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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 to 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 vs other ablative techniques for clinical stage I NSCLC.

1. 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

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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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: 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. 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 to 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 (i.e., N1 vs N2). Other predictors included in the study were patient age, sex, race, Charleson/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 (e.g., 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.

Table 1
Baseline characteristics.

Variable	Median (IQR)/frequency (percentage)
N	13,827
Median age (in years)	68 (61, 75)
Female	7113 (51.4%)
Race	
White/Caucasian	12,477 (90.2%)
Black/African-American	1006 (7.3%)
Other	344 (2.5%)
Charlson/Deyo score	
0	7348 (53.1%)
1	4871 (35.2%)
2	1608 (11.6%)
Median tumor size (cm)	2.5 (1.8, 3.7)
Clinical T Stage 2 (vs 1)	5366 (38.8%)

3. Results

A total of 13,827 patients met study criteria of which 8461 (61.2%) had clinical T1N0 disease while 5366 (38.8%) had clinical T2N0 disease (Table 1). The median age was 68 years (IQR: 61, 75) and 7113 (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, Fig. 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 (Fig. 2). Black race was associated with