Lobe-specific lymph node sampling is associated with lower risk of cancer recurrence

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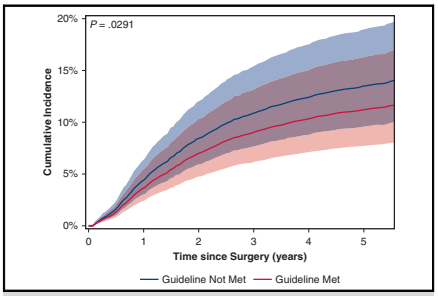
ABSTRACT

Objective: Adequate intraoperative lymph node (LN) assessment is a critical component of early-stage non–small cell lung cancer (NSCLC) resection. The National Comprehensive Cancer Network and the American College of Surgeons Commission on Cancer (CoC) recommend station-based sampling minimums agnostic to tumor location. Other institutions advocate for lobe-specific LN sampling strategies that consider the anatomic likelihood of LN metastases. We examined the relationship between lobe-specific LN assessment and long-term outcomes using a robust, highly curated cohort of stage I NSCLC patients.

Methods: We performed a cohort study using a uniquely compiled dataset from the Veterans Health Administration and manually abstracted data from operative and pathology reports for patients with clinical stage I NSCLC (2006-2016). For simplicity in comparison, we included patients who had right upper lobe (RUL) or left upper lobe (LUL) tumors. Based on modified European Society of Thoracic Surgeons guidelines, lobe-specific sampling was defined for RUL tumors (stations 2, 4, 7, and 10 or 11) and LUL tumors (stations 5 or 6, 7, and 10 or 11). Our primary outcome was the risk of cancer recurrence, as assessed by Fine and Gray competing risks modeling. Secondary outcomes included overall survival (OS) and pathologic upstaging. Analyses were adjusted for relevant patient, disease, and treatment variables.

Results: Our study included 3534 patients with RUL tumors and 2667 patients with LUL tumors. Of these, 277 patients (7.8%) with RUL tumors and 621 patients (23.2%) with LUL tumors met lobe-specific assessment criteria. Comparatively, 34.7% of patients met the criteria for count-based assessment, and 25.8% met the criteria for station-based sampling (ie, any 3 N2 stations and 1 N1 station). Adherence to lobe-specific assessment was associated with lower cumulative incidence of recurrence (adjusted hazard ratio [aHR], 0.83; 95% confidence interval [CI], 0.70-0.98) and a higher likelihood of pathologic upstaging (aHR, 1.49; 95% CI, 1.20-1.86). Lobe-specific assessment was not associated with OS.

Conclusions: Adherence to intraoperative LN sampling guidelines is low. Lobe-specific assessment is associated with superior outcomes in early-stage NSCLC. Quality metrics that assess adherence to intraoperative LN sampling, such as the CoC Operative Standards manual, also should consider lobe-specific criteria. (JTCVS Open 2024;17:271-83)



Lobe-specific lymph node sampling and recurrence.

CENTRAL MESSAGE

Lobe-specific lymph node assessment for early-stage non–small cell lung cancer is associated with lower risk of cancer recurrence.

PERSPECTIVE

Adequate lymph node (LN) assessment is an important component of surgical care of early-stage non–small cell lung cancer (NSCLC). Previous station-based and count-based minimums have been advocated, but there is limited evidence to suggest an optimal strategy. We found that patients with stage I NSCLC who underwent lobe-specific LN assessment had a significantly decreased cumulative risk of recurrence.

See Discussion page 284.

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Abbreviations and Acronyms

ACS = American College of Surgeons
aHR = adjusted hazard ratio
CoC = Commission on Cancer
ESTS = European Society of Thoracic Surgeons
HR = hazard ratio
IQR = interquartile range
LN = lymph node
LUL = left upper lobe
NSCLC = non–small cell lung cancer
OS = overall survival
RUL = right upper lobe
SEER = Surveillance, Epidemiology, and End Results
VHA = Veterans Health Administration

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Lung cancer is the leading cause of cancer-related death in the United States.[1] Surgical resection remains the mainstay of therapy for surgically fit patients with early-stage disease.[2] A key component of surgical management of disease is to obtain accurate pathologic staging, which can guide appropriate receipt of adjuvant therapy. Adequate intraoperative assessment of hilar and mediastinal lymph nodes (LNs) is key to accurate pathologic staging.

The debate on what constitutes appropriate LN assessment has been ongoing for decades. A complete LN dissection was previously touted as standard of care; however, the pivotal randomized controlled trial (ACOSOG-Z0030) reported by Darling and colleagues[3] did not detect any long-term differences in survival or recurrence between LN dissection and LN sampling in patients who underwent anatomic resection for clinical stage I non–small cell lung cancer (NSCLC).[3] This authors concluded that if systematic and thorough sampling of the mediastinal and hilar LNs is negative, then intraoperative LN sampling may be adequate, especially in the context of clinically "node-negative" disease.

What defines adequate intraoperative LN assessment remains unclear, however. Numerous strategies have been championed by various societal guidelines. The American College of Surgeons (ACS) Commission on Cancer (CoC) previously advocated for a count-based sampling strategy of a minimum of 10 LNs sampled, regardless of tumor or station location.[4] In their most recent update, the ACS has modified their recommendation to sampling 3 N2 stations and 1 N1 station, which is similar to guidelines proposed by the National Comprehensive Cancer Network.[4-6] The data linking these strategies to long-term outcomes, including survival and recurrence, are mixed.

