Evidence for Expanding Invasive Mediastinal Staging for Peripheral T1 Lung Tumors

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BACKGROUND: Guidelines recommend invasive mediastinal staging for patients with non-small cell lung cancer and a “central” tumor. However, there is no consensus definition for central location. As such, the decision to perform invasive staging largely remains on an empirical foundation.

RESEARCH QUESTION: Should patients with peripheral T1 lung tumors undergo invasive mediastinal staging?

STUDY DESIGN AND METHODS: All participants with a screen-detected cancer with a solid component between 8 and 30 mm were identified from the National Lung Screening Trial. After translation of CT data, cancer location was identified and the X, Y, Z coordinates were determined as well as distance from the main carina. A multivariable logistic regression model was constructed to evaluate for predictors associated with lymph node metastasis.

RESULTS: Three hundred thirty-two participants were identified, of which 69 had lymph node involvement (20.8%). Of those with lymph node metastasis, 39.1% were N2. There was no difference in rate of lymph node metastasis based on tumor size (OR, 1.03; $P = .248$). There was also no statistical difference in rate of lymph node metastasis based on location, either by distance from the carina (OR, 0.99; $P = .156$) or tumor coordinates (X: $P = .180$; Y: $P = .311$; Z: $P = .292$). When adjusted for age, sex, histology, and smoking history, there was no change in the magnitude of the risk, and tests of significance were not altered.

INTERPRETATION: Our data indicate a high rate of N2 metastasis among T1 tumors and no significant relationship between tumor diameter or location. This suggests that patients with small, peripheral lung cancers may benefit from invasive mediastinal staging.

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ABBREVIATIONS: CHEST = American College of Chest Physicians; EBUS = endobronchial ultrasound; ESTS = European Society of Thoracic Surgery; NLST = National Lung Screening Trial; NSCLC = non-small cell lung cancer; TBNA = transbronchial needle aspiration

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Lung cancer is the leading cause of cancer-related deaths worldwide. In the United States alone, there were more than 200,000 new cases of lung cancer in 2018, and more than 150,000 deaths of lung cancer.¹ Choice of therapy and prognosis both depend on the stage at diagnosis. For instance, patients with clinical stage IIIA non-small cell lung cancer (NSCLC) will be offered chemotherapy or radiation, potentially followed by surgery or immunotherapy, whereas patients with clinical stage I disease will generally go directly to surgery if considered suitable candidates. Distinguishing between stages I, II, and III primarily relies on assessment of the hilar and mediastinal lymph nodes.

CT and PET-CT have limited utility in the detection of hilar and mediastinal lymph node metastasis. Guidelines from the American College of Chest Physicians (CHEST), European Society of Thoracic Surgery (ESTS), and the National Comprehensive Cancer Center

recommend invasive mediastinal staging via a needle-based technique such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TNBA), transesophageal endoscopic ultrasound with fine needle aspiration, or mediastinoscopy in patients with an increased risk of nodal metastasis.²⁻⁵ That risk is generally codified by the presence of a large tumor (eg, T2), an enlarged N1 lymph node (hilar lymph node), or a “central” tumor location.²⁻⁵ However, guidelines do not provide a strict definition of “central,” and several articles have reported no increase in the risk of mediastinal metastasis based on central location of the primary tumor.⁶⁻⁸ Thus, the decision to perform invasive mediastinal staging for T1 lesions without overt lymphadenopathy largely remains on empiric footing. Given these uncertainties, we aimed to better characterize the risk of hilar and mediastinal lymph node metastasis based on a quantitative assessment of cancer location.

Methods

Study Populations

This study was approved through the University of Vermont Medical Center Institutional Review Board (IRB number 16-466). It was also approved as part of a data sharing agreement with National Cancer Institute. Details of the National Lung Screening Trial (NLST) have been published previously (NCT00047385).^{9,10} Briefly, the NLST was a multicenter study that randomized over 50,000 at-risk participants to either annual CT or chest radiograph screening. Participants underwent three rounds of annual CT or chest radiograph screening and were subsequently followed up for 5 years or until an end point was reached. All lung cancer endpoints were adjudicated. All participants with a single, screen-detected NSCLC between 8 and 30 mm and no enlarged lymph nodes based on the interpreting radiologist's assessment were included. Final mediastinal lymph node (N) stage was abstracted from the NLST based on the documented final stage and size-based tumor stage (T), allowing capture of the N stage. Staging was reported according to the 7th edition of the TNM staging system.

