N2 Disease in T1 Non-Small Cell Lung Cancer

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Background. **The optimal management strategy for mediastinal staging in early-stage non-small cell lung cancer (NSCLC) is not clearly defined. The true prevalence of mediastinal lymph node metastases (N2 disease) in resected pathologic T1 (pT1) NSCLC must be known to define the role of invasive mediastinal staging in these patients.**

Methods. **Data of patients with pT1 lesions resected at Mayo Clinic between 1998 and 2006 were retrospectively reviewed. Patients with N2 disease were identified from pathology and operative reports. We reviewed demographics, radiologic data, and surgical procedures for those with pathologic T1 N2 NSCLC.**

Results. **We identified 968 cases of pT1 lesions, 59 with pN2 disease (6.1%). For those with T1 N2 disease, the primary lung lesion was peripheral in 18 (31%) and central in 41 (69%). Of these, 36 had negative non-invasive mediastinal staging (3.7%) and were incidentally discovered. The most frequently affected lymph node station was 7 in 22 patients (37%), followed by 5,6 in 18 (31%). Mediastinoscopy found positive lymph nodes in 3 of 16 patients (19%) in which it was performed. Overall 5-year survival for pT1 N2 incidentally discovered during mediastinal lymph node dissection at the time of lung resection was 46% (95% confidence interval, 31% to 68%).**

Conclusions. **True pT1 NSCLC harbors a relatively low rate of N2 disease. The rate of occult N2 disease not observed on noninvasive preoperative mediastinal staging is even lower. For patients with T1 NSCLC and negative mediastinal imaging, routine mediastinoscopy results in a low yield of occult N2 disease discovery.**

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GENERAL THORACIC

Current treatment algorithms for locally advanced stage III non-small cell lung cancer (NSCLC) typically involve neoadjuvant or definitive chemoradiation therapy. Surgical resection is not normally used as initial treatment in most North American centers. As a consequence, much effort is directed toward the assessment of mediastinal lymph nodes for metastatic disease before any planned surgical resection.

Computed tomography (CT) has a sensitivity of 50% to 76% and specificity of 55% to 86% for predicting metastatic involvement of mediastinal lymph nodes when they exceed 1 cm in the short axis [1–3]. Positron emission tomography (PET) has emerged as a useful tool to evaluate the mediastinum, with a sensitivity of 83% to 91% and specificity of 70% to 91% for lymph node metastases [3, 4]. Despite these numbers, pathologic tissue confirmation is desirable to prove that a lesion is indeed malignant and not exclude potentially resectable tumors from surgical treatment and potential cure.

Some have suggested that the incidence of lymph node metastases in patients with clinical T1 NSCLC and negative noninvasive mediastinal staging might be low enough to preclude routine invasive staging by mediastinoscopy [5, 6]. Reports vary about the true rate of occult N2 disease in NSCLC patients with negative noninvasive staging, particularly for patients with T1 lesions. The objective of this study was to describe the incidence of N2 disease in 968 consecutive cases of resected pathologic T1 (pT1) NSCLC and make inferences about the utility of invasive mediastinal staging in this subgroup of patients.

Material and Methods

This study was approved by the Mayo Clinic College of Medicine's Institutional Review Board.

Patients

We reviewed our prospective database for all patients that underwent resection for pT1 NSCLC between 1998 and 2006 at Mayo Clinic, Rochester, Minnesota. All pathology reports for these patients were reviewed. We identified 968 cases involving surgical procedures in patients with pT1 NSCLC. Of these, 59 (6.1%) were found to have pathologic N2 (pN2) disease. Preoperative data were reviewed for this group, including age, gender, pulmonary function tests, localization of the primary tumor, presence of adenopathy on CT scan, and size and metabolic activity on PET scan in those patients for which it was performed. The surgical and pathology reports were reviewed for the mediastinal lymph nodes stations that were sampled and which of them contained metastases.

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Lesions were staged according to the staging system and mediastinal lymph node map described by Mountain [7, 8]. The size of the lesion was determined from the greatest dimension measured in the pathology laboratory.

Imaging Data

All the available CT scans were reviewed. Peripheral lung nodules were defined on CT scan as tumors with the center located in the outer third of the lung in either the sagittal or coronal plane. If CT images were not available, a peripheral lesion was defined according to its relation to the pleural surface as described in the pathology report. Mediastinal lymph nodes were considered to be positive by CT scan criteria when their short axis was 10 mm or more in size. In patients in whom PET scans were performed, reports were reviewed and considered positive if the described metabolic activity in the mediastinum exceeded 1.5-fold over background levels.

