direct our efforts toward defining the border more precisely and reach consensus on the basis of up-to-date evidence.

We reviewed the records of patients with completely resected non-small cell lung cancer to examine the clinical features of lymph nodal involvement. The purposes of this study were to investigate the pattern of lymph node metastases, to analyze survivals of patients according to the level of nodal involvement, and to bring up an unsolved issue on the anatomic border between N1 and N2 stations. To make the anatomic stream of lymph nodes clearly understandable, patients in this study were limited to those with a primary lesion originating from the lower lobe.

Material and Methods

Between July 1984 and December 2003, a total of 604 consecutive patients operated on for primary non-small cell carcinoma in the

lower lobes of the lungs had pathologic confirmation of complete removal with systematic nodal dissection of the hilum and mediastinum. Approval of the institutional review board was obtained to collect these patients' data in a secure database and report their outcomes. Histologic type of the tumor was determined according to the World Health Organization classification. Patients with low-grade malignancy of the lungs, such as carcinoid, were excluded. Staging was determined according to the international TNM staging system.¹ All dissected lymph nodes were pathologically examined and classified according to anatomic location by Naruke and colleagues' numbering system.² Patients who had been subjected to induction chemoradiotherapy or adjuvant therapy were excluded. For staging, all patients underwent a physical examination; chest radiography; computed tomography of the thorax, brain, and upper abdomen; bone scintigraphy; and bronchoscopy. After surgery, the patients were examined at 3-month intervals for 5 years and thereafter at 1-year intervals in general. The evaluations included physical examination, chest radiography, and tumor markers. Moreover, chest, abdominal, and brain computed tomographic scans and a bone scintiscan were carried out each year.

One hundred sixty-five patients were female and 439 were male, ranging in age from 32 to 83 years with a median of 67 years. The histologic classification was adenocarcinoma in 293 patients, squamous cell carcinoma in 285, adenosquamous carcinoma in 13, and large cell carcinoma in 13. There were 266 patients with left-sided tumors and 338 with right-sided tumors. One hundred ninety-seven patients had pathologic stage IA disease, 164 had IB disease, 33 had IIA disease, 87 had IIB disease, 94 had IIIA disease, and 29 had IIIB disease.

The sites of N2 lymph nodes were grouped as follows: upper mediastinal (highest mediastinal nodes, paratracheal nodes, pretracheal nodes, anterior mediastinal nodes, posterior mediastinal nodes, tracheobronchial angle nodes, Botallo's nodes, para-aortic nodes, and ascending aortic nodes), and lower mediastinal (station 7, subcarinal nodes; station 8, paraesophageal nodes; and station 9, pulmonary ligament nodes) lymph nodes.^{2,3} The N1 lymph nodes comprised hilar (station 10, main bronchus nodes; and station 11, interlobar nodes), and intralobar (lobar bronchial nodes, segmental bronchial nodes, and intrapulmonary nodes) ones. Mediastinal metastasis was considered as "skip metastasis" if any of the N2 nodes, but no N1 nodes were involved. In patients with a tumor in the left side, Botallo's nodes, para-aortic nodes, and ascending aortic nodes were invariably removed although removal of pretracheal nodes was optional.

Survivals were calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis. Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, noncancerous cause, or unknown causes.

Results

Lymph node involvement was recognized in 214 (35.4%) of the 604 patients evaluated; of them 127 patients (21.0%) showed N1 node involvement and 87 (14.4%) showed N2 node involvement. Among 127 patients with N1 disease, 54 had metastasis of intralobar nodes but not hilar nodes. In addition, patients with hilar N1 node metastases were fur-

Figure 1. Overall survival curves of patients subjected to complete resection for non-small cell lung cancer according to pathologic nodal status.

ther categorized as those with ($n = 16$) and those without ($n = 57$) main bronchus node (station 10) involvement. The spread patterns of N2 lymph node metastases according to the side of the primary tumor are presented in Table 1. Of 44 patients with a right tumor involving the N2 region, 5 (11.3%) had skip metastases, all of which were limited to station 7. On the other hand, among 43 patients with a left tumor involving the N2 region, 14 (32.6%) had skip metastases, of whom 9 showed involvement of any N2 node except station 7. To our surprise, skip metastasis to the upper mediastinal node but not the lower mediastinal nodes was found in only 1 patient, who had a bronchioloalveolar cancer 80 mm in diameter as the primary lesion, with node station 5 metastasis. Except for that patient, all the patients with nodal involvement reaching the upper mediastinum showed involvement of N1 nodes.

Follow-up ranged from 3 to 203 months, with a median of 92 months for surviving patients. The overall 5-year survivals of patients with N0, N1, and N2 disease were 71.0%, 50.8%, and 16.7%, respectively (Figure 1). There were statistically significant differences in survival among these groups (N0 vs N1 $P = .0001$, N1 vs N2 $P < .0001$). Next, we investigated the survivals of patients with N0, N1, or N2 disease according to the side of the primary tumor (Figure 2). Although there were no significant differences in survival according to the side of the tumor among patients with N0 or N1 disease, patients with a left N2 tumor had a worse prognosis than those with a right N2 tumor ($P = .0387$). Their 5-year survivals were 6.9% and 28.2%, respectively.