Quantitative CT Analysis

Quantitative image analysis was performed using the freely available Chest Imaging Platform.¹¹⁻¹⁴ After translation of CT image data, cancer location was identified based on information captured as part of the NLST. Pure ground-glass lesions carry a low risk for mediastinal and hilar lymph node metastasis and were excluded.^{15,16} A reference fiducial point was placed on the main carina and defined as the origin for a Cartesian coordinate system, in which X

represents the medial-lateral axis, Z the superior-inferior axis, and Y the anterior-posterior axis. The coordinates for each cancer were then determined. The radial distance from the carina to the center of the cancer was also calculated. The three Cartesian coordinates and the distance from the carina to the cancer were normalized by the cube root of the lung volume; the coordinates were then converted into units (mm) according to an idealized lung based on the average lung volume. All image analysis was performed while blinded to the outcome of N stage.

Statistical Analysis

All statistical analyses were performed using SAS Version 9.4. Two-sided *P* values less than .05 were considered significant. For continuous normally distributed variables, *P* values were based on the two-sample Satterthwaite *t*-test. For all other continuous variables, the Kruskal-Wallis test was used. Categorical variables were compared using Fisher exact test.

The primary outcome for all logistic regression models was the presence of lymph node metastasis. We fit a separate model for each tumor location variable (X coordinate, Y coordinate, Z coordinate, and distance from carina to cancer). Models were adjusted for clinical and epidemiologic variables known to be associated with lymph node metastasis: age, sex, smoking pack-years, lung cancer histopathology, and tumor diameter. Model goodness-of-fit was evaluated using the Hosmer-Lemeshow test. Associations were evaluated using Wald χ^2 test and were summarized by ORs along with 95% CIs.

Results

Three hundred thirty-two cases met inclusion criteria. Of those, 69 were found to have mediastinal lymph node involvement (20.8%). A significant portion of those, 27 of 69, were N2 lymph nodes (39.1%). There were no

significant differences in patient or tumor characteristics between those who did or did not have lymph node metastasis (Table 1). The most common histopathology in those with and without metastasis was adenocarcinoma, at 65.2% and 68.8%, respectively. No

TABLE 1] Characteristics of the National Lung Screening Trial Cohort

Characteristic	Lymph Node Metastasis		P Value
	No (n = 263)	Yes (n = 69)	
Age, y, mean (SD)	63.2 (5.3)	63.2 (5.1)	.975
Sex, No. (%)			.106
Male	135 (51.3)	43 (62.3)	
Female	128 (48.7)	26 (37.7)	
Smoking, mean (SD)	43.0 (7.1)	43.4 (6.4)	.695
Family history of lung cancer, No. (%)			1.000
No	183 (69.6)	50 (72.5)	
Yes	68 (25.9)	18 (26.1)	
Missing/unknown	12 (4.6)	1 (1.4)	
Histopathology, No. (%)			.319
Adenocarcinoma	181 (68.8)	45 (65.2)	
Squamous cell	45 (17.1)	10 (14.5)	
Large cell	12 (4.6)	2 (2.9)	
NOS	25 (9.5)	12 (17.4)	
%LAA-950, median (IQR)	7.7 (14.9)	7.2 (11.4)	.547
Diameter (mm), mean (SD)	13.9 (5.9)	14.9 (7.0)	.296
Carina to cancer (mm), ^a mean (SD)	98.5 (26.6)	93.6 (20.0)	.096
X-axis coordinate (mm), ^a median (IQR)	−34.4 (139.2)	−43.1 (126.1)	.125
Y-axis coordinate (mm), ^a median (IQR)	15.4 (59.6)	13.4 (58.2)	.340
Z-axis coordinate (mm), ^a median (IQR)	7.9 (79.2)	8.6 (73.6)	.414

^aNormalized by the cube root of the lung volume.

significant difference was found in the overall distribution of histologies between patients with and without lymph node metastases ($P = .319$). No significant difference was found in the mean tumor diameter between those with and without lymph node metastasis (14.9 mm vs 13.9 mm, $P = .296$).