Count-based and station-based strategies do not take into account anatomic LN drainage pathways. Moreover, adherence to these sampling strategies remains notoriously poor.[7] Alternative strategies based on mediastinal LN drainage patterns have been proposed. Okada and colleagues[8] were some of the earliest to characterize patterns of LN metastases in patients with early-stage NSCLC. They observed that upper lobe tumors tended to not have subcarinal node metastases and that lower lobe tumors rarely had skip metastasis to superior mediastinal node stations. They suggested that for upper lobe tumors, inferior mediastinal LN dissection is not necessary if the hilar and superior mediastinal nodes are tumor-free. Likewise, they recommended that superior mediastinal and aortic nodes can be omitted for lower lobe tumors. Such LN metastasis patterns have informed the proposal for lobe-specific LN strategies. Some professional societies, including the European Society for Thoracic Surgeons (ESTS), have suggested that a lobe-specific LN strategy may be appropriate for early-stage peripheral NSCLC tumors.[9] However, data on the relationship between lobe-specific LN sampling strategies and long-term outcomes regarding survival, recurrence, and pathologic upstaging are limited. No previous studies have examined lobe-specific LN assessment strategies and important long-term outcomes in a large US cohort. We hypothesized that lobe-specific LN assessment would be associated with improved recurrence-free survival.

We used a novel repository of patients with clinical stage I NSCLC from the Veterans Health Administration (VHA). Our group abstracted detailed clinicopathologic and procedural details from pathology reports and operative notes and assembled LN collection data for nearly 10,000 veterans. We evaluated the relationship between lobe-specific LN assessment criteria adapted from modified ESTS guidelines and long-term outcomes, including risk of cancer recurrence, overall survival (OS), and pathologic upstaging.

METHODS

Data Source and Cohort Selection

We performed a retrospective analysis of a cohort of adults with clinical stage I NSCLC who underwent surgical treatment through the VHA between 2006 and 2016. Data elements for this study were queried using the VHA Informatics and Computing Infrastructure (VINCI) system, which collates clinical and administrative data from multiple platforms in the Corporate Data Warehouse (CDW). Diagnoses of clinical stage I NSCLC (according to the American Joint Committee on Cancer Staging Manual, seventh edition) were determined using International Classification of Diseases (ICD) for Oncology, third edition (ICD-O-3) codes. Surgical resection was confirmed using ICD-9/10 procedure and Current Procedural Terminology (CPT) codes, which were cross-referenced across the VHA oncology (CDW Oncology Raw) and surgery (Veterans Affairs Surgical Quality Improvement Program) data repositories.[10,11] A team of dedicated data analysts and research coordinators performed additional data extraction and verification over a period of more than 20 months using

manual chart review and natural language processing. Exclusion criteria were patients receiving neoadjuvant therapy, patients undergoing surgery for recurrent disease, or patients with a missing date of diagnosis. Our research protocol was approved by the St. Louis VHA Research and Development Committee (1214632; approved August 2, 2019). Our study was considered exempt from the Institutional Review Board approval process, given that patient identifiers were removed prior to analyses. The results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12]

LN Sampling Strategies

We adapted lobe-specific LN strategies from a modified version of the ESTS intraoperative lobe-specific LN sampling. For ease of comparison, we focused on patients with right upper lobe (RUL) or left upper lobe (LUL) tumors. Based on modified ESTS guidelines, lobe-specific assessment was defined for RUL tumors as collecting at least 1 LN from each of the stations 2, 4, 7, and 10 or 11.[9] For LUL, LNs had to be sampled from stations 5 or 6, 7, and 10 or 11. We used recommendations from the National Comprehensive Cancer Network to define station-based LN sampling, which advocates for sampling 3 N2 stations and 1 N1 station regardless of tumor location.[6] These guidelines leave selection of N2 and N1 stations to the surgeon's discretion. This strategy is now being advocated by recently updated guidelines published by the ACS CoC. We defined a count-based strategy of a minimum of 10 LNs sampled (regardless of station) from previous recommendations by the ACS CoC.[4]

LN sampling information, including number of LNs and station locations, was obtained from operative and pathology reports, which were accessed through the Compensation and Pension Record Interchange system. Nodes and stations that were collected during mediastinoscopy or endobronchial ultrasound were included in the assessment. Two clinical research associates who received specialized training performed the data abstraction. To further ensure accuracy, the first 200 report abstractions were supervised by a board-certified thoracic surgeon. The subsequent 300 reports were independently abstracted by these 2 investigators, in which a <3% discordance rate was achieved (which was the prespecified threshold for acceptable concordance per the study protocol). All discordant abstractions were adjudicated by a thoracic surgeon. Patients were classified on the basis of whether they met lobe-specific LN guidelines. These patients also were classified as to whether or not they met count-based or station-based sampling guidelines. All LN stations were defined according to the International Association for the Study of Lung Cancer map.[13]

Covariates

We extracted several additional covariates for our analysis from the VHA CDW, including age, sex, body mass index, and comorbidities. Comorbidities were measured with the composite Charlson-Deyo score by using ICD-9/10 codes to assess specific comorbidities over the span of 5 years preoperatively to 1 month postoperatively.[14,15] We also calculated the Area Deprivation Index, a county-based measure of socioeconomic deprivation that incorporates multiple poverty, education, housing, and employment indicators from the US census.[16] Higher scores represent a higher level of geographically based socioeconomic deprivation (ie, more disadvantaged residential neighborhood), which we presented in quintiles. Of note, the Area Deprivation Index has previously been associated with worse lung cancer outcomes.[17]

Several treatment-related covariates were also extracted, including tumor size, grade, histologic type (adenocarcinoma, squamous, other), year of operation, hospital case load (defined as the volume of lung cancer cases treated in that VHA facility in the year before surgery), surgical approach (minimally invasive or thoracotomy), type of operation (lobectomy, segmentectomy, wedge resection, or pneumonectomy), and final pathologic stage.[18,19]

