Published in final edited form as:

Lung Cancer. 2015 December ; 90(3): 554–560. doi:10.1016/j.lungcan.2015.10.011.

The Impact of Tumor Size on the Association of the Extent of Lymph Node Resection and Survival in Clinical Stage I Non-Small Cell Lung Cancer

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Abstract

Introduction—Lymph node evaluation for node-negative non-small cell lung cancer (NSCLC) is associated with long-term survival but it is not clear if smaller tumors require as extensive a pathologic nodal assessment as larger tumors. This study evaluated the relationship of tumor size and optimal extent of lymph node resection using the National Cancer Data Base (NCDB).

Materials and Methods—The incremental survival benefit of each additional lymph node that was evaluated for patients in the NCDB who underwent lobectomy for clinical Stage I NSCLC from 2003–2006 was evaluated using Cox multivariable proportional hazards regression modeling. The impact of tumor size was assessed by repeating the Cox analysis with patients stratified by tumor size ≥ 2 cm vs <2 cm.

Results—A median of 7 [interquartile range: 4,11] lymph nodes were examined in 13,827 patients who met study criteria. Following adjustment, the evaluation of each additional lymph node demonstrated a significant survival benefit through 11 lymph nodes. After grouping patients by tumor size, patients with tumors <2 cm demonstrated a significant survival benefit for the incremental resection of each additional lymph node through 4 lymph nodes while patients with tumors ≥ 2 cm had a significant survival benefit through 14 lymph nodes.

Conclusion—Pathologic lymph node evaluation is associated with improved survival for clinically node-negative NSCLC, but the extent of the necessary evaluation varies by tumor size. These results have implications for guidelines for lymph node assessment as well as the choice of surgery versus other ablative techniques for clinical stage I NSCLC.

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Keywords

Non-Small Cell Lung Cancer; Lymph Node Resection; Survival

1.0.Introduction

Survival for patients with non-small cell lung cancer (NSCLC) varies significantly with both the stage of disease as well as other known prognostic factors [1, 2]. Five-year survival for stage IA disease is roughly 73%, but drops precipitously to less than 5% for stage IV disease [3, 4]. When technically feasible, complete excision with anatomic pulmonary resection offers the best chance for survival for early-stage disease [5]. Lobectomy is generally the preferred method for surgical resection in Stage I NSCLC, unless limited by other patient-specific factors [6, 7].

National Comprehensive Cancer Network guidelines recommend that N1 and N2 node resection and mapping be included as routine components of lung cancer resections, with a minimum of three N2 stations sampled or completely dissected [5]. Although it is somewhat unclear how to define what an “optimal” pathologic lymph node evaluation should be beyond the number of N2 stations assessed, several previous studies have demonstrated that more extensive lymph node resections in Stage I NSCLC have a beneficial effect on survival [8–10]. For example, *Ludwig et al* used the Surveillance, Epidemiology, and End Results Program database to investigate the impact of lymph node resection for NSCLC, and concluded that between 11 and 16 lymph nodes should be resected in Stage I NSCLC for maximal survival benefit [11].

Several studies have questioned whether lobectomy is necessary to improve survival for all stage I NSCLC subsets, as several retrospective studies have found no difference in survival between sublobar resection and lobectomy for stage I NSCLC tumors less than 2 cm in size [12–18]. Indeed, a prospective, randomized, multi-institutional phase III trial (Cancer and Lymphoma Group B [CALGB] 140503) that compares survival after lobectomy and intentional sublobar resection for peripheral tumors less than or equal to 2 cm in size is currently being conducted [[clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00499330): NCT00499330] [19]. However, final results from this trial are not expected until 2021, and the impact of tumor size on the extent of lymph node resection required to optimize survival has not been characterized [20]. Just as sublobar resection may be adequate for smaller stage I tumors, smaller tumors may also require that fewer lymph nodes be pathologically assessed compared to larger tumors. In this study, we used the National Cancer Data Base (NCDB) to investigate how the extent of lymph node resection correlates with overall survival in Stage I NSCLC, as well as to test the hypothesis that the lymph node resection required to optimize survival for tumors smaller than 2 cm is less extensive than that required for larger tumors.

2.0. Materials and Methods

2.1. National Cancer Data Base

The NCDB is a clinical oncology database run jointly by the American College of Surgeons and the American Cancer Society. Data is collected from over 1500 Commission-on-Cancer (CoC) accredited hospitals including over 70% of newly diagnosed cancers in the United States [21]. Data is available to CoC accredited programs in a de-identified state for clinical research purposes.