We also evaluated the risk of lymph node metastasis by strata of tumor diameter and found that the presence of lymph node metastasis was not significantly different when tumors were broken down by 10-mm size groupings ($P = .56$). Distribution of lymph node metastases was also assessed across strata of tumor diameter (Table 2). Even among tumors smaller than 10 mm, there was a 19.3% risk of lymph

node metastasis, and 31.8% of these nodal metastases were to N2 sites. We did find that 5.8% of the cancers with lymph node involvement had N3 disease; this was restricted to tumors with diameters greater than 10 mm.

Figure 1 demonstrates the normalized location of all tumors. There was not a statistically significant difference in the normalized distance from the carina to the cancer between those with and without metastases (93.6 mm vs 98.5 mm, $P = .096$). None of the normalized tumor coordinate positions (X, Y, or Z) was associated with an increased risk for metastasis (Table 1). Nonnormalized values are presented in e-Table 1.

TABLE 2] Lymph Node Metastasis by Tumor Diameter

Tumor Diameter (mm)	Risk of Any LN Metastasis (%)	Percent of N Stage Metastases, No. (%)			
		N1	N2	N3	Total
≤10	19.3	15 (68.2)	7 (31.8)	0 (0.0)	22 (100.0)
>10 and ≤20	20.1	16 (47.1)	16 (47.1)	2 (5.9)	34 (100.0)
>20	26.5	7 (53.8)	4 (30.8)	2 (15.4)	13 (100.0)

Figure 1 – Absolute lung nodule location by presence or absence of lymph node metastasis, within the normalized lung. The size of the dot is proportional to the diameter of the tumor.

To address potential confounding among potential risk factors, we performed multivariable logistic regression with the outcome of lymph node metastasis. We began by evaluating univariate effects of covariates from Table 1 and found that none were significant in univariate analysis (e-Table 2). We then fit multivariable models to adjust for variables previously reported to be associated with increased risk of lung cancer metastasis: age, sex, smoking, histopathology, and diameter.¹⁷ Adjusted ORs with CIs and tests of significance for cancer location variables are presented in Table 3. When adjusted in multivariable logistic regression, neither the coordinate variables nor the carina-to-cancer distance was significant, confirming the lack of association between the distance/coordinate values and the risk of lymph node metastasis (Table 3; additional detail shown in e-Table 2).

We also evaluated the risk of mediastinal lymph node metastasis. We created a model to predict N2 or N3 (vs N0 or N1) disease by performing multivariable logistic regression analysis using the same adjustment factors described previously. No location parameter (coordinate or carina-to-cancer distance) was significantly associated with risk of N2 or N3 metastasis (e-Table 3).

Discussion

The TNM staging system classifies tumor characteristics into disease stage groups and is used worldwide for the evaluation of lung cancer. One of the primary aims of staging is assessing for metastatic lymph node involvement.¹⁸ Methods for assessing for hilar and mediastinal metastasis include CT, PET-CT, and invasive pathologic nodal assessment. PET-CT has

TABLE 3] Adjusted Risk of Lymph Node Metastasis by Tumor Location

	OR _{Adj} ^a [95% CI]	P Value
X coordinate	1.00 [0.989, 1.003]	.220
Y coordinate	0.99 [0.983, 1.005]	.294
Z coordinate	1.01 [0.996, 1.015]	.262
Carina to Cancer	0.99 [0.967, 1.006]	.163

^aAdjusted for age, sex, smoking, histopathology, and diameter.