Outcomes

Our primary outcome was risk of cancer recurrence. Secondary outcomes included long-term OS and pathologic upstaging. Recurrence was assessed using the CDW Oncology database, which uses the Facility Oncology Registry Data Standards definition of recurrence. However, when not documented, we used a collection of ICD-9/10 diagnosis codes (Table E1) that would delineate between a diagnosis of recurrence as opposed to a new primary (eg, diagnosis of malignant pleural effusion, multiple metastases.) as described previously in the VHA literature and by our group.[20,21] When available, CDW Oncology database captures information on recurrence location (ie, locoregional vs distant recurrence). However, documentation of recurrence location is incomplete in the database. As part of our analysis, we assessed recurrence as a whole (regardless of location). OS was determined using the CDW Vital Status File.[22] Patients were censored at the date of last follow-up (May 1, 2020). We also assessed additional outcomes, including 30-day readmission and 30-day major complications. Major complication was defined as pneumonia, empyema, myocardial infarction, respiratory failure, renal failure, or stroke within 30 days after surgery (consistent with definitions from the Society of Thoracic Surgery).[23,24]

Statistical Analysis

Descriptive statistics were presented for the cohort using mean (SD) for continuous variables and frequency (proportion) for categorical variables, with corresponding t test or χ^2 test statistics. Median and interquartile range (IQR) were recorded for nonnormally distributed covariates. OS was assessed using the multivariable Cox proportional hazards model and displayed using the Kaplan-Meier method. The risk of cancer recurrence was assessed with a multivariable competing risk model (Fine and Gray subdistribution hazard function), with recurrence as the outcome and death as a competing event. Risk of pathologic upstaging was assessed by multivariable logistic regression analysis. Models for OS, cancer recurrence, and pathologic upstaging were adjusted for interested patient, tumor, and treatment-related covariations determined a priori based on clinical significance and the literature. Missing data were reported in the descriptive analyses. Unless specifically listed, complete-case analyses were used. All tests were 2-sided. P values < .05 were considered statistically significant. All analyses were performed in SAS version 9.4 (SAS Institute).

RESULTS

Study Cohort

The study cohort included 6201 patients, of whom 3534 (57.0%) had RUL tumors and 2667 (43.0%) had LUL tumors (Figure E1). Of these patients, 277 (7.8%) with RUL tumors and 621 (23.2%) with LUL tumors met the lobe-specific sampling criteria. In terms of patient demographics, patients who met lobe-specific LN assessment criteria had similar age and sex distributions as well as comorbidity profiles (Table 1). The racial makeup of each subcohort was significantly statistically different ($P < .0001$); however, there were no differences in other sociodemographic variables, including smoking status, Charlson-Deyo score, and Area Deprivation Index.

In terms of preoperative staging, similar rates of positron emission tomography scanning were similar in the patients who met and those who did not meet the lobe-specific LN criteria (755 [86.1%] vs 4403 [83.0%]; $P = .4378$). Rates of invasive preoperative nodal assessment differed,

however. Patients who did not meet the lobe-specific LN criteria had a lower rate of preoperative endobrachial ultrasound or mediastinoscopy (973 [18.4%] vs 243 [27.1%]; $P < .0001$). Approximately 94% of cases in each cohort were performed by a cardiothoracic surgeon (as opposed to a general surgeon). Patients who met the lobe-specific LN criteria were more likely to have a minimally invasive operation (49.67% vs 40.32%; $P < .0001$) (Table 2). Additionally, patients who met the lobe-specific LN criteria were less likely to receive a nonanatomic resection (wedge resection, 10.69% vs 24.57%; $P < .0001$). For short-term outcomes, the lobe-specific LN patients had a somewhat higher 30-day readmission rate (10.79% vs 7.47%; $P = .0039$). The 2 cohorts had similar rates of major complications and 30-day mortality.

Regarding survivorship care, we documented the frequency of computed tomography scan surveillance. We previously published data on imaging surveillance frequency and defined low-frequency CT scanning as <2 scans per year (ie, a scan every 6-12 months within the first 2 years).[25] High-frequency CT scanning was defined as ≥2 scans/year (ie, a scan roughly every 3-6 months). Among the patients who met lobe-specific LN assessment criteria, 297 (33.7%) underwent high-frequency scanning and 601 (66.9%) underwent low-frequency scanning. Among the patients who did not meet lobe-specific LN assessment criteria, 1781 (33.6%) underwent high-frequency scanning and 3522 (66.4%) underwent low-frequency scanning. There was no difference in the distribution of surveillance imaging frequency ($P = .9104$).

Adherence to LN Sampling and Patterns of Metastases

Adherence to LN assessment strategies was low; only 14.5% of the study cohort met lobe-specific sampling criteria. Comparatively, 34.7% of patients met the criteria for count-based sampling, and 25.8% met the criteria for station-based sampling. A low rate of subcarinal LN metastases was observed. Among the 3534 patients with RUL tumors, 710 (20.1%) had station 9 LNs sampled. Only 0.3%

TABLE 1. Patient clinical and demographic characteristics

Characteristic	Did not meet LN-specific sampling criteria (N = 5303)	Met lobe-specific LN sampling criteria (N = 898)	*P* value
Age, y, mean (SD)	67.4 (7.91)	66.97 (7.72)	.1314
Male sex, n (%)	5110 (96.36)	866 (96.40)	.9104
Race, n (%)			<.0001
White	4350 (82.03)	727 (80.96)	
Black	838 (15.81)	132 (14.70)	
Other	58 (1.09)	31 (3.45)	
Unknown	57 (1.07)	8 (0.89)	
BMI, n (%)			.7319
<18.5	425 (8.01)	77 (8.57)	
18.5-24.9	1707 (32.19)	300 (33.41)	
25-29.9	1817 (34.26)	297 (33.07)	
30-34.9	980 (18.48)	155 (17.26)	
35+	374 (7.06)	69 (7.69)	
Smoking status, n (%)			.1119
Current	3188 (60.12)	508 (56.57)	
Former	2051 (38.67)	376 (41.87)	
Never	64 (1.21)	14 (1.56)	
Charlson-Deyo score, mean (SD)	6.86 (2.20)	6.77 (2.19)	.2483
Distance, n (%)			<.0001
≤10 miles	1178 (22.21)	176 (19.60)	
11-50 miles	2191 (41.32)	292 (32.52)	
50+ miles	1934 (36.47)	430 (47.88)	
Area Deprivation Index, n (%)			.9990
Quartile 1	1312 (24.74)	221 (24.61)	
Quartile 2	1316 (24.82)	225 (25.06)	
Quartile 3	1376 (25.95)	234 (26.06)	
Quartile 4	1273 (24.01)	217 (24.16)	
Unknown	26 (0.49)	1 (0.11)	

LN, Lymph node; *BMI*, body mass index.