2.2. Patient Population

The NCDB participant user files from 2003–2006 were queried for adult patients who underwent lobectomy for NSCLC clinically staged as T1 or T2, N0, M0 disease prior to therapy. This time period was selected as this was the period during which both Charlson/Deyo comorbidity index and long-term survival was available at the time of analysis. Only patients treated primarily with lobectomy without induction treatment with chemotherapy or radiation therapy were included. The 6th edition of the tumor node metastasis NSCLC staging system was used, as it was the staging system in use during the years of the study. Patients missing data regarding the number of lymph nodes examined as well as those with unknown tumor size were excluded. The Duke University Institutional Review Board approved this study prior to data analysis.

2.3. Variables

The primary outcome of interest was overall survival. The primary predictor of interest was the number of lymph nodes examined. The NCDB records the number of regional lymph nodes examined, but does not discriminate where nodes are harvested (ie N1 vs N2). Other predictors included in the study were patient age, sex, race, Charlson/Deyo comorbidity index, tumor size, clinical T stage, hospital academic status, and hospital volume.

2.4. Statistical Analysis

Descriptive summaries of baseline characteristics for the overall cohort were compiled. Continuous variables were described as median (interquartile range [IQR]) while categorical variables were described as frequency (percentage). Factors associated with undergoing a more extensive lymph node evaluation were identified by creating a multivariable linear regression model with number of lymph nodes evaluated as the outcome and the following *a priori* determined predictors: age, sex, race, Charlson/Deyo comorbidity index, T-stage, tumor size, hospital academic status, and hospital volume. The effect of the number of lymph nodes examined on overall survival was evaluated using a cox proportional hazards regression model that adjusted for age, gender, race, Charlson/Deyo comorbidity index, tumor size, hospital academic status, and hospital volume. The impact of the number of lymph nodes examined was evaluated in binary fashion as follows. For each specific number of examined lymph nodes, survival was incrementally compared between any patient with greater than that number of lymph nodes examined, to those with 0 up to that specific number of lymph nodes examined. The first lymph node number for which the evaluation of an additional lymph node was not associated with a significant survival benefit (eg the 95%

confidence interval of the hazard ratio for overall survival included 1.0) was chosen as the “optimal” lymph node number to be examined to optimize survival.

The cohort was then divided into two groups in order to determine the interaction of tumor size and the number of examined lymph nodes on survival. Groups were separated based on an *a priori* determined cut-off of 2 cm, as existing studies have suggested that this tumor size may be the cutoff at which the extent of surgical resection can be modified [12]. Group 1 included patients with tumors less than 2 cm while group 2 included patients with tumors greater than or equal to 2 cm. Cox proportional hazards regression modeling with the same covariates described above was performed in each group to determine the adjusted correlation of the number of examined lymph nodes and survival.

All statistical analyses were performed with SAS for Windows, Version 9.3; SAS Institute Inc.; Cary, NC. A p-value of 0.05 was used to define significance.

3.0. Results

A total of 13,827 patients met study criteria of which 8,461 (61.2%) had clinical T1N0 disease while 5,366 (38.8%) had clinical T2N0 disease (Table 1). The median age was 68 years (IQR: 61, 75) and 7,113 (51.4%) patients were female. Median tumor size was 2.5 cm (IQR: 1.8, 3.7). The median number of examined lymph nodes was 7 (IQR: 4, 11, Figure 1A). Following multivariable linear regression, clinical T2 status (compared to T1 status), increasing tumor size, surgery at an academic center, and increasing hospital volume were significantly associated with increasing extent of lymph node examination (Figure 2). Black race was associated with a significantly decreased extent of lymph node examination compared to White race.

Overall 5-year survival was 60.5% (95% CI: 59.7%, 61.4%). Overall, 1,560 (11.3%) patients with clinically node negative disease were found to have node positive disease on pathologic examination, 1,044 (7.6%) of which had pathologic N1 disease and 513 (3.7%) had pathologic N2 disease. 11.7% (n=1,617) of patients received adjuvant chemotherapy while 4.4% (n=603) of patients received adjuvant radiation. Patients with positive nodal disease on pathologic examination were significantly more likely to receive adjuvant chemotherapy (35.9% vs 8.6%, $p<0.001$) as well as adjuvant radiation (19.6% vs 2.4%, $p<0.001$) than patients with negative nodes.