improved the accuracy of N staging compared with either test alone, but the poor spatial detail and use of the nonspecific marker fluorodeoxyglucose result in inaccuracies that limit its utility.¹⁹ Noninvasive staging with PET-CT has only a 65% to 70% sensitivity for detection of metastases to the hilar and mediastinal lymph nodes.^{2,20} Because of this limitation, guidelines recommend invasive mediastinal sampling via a needle-based technique (EBUS or transesophageal endoscopic ultrasound) or mediastinoscopy in patients with an increased risk for nodal metastasis.²⁻⁵ One of the factors thought to portend an increased risk is tumor location. The ESTS, National Comprehensive Cancer Center, and CHEST all recommend invasive mediastinal staging for patients with a radiographically negative mediastinum and a “central” tumor, regardless of the tumor size, but no strict definition of central tumor location exists.²⁻⁴

Studies that have evaluated central vs peripheral location as a risk for lymph node metastasis have used varying definitions of “central.” Prior designations of “central” have included lesions within the inner two thirds of the hemithorax,^{6,21} within the inner one third of the hemithorax,^{22,23} visible during standard video bronchoscopy,²⁴ located within 2 cm of any critical structure in the mediastinum,²⁵ located within 2 cm of the proximal bronchial tree,²⁶ and in proximity to the first intrapulmonary branches.²⁷ Data from a survey distributed to members of the American Association of Bronchology and Interventional Pulmonology and the Cardiothoracic Surgery Network demonstrated that most (55%) of providers defined “central” as within the inner one third of the hemithorax, although there were still discrepancies with how providers delineated thirds of the hemithorax.²⁸ These considerations motivated our approach of leveraging quantitative metrics of tumor location and distance from the carina to define the risk of lymph node metastasis.

There are several notable findings from the current study. One of the most prominent is the overall risk of N2 disease (8.13%), even among T1 tumors. These data highlight the fact that the cellular capacities for proliferation and invasion are distinct, though related, hallmarks of cancer, and even small tumors possess the ability to metastasize.²⁹⁻³¹ The 9.34% overall risk of N2 or N3 disease is consistent with prior reports.^{6,32} In a subset of patients with NSCLC and negative PET-CT, Gonzalez-Stawinski et al³³ reported a rate of N2 or N3 disease of 11.6%. Using data from surgical databases, Shin and colleagues²³ reported a 6.9% rate of N2 or N3 disease. Similarly, a single-center retrospective review reported a

13% rate of N2 disease in patients who had shown no radiographic evidence of lymph node metastasis.⁷

Second, we did not find a statistically significant association between absolute tumor location and risk of lymph node metastasis. This is the first study to evaluate this question in a blinded, quantitative manner. Unlike prior studies, we evaluated a population at the time of diagnosis, thereby minimizing potential selection bias associated with evaluating patients already chosen for surgery or radiation.³⁴ Other studies have also failed to demonstrate an effect of tumor location on risk of lymph node metastasis. Bao et al⁷ evaluated T1 lesions; they found a 12.4% risk of N2 metastasis among peripheral <2 cm tumors, which was not significant compared with central tumors when “central” was defined as within the inner two thirds of the hemithorax.⁷ Using the same definition of “central,” Lee and colleagues found that among tumors <2 cm with a PET-negative mediastinum, there was no significant difference in occult N2 metastasis for central vs peripheral lesions.⁶ Recently, a study by Roy et al⁸ showed no difference in likelihood of nodal metastasis when defining a lesion as “central” by either the inner one third or inner two thirds of the hemithorax.⁸ These data support our findings that among T1 tumors, peripheral/central categorization of tumors is not predictive of N2 metastasis.

We created a series of systemic metrics to quantify lung cancer location on a continuous scale to better define whether any location signifies a higher risk of nodal involvement. The quantitative metrics deployed here would be expected to capture the effect of location on the risk of metastasis with maximal sensitivity because they do not rely on an arbitrarily chosen distance cutoff. Despite this, we did not find an effect of tumor location, in terms of either an X, Y, Z coordinates or radial distance from the carina to the cancer. We also specifically evaluated the risk of advanced lymph node metastasis by creating a multivariable logistic regression model to predict the risk of N2 and N3 disease. This model similarly failed to identify a location for which advanced lymph node metastasis is increased. This data also did not demonstrate that size was a contributing risk factor for increasing likelihood of lymph node metastasis, which is likely attributable to the fact that all lesions in this study were T1 tumors.