Mediastinoscopy

Cervical mediastinoscopy was performed in the standard fashion and selectively, determined by the presence of significant lymph nodes in the mediastinum observed on CT scan, by increased metabolic activity on PET, or by surgeon preference. After introduction of the mediastinoscope, biopsy specimens from station 4R, 7, and 4L were typically obtained. Biopsy specimens were also obtained from other stations when lymph nodes were encountered or specifically sought out.

Mediastinal Lymph Node Dissection

Mediastinal lymph node dissection (MLND) was performed as part of lung resections. For right-sided procedures, the lymph node stations 2R, 4R, 7, and 9 were routinely dissected; for left-sided procedures, the nodes from stations 5, 6, 7, and 9 were included. On both sides, other lymph node stations encountered or specifically sought out at the time of the lung resection were also removed.

Statistics

Descriptive statistics are reported as median and range for continuous variables and as frequency and percentage for discrete variables, based on tumor status (N2 vs N0/N1). Associations with tumor status were made using the Wilcoxon rank sum test for continuous variables and χ^2 test or Fisher exact test as appropriate for discrete variables. The α-level was set at 0.05 for statistical significance.

Results

Between 1998 and 2006, 968 patients underwent lung resection for pT1 NSCLC. Of these, 59 (6.1%) were found to have N2 disease (32 men, 27 women). Peripheral lesions were found in 18 patients and central lesions in 41 (69%). Lung tumors were on the right side in 25 (43%) and on the left side in 34 (57%). Lobectomy by open thoracotomy was performed in 54 (92%), and wedge resection in 5 (8%). Patient characteristics are listed in Table 1.

Table 1. Characteristics for pT1 N2 Patients

Variable	No. (%)
Gender	
Males	32 (54)
Females	27 (46)
Prior smoking history	49 (83)
Median FEV_1, % of predicted (range)	82 (37–159)
Median DLCO, % of predicted (range)	86 (32–113)
Median MVV, % of predicted (range)	77.5 (33–136)
Peripheral lesions	18 (31)
Central lesions	41 (69)
Location of the primary lesion	
Right upper lobe	15 (25)
Right middle lobe	5 (8)
Right lower lobe	5 (8)
Left upper lobe	21 (37)
Left lower lobe	13 (22)
Histology of the lesions	
Adenocarcinoma	46 (78)
Squamous cell carcinoma	8 (14)
Large cell carcinoma	2 (3)
Mucinous adenocarcinoma	1 (2)
Others	2 (3)
Type of resection	
Lobectomy	54 (92)
Wedge resection	5 (8)

DLCO = diffusion capacity of the lung for carbon monoxide; FEV1 = forced expiratory volume in 1 second; MVV = maximum voluntary ventilation.

Imaging Data

CT criteria were used to establish mediastinal adenopathy in 17 of 59 patients (29%). The most frequent lymph node station found to be positive by CT scan criteria was station 4R in 10 patients (17%), followed by station 7 in 6 (10%). In 8 patients (14%), CT showed adenopathy in N1-level lymph nodes.

PET scan was done in 27 patients (46%), resulting in 18 (31%) with negative mediastinal lymph nodes and 9 (15%) with positive nodes. In 3 patients the CT and PET scans were both positive for the same lymph node stations. In 2 patients this involved station 4R with metastases found at time of operation after a negative mediastinoscopy. The remaining case involved a 5,6 lymph node station, with metastasis confirmed during left-sided lung resection.

Surgical Data

Mediastinoscopy was performed in 16 of 59 T1 N2 patients (27%), and in 11 of 23 with preoperative features of N2 disease. In 3 of 16 patients (19%), mediastinoscopy found lymph node metastases in the mediastinum, and 2 subsequently received neoadjuvant chemoradiation therapy, followed by pulmonary resection. The third patient had complications with bleeding during the mediastinoscopy procedure, for which a thoracotomy was performed along with the lung resection. In the remain-