Cox proportional hazards regression modeling was performed to determine the adjusted mortality benefit of examining each additional lymph node (Figure 3A). A statistically significant survival benefit was associated with each additional lymph node examined through 11 lymph nodes. The cohort was then divided into two groups on the basis of the *a priori* determined tumor size of 2cm. The median number of excised lymph nodes was 7 (IQR: 4, 11) for tumors < 2 cm (Figure 1B) and 7 (IQR: 4, 11) for tumors ≥ 2 cm (Figure 1C). Following adjustment, a significant survival benefit was associated with each additional lymph node that was examined through 4 lymph nodes for patients with tumors < 2 cm (Figure 3B), while an additional survival benefit was associated with each additional lymph node examined through 14 lymph nodes for the patients with tumors ≥ 2cm (Figure 3C).

However, a significant survival benefit was again seen when examining the effect of evaluating each additional lymph node for lymph nodes 16, 21, 22, and 23.

4.0. Discussion

Lung cancer is the leading cause of cancer death in the United States, estimated to be responsible for approximately 160,000 deaths in 2014 [22]. Despite strong evidence that surgical resection provides the optimal chance for survival in NSCLC, data is limited on the extent of lymph node evaluation necessary for patients with T1 or T2 tumors who do not have signs of nodal or metastatic disease on clinical staging studies [5]. In this study, similar to previous studies, we have demonstrated that the number of examined lymph nodes is associated with survival in this patient population [10, 11]. However, we have also demonstrated that the association of survival and the extensiveness of lymph node examination is dependent on tumor size, with tumors smaller than 2 cm requiring a less extensive lymph node excision (at least 4 nodes) while tumors greater than or equal to 2 cm requiring a more extensive lymph node excision (at least 14 nodes).

This interaction of tumor size and extent of lymph node examination has important implications for the evaluation and management of early stage NSCLC. Findings from previous studies investigating the optimal number of lymph nodes to resect are not generalizable to all-comers, and surgeons cannot approach all of these patients in a similar manner. The larger the tumor, the more likely additional lymph node evaluation could impact survival. In addition, an association between survival and pathologic lymph assessment exists even for patients with small tumors. This finding should be considered when evaluating potential therapies other than a lobectomy for clinical stage I NSCLC, including sublobar resections or non-surgical ablative therapies such as stereotactic radiation. Although these therapies hold promise for small, early-stage NSCLC, distant failure appears to be more problematic than local failure [23–26]. Clearly, more investigation is needed to determine if other factors can be identified that can be used to determine the importance of the extent of lymph node evaluation. For example, other studies have demonstrated that factors including the degree of differentiation as well as the presence of lymphatic vessel invasion are significant prognostic factors in NSCLC [27, 28]. Although these were not examined in this study, patients with poorly differentiated tumors and those with lymphatic vessel invasion may achieve a more substantial survival benefit for each additional lymph node resected and examined.

This study may also have important implications with regards to national policies and quality-metrics. Although additional lymph node evaluation is associated with improved survival, one cannot definitively claim that a specific number of lymph nodes should be resected and examined in all patients due to the variability in benefit by tumor size. Therefore neither national policies nor quality metrics should focus on a specific number of lymph nodes that should be resected in all patients with Stage I NSCLC. However, the inclusion of a requirement for at least some lymph node excision appears mandatory when surgery is utilized.

Although we can only speculate as to why a more extensive lymph node examination is associated with improved overall survival, we hypothesize it is due to more accurate pathologic staging of disease. Although only 11% of patients were upstaged, upstaged patients were significantly more likely to receive adjuvant therapy. Patients who received less extensive lymph node evaluations are less likely to be upstaged, and therefore less likely to receive this therapy which may increase the chance of cure, although we acknowledge that current data has demonstrated the use of adjuvant chemotherapy in this patient population may only provide a minimal benefit to overall survival [29]. In addition, resection of lymph nodes that contain metastatic disease may have a therapeutic effect. Previous data has demonstrated that a proportion of patients who undergo surgery alone in the setting of nodal disease still achieve long-term survival compatible with cure even when they do not receive adjuvant chemotherapy [30–33].

Our findings among patients with tumors greater than or equal to 2.0 cm is not as clear as among patients with smaller tumors. Specifically, there is variance in our findings and although upon initial inspection it appears each additional lymph node examined is beneficial through 14 lymph nodes, there is also a benefit regarding the examination of 22–24 lymph nodes as compared to a less comprehensive evaluation. This is most likely due to a heterogenous patient population. Tumors greater than or equal to 2.0 cm in diameter include a wide variety of tumors, including those now classified as T3 per the seventh edition of the TNM classification system for lung cancer. The variation in our findings is most likely second to this heterogeneity. We chose not to break apart this group however as the goal of our study is to demonstrate not the optimal number of lymph nodes which should be evaluated based on a specific tumor size or stage, but that there is substantial heterogeneity in this number depending on tumor specific characteristics.