TABLE 2. Treatment- and tumor-related characteristics

Characteristic	Did not meet LN-specific sampling criteria (N = 5303)	Met lobe-specific LN sampling criteria (N = 898)	*P* value
Treatment-related			
Delay in surgery, n (%)	1633 (30.79)	267 (29.73)	.5235
Surgeon specialty, n (%)			.4585
Cardiothoracic	4838 (93.74)	841 (94.39)	
Other	465 (6.26)	57 (5.61)	
Incision, n (%)			<.0001
Thoracotomy	3149 (59.38)	451 (50.33)	
Minimally invasive	2138 (40.32)	445 (49.67)	
Unknown	16 (0.30)	2 (0.22)	
Resection, n (%)			<.0001
Lobectomy	3665 (69.11)	742 (82.63)	
Pneumonectomy	73 (1.38)	13 (1.45)	
Segmentectomy	262 (4.94)	47 (5.23)	
Wedge	1303 (24.57)	96 (10.69)	
Unknown	10 (0.19)	0 (0.0)	
Margins, n (%)			.2164
Negative	5063 (95.47)	871 (97.32)	
Positive	183 (3.45)	24 (2.68)	
Unknown	57 (1.07)	3 (0.33)	
Adjuvant therapy, n (%)			.4378
No	4685 (88.35)	782 (87.10)	
Yes	618 (11.65)	116 (12.92)	
30-d readmission (%)			.0039
No	4906 (92.51)	803 (89.42)	
Yes	396 (7.47)	92 (10.24)	
Unknown	1 (0.02)	3 (0.33)	
Major complications, n (%)			.7681
No	4569 (86.16)	777 (86.53)	
Yes	734 (13.84)	121 (13.47)	
30-d mortality, n (%)			.9942
No	5191 (97.89)	879 (97.88)	
Yes	112 (2.11)	19 (2.12)	
Tumor-related			
Tumor size, n (%)			.2659
≤10 mm	515 (9.71)	79 (8.80)	
11-20 mm	2224 (41.94)	349 (38.86)	
21-30 mm	1452 (27.38)	263 (29.29)	
31-40 mm	765 (14.43)	134 (14.92)	
40+ mm	343 (6.47)	72 (8.02)	
Unknown	4 (0.08)	1 (0.11)	
Histology (%)			.4156
Adenocarcinoma	2891 (54.52)	477 (53.12)	
Squamous cell	1715 (32.34)	310 (34.52)	
Other	697 (13.14)	111 (12.36)	
Grade (%)			.4791
I	588 (11.09)	100 (11.14)	
II	2662 (50.20)	426 (50.53)	
III	1672 (31.53)	304 (35.06)	
IV	79 (1.49)	13 (1.54)	
Unknown	302 (5.69)	55 (6.13)	
Margins, n (%)			.2164
Negative	5063 (95.47)	871 (97.32)	
Positive	183 (3.45)	24 (2.68)	
Pathologic upstaging, n (%)	622 (11.70)	148 (16.50)	<.0001

LN, Lymph node.

of these patients had positive LNs in station 9. Among the 2670 patients with LUL tumors, 943 (35.3%) had station 9 LNs sampled, and only 0.4% had positive station 9 LNs.

Competing Risks Analysis and Risk of Cancer Recurrence

The median time to disease recurrence was not achieved during the study period for the entire cohort. In the cohort, 1442 veterans (23.3%) had documented recurrence during the study period. Patients who met the lobe-specific LN assessment guidelines had a 25% lower risk of disease recurrence (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.70-0.98) (Table 3). Additional risk factors associated with disease recurrence included age, distance from treatment facility, tumor grade, tumor size, resection type, and receipt of pathologic upstaging ($P < .05$). The cumulative incidence of disease recurrence over 5 years in the 2 cohorts is shown in Figure 1. Location of recurrence was documented in 834 patients (57.8%) (Table E2). Patients who met the lobe-specific LN assessment criteria had an almost 10% higher absolute incidence of distant recurrence. Approximately 62% of the recurrences in patients who met the lobe-specific LN criteria were distant, compared to 52% in patients who did not meet the lobe-specific LN criteria; however, distribution of recurrence did not differ significantly between the cohorts ($P = .0755$).

Cox Proportional Hazards Modeling and OS

The median OS for the entire cohort was 6.37 years (IQR, 2.61-11.53 years), including 6.76 years (IQR, 2.56-11.49 years) for the patients who met the lobe-specific LN sampling criteria 6.27 years (IQR, .56-11.49 years) for those who did not ($P = .0871$). Age, race, sex, body mass index, smoking status, and comorbidity burden were patient-related factors independently associated with OS ($P < .05$) (Table 4). In terms of treatment- and tumor-related factors, increasing tumor size (T stage), histology, increasing tumor grade, nonanatomic resection type, surgical approach, delay in surgery, pathologic upstaging, and presence of positive margins were associated with OS ($P < .05$). Lobe-specific LN assessment was not independently associated with OS (Table 4). Adjusted Kaplan-Meier analysis modeling OS is shown in Figure 2.

Pathologic Upstaging

The rate of pathologic upstaging was 16.5% (n = 148) in patients who met the lobe-specific LN sampling criteria 11.7% (n = 622) in those who did not. Multivariable logistic regression analysis was performed for pathologic upstaging. Morbid obesity, adenocarcinoma histology, increasing tumor grade, increasing tumor size, and pneumonectomy resection were significantly associated with increased odds of pathologic upstaging ($P < .05$) (Table 5). Lobe-specific LN assessment (odds ratio, 1.49; 95% CI, 1.20-1.86) was significantly associated with increased odds of pathologic upstaging. Of the 148 upstaged patients who met the lobe-specific LN assessment criteria, 72 patients (48.6%) received adjuvant therapy. Of the 622 upstaged patients who did not meet the lobe-specific LN assessment criteria, 282 (45.3%) underwent adjuvant therapy. Receipt of adjuvant therapy was similar in the 2 cohorts ($P = .4676$).