Table 2. Frequency of lymph node metastases

	Primary Tumor Location, Frequency (% of Total)							
Lobe	4R	4L	7	5,6	8R	8L	9R	9L
RUL	13 (87)	0	2 (13)	0	0	0	0	0
RML	2 (33)	0	4 (67)	0	0	0	0	0
RLL	0	0	5 (72)	0	1 (14)	0	1 (14)	0
LUL	0	4 (17)	3 (12)	16 (67)	0	0	0	1 (4)
LLL	0	1 (7)	8 (57)	2 (14)	0	0	0	3 (22)

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lob; RUL = right upper lobe.

ing 13 patients (81%), mediastinoscopy did not reveal the presence of lymph node metastases, despite the discovery of N2 disease during MLND at the time of lung resection. Overall, mediastinoscopy was able to identify mediastinal lymph node involvement in only 3 of 9 patients (33%) where the positive lymph nodes were within the field accessible by cervical mediastinoscopy.

In N2-positive cases, the median size of the T1 pulmonary lesions was 2 cm (range, 0.9 to 3 cm). Only 1 lesion was less than 1 cm, 37 lesions measured between 1 and 2 cm, and 21 lesions were more than 2 cm in the greatest dimension. The location of the primary lesion for specific N2-positive stations is described in Table 2.

A median of 4 lymph node stations (range, 1 to 7) were sampled or dissected at the time of pulmonary resection. The most frequently dissected lymph node station was station 7, in 58 patients (98%). The surgical procedure was left-sided in 34 and right-sided in 25. Station 4R lymph nodes were dissected or sampled in all of the right-sided cases, and the nodes of station 5,6 in 94.1% of left-sided cases. The dissected lymph node stations on each side are presented in Table 3.

We identified 7 patients (12%) with mediastinal lymph node metastases in 2 lymph node stations (multistation N2 disease), but the remaining 52 patients (88%) had disease in only 1 station. Of these, 33 (56%) also had metastases in N1-level lymph nodes. A total of 26 patients (44%) had nodal skip metastases, with N2 disease but no N1 nodes identified at lung resection after pathology review.

The 59 patients presented with 66 distinct mediastinal lymph node stations that contained metastases, and station 7 was the most frequent in 7 in 22 (37%). The primary tumors in these patients were equally distributed between right and left sides. The most frequent localization was the left lower lobe in 8 (36%). The second most common affected station was 5,6 in 18 (30%). The primary tumor was in the left upper lobe in 16 (89%) of these 18 patients. Station 4R was affected in 15 patients (25%), with 13 lesions (87%) located in the right upper lobe and 2 (13%) in the middle lobe. The most frequent lymph node station affected was 4R (60%) for the right-sided lesions, and station 5,6 lymph nodes (44%) for left-sided lesions. Of the 66 lymph node stations that contained metastases, 24 (36%) were in locations not accessible by routine mediastinoscopy, including 18 in station 5,6 lymph nodes, 5 in station 9 lymph nodes, and 1 in a station 8 node.

Among the 22 patients with pathologic involvement of station 7, 6 (27%) had a positive CT scan for mediastinal adenopathy in the same station. The rest of the metastases were found during the operation. For the 18 patients found to have positive station 5,6 lymph nodes, 6 patients (33%) had a CT scan or PET scan positive in that station. For the 15 patients (25%) that had metastatic involvement of the 4R lymph node station, 7 (47%) had a CT scan or PET scan positive in that lymph node station: 3 had a positive PET scan, 2 had a positive CT scan, and the other 2 had both a positive PET and CT.

Of the 59 patients with pT1 N2 NSCLC, 23 (39%) presented with preoperative features of N2 disease on noninvasive imaging and were not clinical N0 patients. Overall, 36 of 968 (3.7%) pT1 lesions had negative noninvasive staging and true occult N2 disease.

The 5-year survival for the entire T1N2 cohort was 41 % (95% confidence interval, 29% to 58%). When survival of the subgroup of patients with preoperative noninvasive imaging features of N2 disease was compared with survival of those without them, the true clinical N0 group presented a trend towards better survival than the cN2 patients, although the difference was not statistically significant (46% vs 36%; $p = 0.43$; Fig 1).

Comment

Mediastinal staging is recognized as an integral part of lung cancer management and treatment planning [9]. We reviewed 968 consecutive cases of pulmonary resection

Table 3. Frequency of Specific Lymph Node Stations Dissected During Mediastinal Lymph Node Dissection at Lung Resection

	Lesion Side, No. (%)	
LN Station	Right	Left
Total patients	25 (43)	34 (57)
2R	23 (92)	N/A
2L	N/A	None
4R	25 (100)	N/A
4L	N/A	18 (53)
5,6	N/A	32 (94)
7	25 (100)	33 (97)

LN = lymph node; N/A = not applicable.