In our study, we have also demonstrated that race is significantly associated with the extent of lymph node evaluation, which is consistent with other studies that have demonstrated racial disparities of care in the treatment of lung cancer [34, 35]. We have additionally demonstrated that treatment at a high-volume center as well as at a center with an academic association are both associated with the extent of lymph node evaluation, which also corresponds to other studies that have demonstrated a survival benefit in lung cancer resection by treatment at academic and high volume centers [36]. Although many factors may contribute to this finding, these types of institutions may place an increased emphasis on lymph node removal and analysis by both surgeons and pathologists.

There are some potentially important limitations to this study. First, the retrospective nature of the study precludes assessment of why some patients had limited lymph node evaluations. Surgeons may have been restricted by constraints such as patient instability or difficult dissections, which would have limited how many lymph nodes could be resected and could have a direct effect on outcomes. Second, the analysis could not adjust for other variables that are known to be important prognostic indicators in NSCLC [i.e. microscopic vascular invasion or mutations in epidermal growth factor receptor (EGFR)] but are not available in the NCDB [37, 38]. Third, although the number of examined lymph nodes is recorded in the NCDB, the location of lymph node retrieval is not, which may be more important than the total number of lymph nodes resected [39]. Another important limitation to not only this

study but any study that considers lymph node evaluation is that the mechanism for removing and counting lymph nodes is generally not standardized across institutions. Therefore the number of lymph nodes recorded may vary with pathologic processing, and counts in some institutions may include lymph node fragments while others rely on complete lymph nodes. Furthermore, we can only determine the number of lymph nodes examined, which is not necessarily the true number of lymph nodes resected. It is therefore difficult to determine if a survival benefit is potentially due to a more extensive resection or a higher likelihood of being properly upstaged. In addition although performance of a lobectomy without any lymph node removal should be unlikely from a technical standpoint, it is possible that some of the cases recorded as lobectomy were not true anatomic resections but rather “simultaneous-stapled” lobectomies that did not involve individual hilar vessel dissection. Lastly, the NCDB only records overall survival, not disease-specific survival, and therefore this outcome could not be assessed.

5.0. Conclusions

In this study, we demonstrate a significant association between pathologic lymph node evaluation and survival in early-stage NSCLC patients who are clinically node-negative prior to surgery. However, the extent of pathologic lymph node evaluation necessary to optimize survival varies based on tumor size, and is not standardizable for all-comers. These results may have implications for guidelines for lymph node assessment as well as the choice of surgery versus other ablative techniques for clinical stage I NSCLC.

Acknowledgements

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators. In addition, one of the authors (TAD) serves as a consultant for Scanlan, Inc. CJY has stipend support from the American College of Surgeons Resident Research Scholarship. Lastly, BCG, JMM, and MGH are supported by the NIH funded Cardiothoracic Surgery Trials Network, 5U01HL088953-05.

Abbreviations

CoC	Commission on Cancer
IQR	Interquartile Range
NCDB	National Cancer Data Base
NSCLC	Non small cell lung cancer
VATS	Video-assisted thoracoscopic surgery

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Highlights

- We analyzed patients with stage I NSCLC in the NCDB.
- We evaluated the association of the extent of lymph node evaluation and survival.
- More extensive lymph node evaluations were associated with improved survival.
- However, the optimal number of lymph nodes evaluated depended on tumor size.
- Policy should not dictate a lymph node evaluation cut-off among patients with resectable NSCLC.

Figure 1. The distribution of lymph nodes examined in patients with T1N0-T2N0 non-small cell lung cancer (A), as well as among only those patients with tumors <2 cm (B), and among only those patients with tumors ≥ 2 cm (C).

Figure 2.
Variables associated with the extent of lymph node evaluation.

Figure 3.

Hazard for mortality and 95% confidence interval by extent of lymph node evaluation by comparing greater than i versus 0-i lymph nodes (where “i” is the number of lymph nodes resected) among patients with T1N0–T2N0 non-small cell lung cancer among all-comers (A), patients with tumors < 2 cm (B), and patients with tumor ≥ 2 cm (C).

Table 1

Baseline characteristics

Variable	Median (IQR) / Frequency (Percentage)
N	13,827
Median Age (in years)	68 (61, 75)
Female	7,113 (51.4%)
Race	
White/Caucasian	12,477 (90.2%)
Black/African-American	1,006 (7.3%)
Other	344 (2.5%)
Charlson/Deyo Score	
0	7,348 (53.1%)
1	4,871 (35.2%)
2	1,608 (11.6%)
Median Tumor Size (cm)	2.5 (1.8, 3.7)
Clinical T Stage 2 (vs 1)	5,366 (38.8%)