A high rate of hilar and mediastinal metastasis that is present even in tumors <10 mm, and that is not dependent on tumor location, implies that patients with

small, peripheral tumors may benefit from invasive mediastinal staging. The results presented here, taken together with variances in definition, practice, and outcomes related to “central” location, now beg the question of whether this definition should be abandoned. The CHEST and ESTS both advocate for endoscopic needle-based techniques, rather than mediastinoscopy, for initial mediastinal staging, with the most common needle-based staging modality being EBUS-TBNA. EBUS-TBNA has been shown to have a sensitivity of >90% for patients with enlarged or PET-CT-positive N2/N3 lymph nodes.³⁵⁻³⁷ In patients who are identified to have very early stage NSCLC, such as those with N0 or N1 lymph nodes, a recent meta-analysis found that systematic staging by EBUS-TBNA had a negative predictive value of 91% for detection of occult N2/N3 disease in the radiologically negative mediastinum, with a number needed to test 14 patients.³⁸ Therefore, consideration must be taken when deciding whether a patient should undergo these procedures. However, EBUS-TBNA has a risk of complications of <1%, which implies a relatively robust benefit-to-risk ratio when considering expanding the indications for invasive mediastinal staging.³⁹

There are several important limitations to these data. First, patients enrolled in the NLST did not undergo a strict staging protocol. However, the study did include over 30 centers, implying that these data likely reflect standard US practice and imply generalizability of the results; this is also supported by the fact that overall rates of lymph node metastasis reported here are consistent with prior reports. Second, how many patients underwent PET-CT staging is unknown. Although PET-CT is a standard component of staging for NSCLC, evidence suggests that PET may not provide significant benefit for preoperative assessment of the mediastinum because of low sensitivity.^{7,40,41} Additionally, given the size and location of the tumors included in this study, guidelines do not strictly recommend PET-CT for evaluation of the mediastinum.^{2,3,5} In a retrospective review of patients who had a negative PET-CT, Gao et al⁴² found a rate of N2 metastasis in T1 tumors of only 3.6%, which is considerably less than the rate

reported here.⁴² However, they included pure ground-glass lesions, which are known to carry a low risk of mediastinal or hilar metastasis and were excluded from this study. Interestingly, the likelihood of N2 disease in solid T1 lesions was 5.6%; a value more similar to the 8.13% incidence of N2 disease found in this study, particularly given that the patients included in that study underwent PET-CT in addition to a diagnostic CT scan.

Third, we cannot comment on the location or number of sites of metastasis in the mediastinum, as we only have information regarding the highest N stage. Thus, it is difficult to make further inferences regarding the potential benefits of different invasive staging modalities. Finally, the NLST only provides the final clinical stage according to the TNM staging criteria, so the N stage was inferred using tumor size to determine T stage. Variables other than size can increase the T stage, namely invasion of the visceral pleural, resulting in obstructive pneumonitis that extends to the hilar region or involvement of a main bronchus. This information is not available in the NLST, so it is possible that some of the reported clinical stages reflect cancers with a higher T stage and lower N stage than what was concluded. However, all images were reviewed to determine the fiducial point, and obstructive atelectasis and frank visceral invasion were not present. Similarly, the average distance from the carina to the cancer was 93.6 mm, highlighting the fact that these were predominantly peripheral lesions (Fig 1) and would be very unlikely to be upstaged based on obstruction or invasion of central mediastinal structures. Similarly, limiting the analysis to only N2 or N3 lymph node metastases did not demonstrate a significant difference in the results.

In summary, we performed a blinded, quantitative assessment of tumor location as a risk factor for hilar and mediastinal lymph node metastasis from a multicenter cohort of patients with T1 lung tumors. We found that there remains a high rate of N2 or N3 metastasis even among small tumors, and no clear definition of “central” modifies this risk. These data may justify expanding current invasive staging practice to include small, peripheral tumors.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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