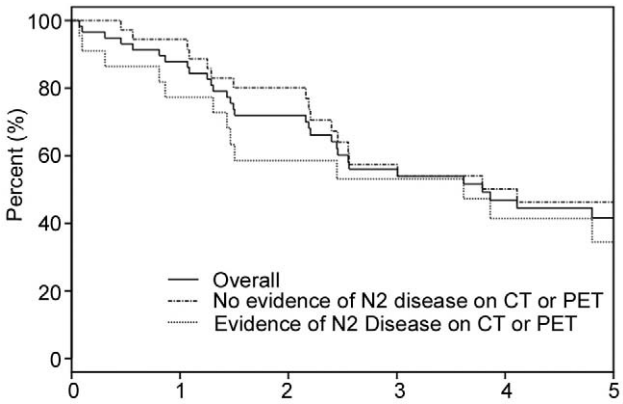

Fig 1. Overall 5-year survival (black line) is shown for patients with preoperative features of N2 disease (clinical T1 N2) on computed tomography (CT) or positron-emission tomography (PET, gray line) imaging and for those with negative results on noninvasive staging (clinical T1 N0, dotted line).

for pT1 NSCLC and found a 6.1% incidence of metastatic involvement of N2-level lymph nodes in the mediastinum. Accurate statistics regarding the incidence of metastatic lymph node involvement in these patients is helpful to guide preoperative staging algorithms of the mediastinum and to assess the yield of invasive procedures such as mediastinoscopy. Previous studies have found a similar incidence of occult N2 disease in patients with negative integrated PET/CT, but without data for exclusively pT1 disease [10, 11].

Mediastinoscopy is typically performed on a selective basis at Mayo Clinic. Patients with mediastinal adenopathy (> 10 mm in the shortest axis) on CT scan or a PET-CT standardized uptake value exceeding 1.5-fold increased over background are usually referred for invasive staging. Currently, this involves endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) as the initial approach with mediastinoscopy used selectively according to the EBUS-FNA result. A limited number of EBUS-FNA procedures were done in this cohort of patients given its recent introduction.

Mediastinoscopy was performed in 16 of the 59 patients with pN2 disease and was able to identify mediastinal lymph node involvement in only 3 of 9 patients (33%) where the positive lymph nodes were within the field accessible by cervical mediastinoscopy. In 2 patients, affected lymph nodes in the 4R position contained nodal metastases, whereas in the other patient, lymph node metastases were found in the subcarinal station. No other positive stations were found in these patients during mediastinoscopy. Two of these patients underwent neoadjuvant treatment, followed by lung resection. The third patient had bleeding at the time of the mediastinoscopy that prompted a right thoracotomy with lung resection of the primary tumor at the same time. Results of mediastinoscopy were negative in the rest of the cohort or they underwent lung resection without mediastinoscopy.

Meyers and colleagues [5], in their review of the data, proposed that mediastinoscopy is not cost-effective in the setting of early-stage lung cancer. In their cohort, mediastinoscopy detected only 5 of 14 patients with occult N2 disease from 248 clinical stage I NSCLC patients. The overall rate of occult N2 disease for this group was 5.6%. Our results are similar: Mediastinoscopy revealed 3 of 16 (19%) with metastatic N2-level lymph nodes in patients with pT1 lesions. In 7 patients, lymph node metastases were found in stations that are not accessible by standard mediastinoscopy (station 9 and station 5,6 lymph nodes), whereas in the remaining 6 patients, it missed metastases in stations 4R or 7. These results reveal a low yield for mediastinoscopy to discover occult mediastinal disease in patients with pT1 NSCLC and negative results from noninvasive staging. It should be noted that 24 of 66 (34%) of the lymph node metastases detected in this cohort were in lymph node stations not accessible by routine mediastinoscopy (lymph node stations 5,6, 8, and 9).