DISCUSSION

The ability to perform nodal assessment is a critical part of surgical resection. First and foremost, accurate nodal assessment is crucial for accurate pathologic staging. There is significant heterogeneity when it comes to LN examination. Studies have shown that nonexamination of LNs (pNX) occurs in approximately 18% of all "node-negative" lung resections in the United States.[26,27] These patients have been shown to have worse long-term survival compared to matched pN0 cases in which at least 1 LN was examined.[26]

Several retrospective studies using large databases and/or registries have demonstrated a link between adequate LN sampling and long-term outcomes. Osarogiagbon and colleagues[28] queried the US Surveillance, Epidemiology, and End Results (SEER) database to characterize the relationship between intraoperative LNs sampled in pN0 patients and mortality risk. They hypothesized that the number of LNs sampled was a proxy measure for thoroughness of intraoperative examination, and that there was a direct relationship between LN numbers sampled and survival. They aimed to determine the optimal number of LNs sampled to accurately determine the absence of nodal metastases. They used a cohort of 24,650 pathologic stage I to III "node-negative" patients who had at least 1 LN sampled to characterize distributions of LNs sampled and determine the "cutoff" associated with optimal 5-year OS. The median number of LNs sampled was 6, and the number of LNs sampled tended to correlate with the degree of surgical resection. The HR for mortality decreased sequentially with an increasing number of LNs examined, and a maximal benefit was achieved with the examination of 20 nodes. Liang and colleagues[29] reached similar conclusions regarding minimum LN sampling thresholds when examining the correlation between the number of examined LNs, correct staging, and long-term survival in patients with early-stage NSCLC in both a Chinese multi-institutional registry and the US SEER database. They performed cutpoint analysis in the Chinese cohort and validation in the SEER database to determine the optimal LN sampling threshold and identified that sampling of 16 LNs was associated with optimal long-term OS. Observed practices fall dramatically short of this recommendation, however.[18]

TABLE 3. Competing risks model for disease recurrence

Covariate	aHR	*P* value
Age	0.99 (0.98-1.00)	.0441
Female sex	0.91 (0.67-1.23)	.5259
Race		.8216
Caucasian	Reference	
Black	1.01 (0.86-1.18)	
Other	0.86 (0.54-1.37)	
Unknown	0.79 (0.42-1.50)	
BMI		.6437
18.5-24.9	Reference	
<18.5	0.91 (0.73-1.14)	
25-29.9	0.91 (0.79-1.04)	
30-34.9	0.98 (0.83-1.16)	
35+	0.93 (0.74-1.18)	
Smoking status		.2880
Current	Reference	
Former	1.01 (0.90-1.14)	
Never	1.44 (0.92-2.28)	
Charlson-Deyo score	1.01 (0.98-1.04)	.6780
FEV1		.3665
<50	Reference	
50-79	1.06 (0.85-1.32)	
80+	1.09 (0.97-1.22)	
Area Deprivation Index		.3989
Q1	Reference	
Q2	1.00 (0.85-1.18)	
Q3	1.10 (0.93-1.28)	
Q4	1.11 (0.95-1.31)	
Surgeon specialty	1.03 (0.81-1.31)	.8227
Hospital case load	1.00 (1.00-1.00)	.1120
Histology		.1422
Adenocarcinoma	Reference	
Squamous cell	0.89 (0.78-1.01)	
Other	1.04 (0.86-1.24)	
Grade		.0884
I	Reference	
II	1.24 (1.02-1.51)	
III	1.28 (1.04-1.58)	
IV	0.98 (0.58-1.66)	
Delay in surgery		.6449
≤12 wk	Reference	
>12 wk	1.03 (0.91-1.16)	
Tumor size		<.0001
≤10 mm	Reference	
11-20 mm	1.09 (0.88-1.34)	
21-30 mm	1.36 (1.09-1.69)	
31-40 mm	1.50 (1.18-1.90)	
40+ mm	1.10 (0.82-1.49)	
Surgical resection		<.0001
Lobectomy	Reference	
Wedge	1.47 (1.28-1.68)	
Segmentectomy	1.36 (1.06-1.74)	
Pneumonectomy	0.71 (0.41-1.23)	
Surgical approach		.2669
Thoracotomy	Reference	
Minimally invasive	0.94 (0.83-1.05)	
Pathologic upstaging	1.08 (0.90-1.29)	.4047
Positive margin	1.19 (0.90-1.57)	.2244
Receipt of adjuvant therapy	1.79 (1.50-2.13)	<.0001
Lobe-specific LN sampling criteria met	0.83 (0.70-0.98)	.0291

aHR, Adjusted hazard ratio; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *LN*, lymph node.

Lobe-specific LN assessment has been proposed as an alternative to traditional count-based and station-based assessment strategies. The reasoning behind the development of lobe-specific LN assessment was based on previous studies that examined patterns of LN drainage and metastases in patients with early-stage NSCLC. In the 1950s, Nohl and colleagues[30] at the London Chest Hospital first reported that subcarinal LN involvement was rare for upper lobe tumors and when it occurred was most likely a result of nodal involvement around the main bronchus. Okada and colleagues[8] were some of the earliest to formally publish on patterns of LN metastases for patients with clinical stage I NSCLC.[8] They performed a retrospective institutional review of 377 surgical patients with clinical stage I NSCLC patients who underwent lobe-specific LN dissection and compared them to 358 patients who underwent complete lymphadenectomy and observed no difference between the cohorts in disease-free or OS. However, postoperative morbidity was significantly higher in the complete lymphadenectomy group (17.3% vs 10.1%; $P = .005$). When examining LN patterns of metastases, the authors observed that no patients with upper lobe tumors had metastases to the subcarinal nodes. Among the 271 patients with lower lobe tumors, only 1 patient had evidence of disease in a superior mediastinal node. The authors concluded that selective LN dissection for clinical stage I NSCLC is a reasonable strategy that potentially could result in less postoperative morbidity.