In addition, we examined survivals after classifying patients with N1 disease into those with and without hilar node (stations 10, 11) metastasis, and patients with N2 disease as

Figure 2. Overall survival curves of patients subjected to complete resection for pN0 (A), pN1 (B), and pN2 (C) non-small cell lung cancer according to side of primary lesion.

those with and without upper mediastinal node metastasis. Overall 5-year survivals of patients with N0, intralobar N1, hilar N1, lower mediastinal N2, and upper mediastinal N2 disease were 71.0%, 60.1%, 38.8%, 24.8%, and 0%, respectively (Figure 3, A). Significant differences were observed between intralobar N1 and hilar N1 disease ($P = .0489$), between hilar N1 and lower mediastinal N2 disease ($P =$

Figure 3. Overall survival curves of patients subjected to complete resection for non-small cell lung cancer according to pathologic nodal status. (A) Disease was classified as N0 disease, intralobar N1 disease, hilar N1 disease, lower mediastinal N2 disease, and upper mediastinal N2 disease. (B) Disease was further classified tumor involving up to either interlobar (station 11), main bronchus (station 10), or subcarinal (station 7) nodes.

.0158), and between lower and upper mediastinal N2 disease ($P = .0446$), but not between N0 and intralobar N1 disease ($P = .1806$). Finally, we debated whether the survivals of patients with nodal involvement up to either station 11, station 10, or station 7, differed. The 5-year survivals were 41.4%, 37.9%, and 37.7%, respectively. Comparison of the survivals among the three subgroups demonstrated no significant differences, and their curves were overlaid (Figure 3, B).

Discussion

Even now, optimal lymph node dissection remains controversial among thoracic surgical oncologists. On the one hand, lymphadenectomy can improve the accuracy of lung cancer staging and decrease locoregional recurrence; on the

other, it increases operative time, blood loss, and the frequencies of recurrent laryngeal nerve injury, chylothorax, and bronchopleural fistula. Thus it is important to develop a more reasonable approach for dissecting mediastinal lymph nodes.

In this series, we acknowledged so-called skip metastasis to mediastinal lymph nodes in approximately 22% of our patients with N2 disease. This percentage is close to those of previous reports: 27% by Martini and colleagues⁹ and 28.6% by Ishida and colleagues.¹⁰ Skip metastasis may possibly develop as a result of the existence of lymphatic channels opening directly to the mediastinum. Subpleural lymphatics have been reported to have straight passages to the mediastinal lymph nodes in 22% of the segments in the right lung and in 25% of the segments in the left lung.¹¹

Consistent with these data, we found skip metastases more frequently and at more complicated modes in the left lung than in the right lung, suggesting that dissection of mediastinal lymph nodes on the left side requires more careful handling. In addition, survival of patients with a right N2 lesion was significantly better than that of patients with a left N2 lesion, although no significant difference in survival according to the side of disease was observed in patients with N0 or N1 disease. Drainage patterns of lymph nodes and quicker operative access to the right side of mediastinal lymph nodes may explain restriction of the better survival results to patients with right-sided lesions. Although paratracheal, pretracheal, and tracheobronchial angle nodes can be dissected through a right thoracotomy without difficulty, it is hard to reach some of these nodes from the left side. Moreover although right-sided tumors generally spread to the ipsilateral mediastinal lymph nodes, tumors in the left lower lobe are recognized to metastasize passing through the subcarinal nodes not only to the ipsilateral (left) but also to the contralateral (right) mediastinum. We should understand the importance of the left side in lymphadenectomy.

Metastatic spread may occur in nonregional mediastinum without involving lymph nodes of the regional mediastinum. Because the extent and the mode of nodal spread are affected by location of the tumor, we classified the mediastinum into an upper region, including the aortic region, and a lower region. All patients with skip N2 metastasis from a lower-lobe lesion showed no involvement of upper mediastinal nodes, except for 1 patient who had a huge primary tumor. In patients with a lower-lobe tumor without N1 node involvement, very little prevalence of upper mediastinal node involvement can exist. Therefore if N1 nodes are found to be free of tumor by an adequate use of frozen sections, upper mediastinal lymphadenectomy is basically dispensable. An exception is when the patients have advanced disease suspected on the basis of findings such as size of tumor and extent of invasion; in such cases complete hilar and mediastinal lymphadenectomy should be routinely done as long as the patient is considered able to tolerate the procedure. In addition, fluorodeoxyglucose positron emission tomography, reported to be superior to computed tomography in assessing lymph node metastasis,¹² can help to decide the extent of lymphadenectomy.

There are ongoing controversies concerning lymph node stations as a result of the lack of a universally widespread map. One of the biggest problems is the distinction between N1 and N2 stations. In general, pleural reflection has been accepted as an anatomic border between N1 and N2 regions, as the American Joint Committee established in 1973 and Mountain¹ revised in 1997. Management of nodes around the main bronchus (stations 7, 10, 11), is the point, because the main bronchus is positioned partially within the pleural envelope and partially outside it. Indeed, one of the most

important problems is to decide whether the main bronchus nodes belong to the N1 or N2 station in relation to prognosis as well as anatomy. In this study, we found no differences in survival among patients with nodal metastases up to either station 11, station 10, or station 7, suggesting that these nodes could be designated as intermediate between N1 and N2 and that there might be no borderline between N1 and N2 nodes around the main bronchus. Some reports have also shown the prognoses of patients with hilar N1 disease and single-station N2 disease to be identical.^{13,14} Those data suggest that pleural reflection is not a suitable anatomic border between N1 and N2 stations in lung cancer.

Another important finding of this study was that patients with intralobar metastasis had a significantly better prognosis than those with hilar metastasis, who in turn had a significantly better prognosis than those with lower mediastinal metastasis. In addition, patients with lower mediastinal metastasis had a significantly better prognosis than those with upper mediastinal metastasis. Upper mediastinal nodes might be considered as representing an N3 station for a lower-lobe lesion, although clearer and more extensive evidence is required. The map for lymph node stations in lung cancer is still under development. We fervently hope to have a single, accurate map of lymph node stations that can be used universally. Otherwise, it will be impossible to make progress in therapeutic strategies for lung cancer.

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