The 5,6 lymph node stations were affected in 18 patients (30%). Metastases in lymph node stations 5,6 can be sampled by a Chamberlain procedure, an extended cervical mediastinoscopy, by a left video-assisted thoracoscopic (VATS) approach, or by EUS-FNA. When isolated and resectable lymph node metastases are suspected in station 5,6 lymph nodes by noninvasive preoperative staging in the context of a clinical T1 lesion, and a diagnosis has not been made by other means, our usual approach is to proceed with thoracotomy and lung resection, followed by adjuvant treatment if MLND does indeed show metastatic disease. This group appears to have a better survival than other patient subgroups with N2 disease, with survival rates closer to that of patients with N1 disease [6, 12].

The most frequent lymph node station found to harbor occult N2 disease was the subcarinal station 7. The most common locations for the primary tumor in cases with station 7 lymph node metastases were in the left lower lobe (36%) and right lower lobe (23%). Although it is technically possible to fully dissect this station by mediastinoscopy, most often the subcarinal station is at best sampled, leaving the possibility for sampling error. This is particularly the case for metastases located caudally or deep within the level 7 lymph nodes, or when this location is not entirely involved with metastatic tumor. Station 4R can usually be more aggressively sampled during mediastinoscopy, with appropriate caution for the position of the azygous vein. This was the most frequent station affected in right-sided tumors, with most located in the right upper lobe.

We also found metastatic nodal involvement in station 8 and 9 for a limited number of T1 lesions. Despite this, there were no preoperative features of station 9 involvement in our series, and we do not think that routine preoperative sampling of this location by EUS or VATS is indicated in T1 lesions given the low yield [13]. Nevertheless, these findings at least support the routine sampling, if not dissection, of level 9 lymph nodes as part of the transthoracic mediastinal staging at the time of pulmonary resection.

Overall, only 23 of 968 patients (2.4%) demonstrated mediastinal nodal metastases by a positive CT scan, a positive PET scan, or both. The remaining 36 (3.7%) were found to have mediastinal node metastases during the operation, despite negative preoperative noninvasive stag-

ing. This is the rate of clinically occult N2 disease in T1 lesions before invasive surgical staging. It is from this point that a decision can be made about the utility and yield of further invasive mediastinal staging, including mediastinoscopy, thoracoscopy, EBUS, and esophageal ultrasound.

All lesions were 3 cm or smaller in greatest dimension as defined by T1 criteria. Classifying these lesions according to the new proposed pathologic T classification of NSCLC by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project [14] identifies 38 lesions 2 cm or smaller that would be classified as T1a lesions, and 21 T1b lesions exceeding 2 cm in greatest dimension. The prevalence of mediastinal lymph node metastases is typically associated with increased lesion size [15, 16], although we did not observe this for T1 lesions. Two other factors that have been associated with an increasing risk of N2 disease are a centrally located lesion and the diagnosis of adenocarcinoma [14]. In agreement with this, we identified central lesions in 69% and adenocarcinoma in 78% of our cohort with positive N2 nodes.

The 41% overall 5-year survival in this study is higher than the 20% (95% CI, 12% to 33%) previously reported for a group of T1 N2 patients diagnosed or treated, or both, at our institution [17]. The recent IASLC staging revision reported a 5-year survival of 22% for patients with pN2 disease [18]. We find the explanation for these dissimilar numbers in that the patients with N2 disease are a heterogenous group with varying amounts of disease in the mediastinum, ranging from bulky mediastinal disease to microscopic lymph node involvement. A number of studies suggest differing outcomes for N2 disease based on these factors [19–21].

In summary, we identified 59 patients (6.1%) with N2 disease from 968 resected pT1 lesions. Of these, noninvasive mediastinal staging was negative in 36 (3.7%), but N2 disease was discovered at MLND. Given the low prevalence of N2 disease among patients with pT1 NSCLC and negative noninvasive mediastinal staging, routine invasive staging by cervical mediastinoscopy in this group will result in a low yield of occult N2 disease discovery for clinical T1 N0 NSCLC. The benefit of pursuing routine cervical mediastinoscopy will have to be weighed against this low prevalence, depending on the specific clinical situation. Independent of the approach to mediastinal staging before lung resection, MLND, or at least sampling, is an essential component of quality treatment for lung cancer [9].

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INVITED COMMENTARY

The optimal management of patients with N2 disease remains one of the most contentious areas of care for patients with nonsmall cell lung cancer (NSCLC). This is likely due to the wide pathologic variations in this stage. Defranchi and colleagues [1] present a series of 59 patients from a cohort of 968 who had clinical stage I disease

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