The majority of recent studies focusing on lobe-specific LN dissection come from academic centers in Asia. Deng and colleagues[31] performed a study of 590 Chinese patients with clinical stage IA NSCLC who underwent lobectomy or segmentectomy and found an exceedingly rare incidence of metastases (<0.5%) to subcarinal and lower LN stations in patients with upper lobe tumors. The authors concluded that lobe-specific LN assessment was safe for patients with clinical stage IA tumors. Hishida and colleagues[32] published an analysis of 5392 patients with clinical stage I and II NSCLC lobectomy from the multi-institution Japanese Lung Cancer

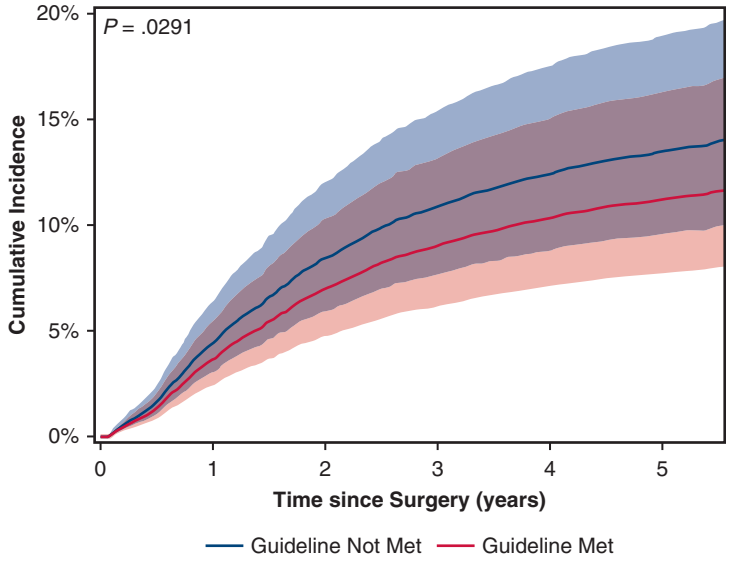

FIGURE 1. Cumulative incidence of disease recurrence stratified by lobe-specific lymph node assessment criteria.

Registry. They used inverse probability of treatment weighting to compare long-term OS between lobe-specific dissection and systematic node dissection. Approximately one-quarter (23.5%) of patients underwent lobe-specific LN dissection. These patients were more likely to have upper lobe tumors and clinical stage I disease. The authors found a relatively low incidence of hypothetical "missed N2" disease in patients who underwent lobe-specific LN dissection. In the systematic node dissection group, N2 disease outside the lobe-specific sampling patterns and accessible only by a systematic approach was found in 3.2% of patients with upper lobe tumors and 5.5% of patients with lower lobe tumors. However, this did not translate to negative long-term survival differences. On propensity score analysis, patients who underwent lobe-specific LN dissection had favorable long-term survival (HR, 0.68; 95% CI, 0.60-0.77).

Our study is one of the few examining lobe-specific LN assessment and long-term outcomes in a US cohort. We used a novel data set of more than 6000 veterans with

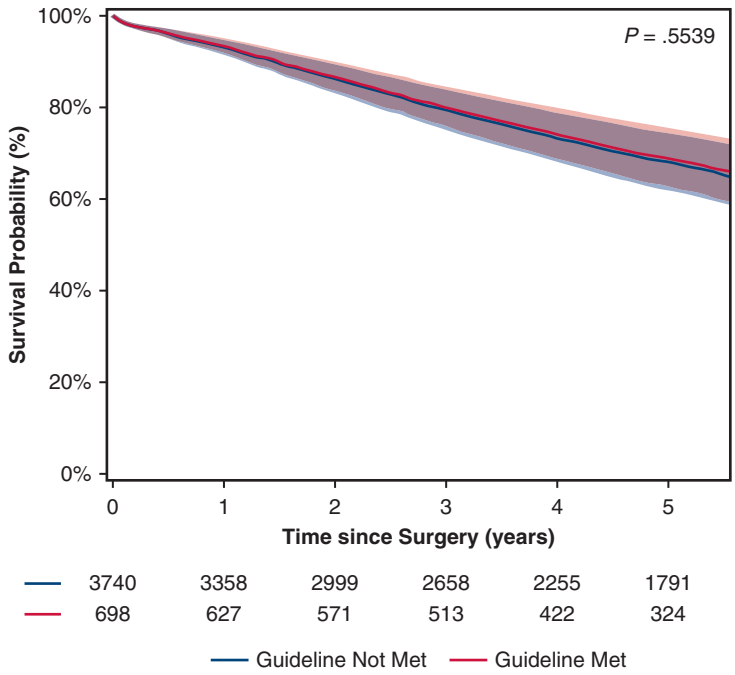

FIGURE 2. Adjusted Kaplan-Meier curve of overall survival stratified by lobe-specific lymph node assessment criteria.

TABLE 4. Cox proportional hazard model, OS

Covariate	aHR	*P* value
Age	1.03 (1.02-1.03)	<.0001
Female sex	0.73 (0.58-0.92)	.0067
Race		.0491
Caucasian	Reference	
Black	0.86 (0.78-0.96)	
Other	0.97 (0.72-1.31)	
Unknown	1.04 (0.73-1.50)	
BMI		<.0001
18.5-24.9	Reference	
<18.5	1.02 (0.90-1.16)	
25-29.9	0.76 (0.70-0.83)	
30-34.9	0.73 (0.65-0.81)	
35+	0.82 (0.71-0.95)	
Smoking status		.0114
Current	Reference	
Former	0.92 (0.85-0.99)	
Never	0.65 (0.44-0.97)	
Charlson-Deyo score	1.09 (1.07-1.11)	<.0001
FEV1		<.0001
<50	Reference	
50-79	1.47 (1.29-1.69)	
80+	1.23 (1.14-1.33)	
Area Deprivation Index		.8231
Q1	Reference	
Q2	1.01 (0.91-1.12)	
Q3	0.97 (0.87-1.07)	
Q4	0.98 (0.88-1.08)	
Surgeon specialty	0.93 (0.79-1.08)	.3138
Hospital case load	1.00 (1.00-1.00)	.5388
Histology		.0126
Adenocarcinoma	Reference	
Squamous cell	1.10 (1.01-1.19)	
Other	1.16 (1.03-1.30)	
Grade		.0001
I	Reference	
II	1.22 (1.07-1.38)	
III	1.34 (1.17-1.53)	
IV	1.09 (0.80-1.49)	
Delay in surgery		<.0001
≤12 wk	Reference	
>12 wk	1.20 (1.12-1.30)	
Tumor size		.0004
≤10 mm	Reference	
11-20 mm	1.03 (0.90-1.17)	
21-30 mm	1.09 (0.95-1.25)	
31-40 mm	1.27 (1.09-1.48)	
40+ mm	1.31 (1.09-1.57)	
Surgical resection		<.0001
Lobectomy	Reference	
Wedge	1.23 (1.13-1.35)	
Segmentectomy	1.10 (0.93-1.30)	
Pneumonectomy	1.16 (0.88-1.54)	
Surgical approach		.0230
Thoracotomy	Reference	
Minimally invasive	0.92 (0.85-0.99)	
Pathologic upstaging	1.54 (1.38-1.73)	<.0001
Positive margins	1.80 (1.51-2.14)	<.0001
Receipt of adjuvant therapy	1.01 (0.89-1.14)	.8776
Lobe-specific LN sampling criteria met	0.97 (0.87-1.0 8)	.5539

aHR, Adjusted hazard ratio; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *LN*, lymph node; *OS*, overall survival.

early-stage NSCLC receiving surgical treatment. Our analysis of operative LN sampling data obtained by an intensive review of pathology and operative reports revealed that adherence to lobe-specific assessment was associated with a lower cumulative incidence of recurrence (adjusted HR [aHR], 0.83; 95% CI, 0.70-0.98) and higher likelihood of pathologic upstaging (aHR, 1.49; 95% CI, 1.20-1.86). Although lobe-specific LN assessment was associated with a decreased risk of recurrence, interestingly, there was no association with OS.

There is no definitive explanation for this observation. It is possible that the duration of follow-up was insufficient to observe a real difference for these patients with stage I NSCLC. It is also possible that advances in chemoimmunotherapy may have led to improved survival in patients with locoregional recurrence. When looking at the cohort of patients with documented recurrence, patients who met the lobe-specific LN assessment criteria had an almost 10% greater incidence of distant recurrence compared to their unexposed cohorts, a non–statistically significant difference. However, when extrapolated to a larger cohort of patients, it is possible that patients who met lobe-specific LN criteria with recurrence might not receive a greater survival benefit with receipt of chemoimmunotherapy given the predilection for distant metastases, which could mitigate long-term survival differences between cohorts. This could result in an equilibration of OS time. Finally, in general, veterans have been found to have more comorbidities compared to the civilian population.[33] It is possible that those with recurrence are dying from non–cancer-related causes.

The results of this study can add to the available literature supporting nodal assessment based on tumor location and likelihood of metastases. Our study parallels the findings observed in studies from Chinese and Japanese institutions on lobe-specific nodal assessment. Another important finding of our study is that overall adherence rates to LN sampling (regardless of strategy) were markedly low; only 14.5% of the study cohort met lobe-specific sampling guidelines. Comparatively, 34.7% of cases met the criteria

TABLE 5. Cumulative risk of pathologic upstaging

Covariate	aOR	*P* value
Age	0.99 (0.98-1.01)	.2052
Female sex	0.94 (0.59-1.49)	.7838
Race		.7144
Caucasian	Reference	
Black	1.05 (0.82-1.33)	
Other	0.70 (0.33-1.50)	
Unknown	0.75 (0.29-1.92)	
BMI		.0009
18.5-24.9	Reference	
<18.5	0.90 (0.63-1.28)	
25-29.9	1.20 (0.97-1.49)	
30-34.9	1.27 (0.96-1.63)	
35+	1.92 (1.39-2.65)	
Smoking status		.2160
Current	Reference	
Former	1.02 (0.85-1.22)	
Never	1.80 (0.93-3.46)	
Charlson-Deyo score	0.99 (0.94-1.04)	.5854
FEV1		.7392
<50	Reference	
50-79	0.91 (0.63-1.33)	
80+	1.04 (0.88-1.24)	
Area Deprivation Index		.7399
Q1	Reference	
Q2	1.12 (0.88-1.44)	
Q3	1.13 (0.88-1.44)	
Q4	1.05 (0.82-1.36)	
Surgeon specialty	1.36 (0.99-1.88)	.0603
Hospital case load	0.93 (0.66-1.32)	.5355
Histology		.0045
Adenocarcinoma	Reference	
Squamous cell	0.74 (0.61-0.90)	
Other	0.76 (0.57-1.00)	
Grade		<.0001
I	Reference	
II	2.15 (1.52-3.04)	
III	2.60 (1.82-3.72)	
IV	2.68 (1.29-5.56)	
Delay in surgery		.5614
≤12 wk	Reference	
>12 wk	0.95 (0.79-1.14)	
Tumor size		<.0001
≤10 mm	Reference	
11-20 mm	0.93 (0.66-1.32)	
21-30 mm	1.42 (1.00-2.33)	
31-40 mm	1.61 (1.11-2.33)	
40+ mm	2.46 (1.63-3.70)	
Surgical resection		<.0001
Lobectomy	Reference	
Wedge	0.68 (0.53-0.87)	
Segmentectomy	0.68 (0.44-1.07)	
Pneumonectomy	3.37 (2.03-5.59)	
Surgical approach		.2220
Thoracotomy	Reference	
Minimally invasive	0.89 (0.74-1.07)	
Lobe-specific LN sampling criteria met	1.49 (1.20-1.86)	.0003

aHR, Adjusted odds ratio; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *LN*, lymph node.

for count-based sampling, and 25.8% met the criteria for station-based sampling. Previous studies using different databases, including the National Cancer Database, have demonstrated that adherence to LN sampling guidelines in addition to other quality measures, including timely receipt of surgery, anatomic resection, and R0 resection, provided a stepwise increase in association with OS.[18] Lobe-specific LN assessment may require less intraoperative time and dissection and thus may present a more achievable target for surgeons. Additionally, lobe-specific LN assessment is not subject to the potential biasing of results that can occur with count-based sampling, including back-tabling and/or fractioning of LNs to inflate counts.[28,34]

This study has some important limitations. The veterans population is composed primarily of male patients with a heavy comorbidity burden and significant smoking history. This is reflected in our study cohort and may reduce the generalizability of our findings. However, lung cancer treatment patterns and outcomes in veterans have been shown to be similar to those of the US population.[33] Thus, our study remains highly relevant to a typical US patient with early-stage lung cancer. Additionally, although we have relatively granular operative information, we do not have consistent capture of information related to intralobar tumor location and use of complete LN dissection versus sampling. This is a limitation of our data set. In addition, we do not have complete data on location of recurrence. Nonetheless, this study has some notable strengths. Our study used VHA data with augmented data that provided granular information on tumor characteristics and operative reports that is rarely available in other nationally representative databases. There is a general paucity of complete information on LN sampling by station in other databases, including SEER, the Society of Thoracic Surgeons General Thoracic Database, and National Cancer Database.[35,36]

In summary, using a large national cohort of veterans with clinical stage I NSCLC with clinically node-negative NSCLC who underwent surgical resection, we found that lobe-specific LN assessment was associated with increased odds of pathologic upstaging and lower risk of disease recurrence. These findings can be used to help inform strategies to improve nodal assessment and high-quality intraoperative surgical care.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/lobe-specific-lymph-node-sampling-in-clinical-stage-i-lung-cancer-is-associated-with-improved-recurrence-free-survival.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: lymph node, survival, recurrence, lung cancer

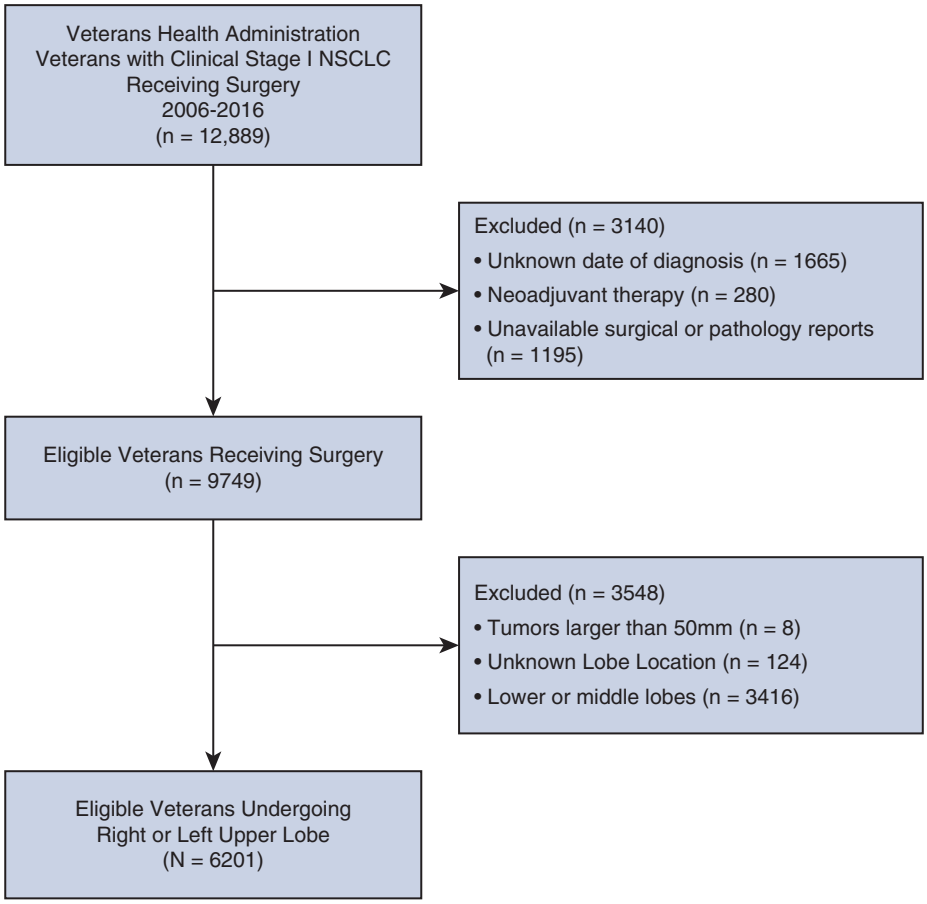

FIGURE E1. CONSORT diagram. *NSCLC*, Non–small cell lung cancer.

TABLE E1. ICD-9/10 diagnosis and procedure codes for recurrence

Disorder	Codes
Secondary malignant neoplasm	196, 196.0, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197, 197.0, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198, 198.0, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.8, 198.81, 198.82, 198.89, 789.51

Adapted from Tarlov and colleagues.[21]

TABLE E2. Locoregional versus distant recurrence

Parameter*	Locoregional recurrence, n (%)	Distant recurrence, n (%)
Met lobe-specific LN assessment criteria	35 (38.5)	91 (61.5)
Did not meet lobe-specific LN assessment criteria	359 (48.3)	384 (51.7)

*Percentages by row. *LN*, Lymph node.