Does Lymph Node Count Influence Survival in Surgically Resected Non-Small Cell Lung Cancer?

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Background. **The prognostic significance of the number of lymph nodes sampled (NLNS) during resection for non-small cell lung cancer (NSCLC) is unclear. The NLNS is influenced by many factors, and some have argued that it should be a surrogate for quality. We sought to determine the influence of the NLNS on overall survival and cancer-specific survival for surgically resected NSCLC.**

Methods. **The California Cancer Registry was queried from 2004 to 2011 for cases of stage I to III NSCLC treated with surgical resection, identifying 16,393 patients. Kaplan-Meier and Cox proportional hazards modeling were used to determine the influence of NLNS on overall survival and cancer-specific survival.**

Results. **In all, 15,195 patients had information regarding nodal sampling. Eighty percent (13,167 of 15,195) were treated with lobectomy. Patients who were younger, male, non-Hispanic white, highest socioeconomic status, higher stage, or larger size tumor had more nodes removed. Sampling fewer than 10 nodes was associated with poorer overall survival when compared with sampling 10 or more nodes after adjustment for demographic and clinical factors for stage I: overall survival hazard ratio 1.78 (95% confidence interval: 1.54 to 2.05, $p < 0.0001$), hazard ratio 1.43 (95% confidence interval: 1.27 to 1.59, $p < 0.0001$), and hazard ratio 1.16 (95% confidence interval: 1.05 to 1.28, $p = 0.004$), for 0, 1 to 3, and 4 to 10 nodes, respectively. Of patients who underwent sublobar resection, 43.8% had no nodes sampled.**

Conclusions. **For NSCLC, the NLNS influenced both overall survival and cancer-specific survival, but the influence is dependent on stage. Surgeons should perform mediastinal lymphadenectomy to maximize patient survival, but the optimal NLNS remains unclear.**

(Ann Thorac Surg 2016;■:■–■)

The prognosis and survival of non-small cell lung cancer (NSCLC) patients is dependent on the stage of disease, which is based on tumor size and nodal and distant metastasis at presentation [1]. Controversy exists concerning lymph node assessment at the time of surgical resection for NSCLC, and studies have evaluated the impact of various assessment techniques [2–7]. Data exist to support a minimum threshold for lymph node assessment in the management of NSCLC, but there is no consensus for the optimal number of nodes. Ludwig and colleagues [5] showed that increasing the number of lymph nodes examined in stage I NCSLC was associated with a statistically significant increase in overall survival, peaking at 13 to 16 lymph nodes [5]. Similarly, Osarogiagbon and associates [6] demonstrated the lowest overall mortality among patients who had 18 to 21 nodes sampled (hazard ratio [HR] 0.65, 95% confidence interval [CI]: 0.57 to 0.73) when compared with patients who had one to three nodes sampled.

Despite data suggesting improved oncologic outcomes with more lymph nodes removed during surgery for NSCLC, critics have pointed out the possible confounding effects of stage migration and variability in lymph node retrieval on outcomes. For example, in a subset analysis of the American College of Surgeons Oncology Group Z0030 trial, Darling and associates [3] observed wide variability in the number of nodes removed (from one to 72) with a median of 18 for patients undergoing mediastinal lymph node dissection. Similarly, epidemiologic studies using the Surveillance, Epidemiology and End Results (SEER) database have demonstrated wide variability in the number of nodes removed, ranging from zero to 39 for patients with surgically treated NSCLC [5–7]. As a result, a clear numerical standard for number of lymph nodes sampled (NLNS) has not emerged, likely secondary to the variability inherent to NLNS based on patient, surgeon, and pathologic factors [8].

Lymphadenectomy at the time of surgical resection of NSCLC has important diagnostic and therapeutic implications, and some have advocated for NLNS thresholds as a surgical and institutional quality metric [9–11]. Therefore, we sought to determine the influence of NLNS on

Accepted for publication May 3, 2016.

Presented at the Sixty-second Annual Meeting of the Southern Thoracic Surgical Association, Orlando, FL, Nov 4–7, 2015.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.05.018

Abbreviations and Acronyms

CI = confidence interval
CCR = California Cancer Registry
CSS = cancer-specific survival
HR = hazard ratio
NLNS = number of lymph nodes sampled
NSCLC = non-small cell lung cancer
OS = overall survival
SES = socioeconomic status

overall survival (OS) and cancer-specific survival (CSS) for NSCLC patients treated surgically using a population-based sample, hypothesizing that because of its inherent variability, NLNS would not influence OS or CSS for NSCLC patients treated with surgery.

Patients and Methods

This was a University of California, Davis, Institutional Review Board reviewed, retrospective, cross-sectional study of patients with NSCLC identified through the California Cancer Registry (CCR). The CCR, a program of the California Department of Public Health, is a population-based registry that has collected cancer incidence and mortality data for the entire population of California since 1988. By state law, all new reportable cancer cases diagnosed in California residents must be provided to the CCR, and data are collected from diagnostic and treatment facilities. To ensure current follow-up for vital status and cause of death, the CCR database is linked annually to death certificates, hospital discharge data, Medicare files, the Department of Motor Vehicles, Social Security, and other administrative databases. Linkage to the National Death Index ensures capture of deaths occurring outside California as well as cause of death, and follow-up is more than 96% for patients diagnosed since 2000. The CCR has consistently earned gold certification for complete, accurate, and timely data from the North American Association of Central Cancer Registries [12].

We abstracted data on patient demographics (age, sex, race), year of diagnosis, tumor characteristics, stage at diagnosis, and type of surgical resection. Race/ethnicity in the CCR is based on information collected from medical records supplemented with linkage to algorithms to better identify Hispanics and Asian/Pacific Islanders. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic Asian/Pacific Islander. Patient address at diagnosis is assigned to a census tract, and neighborhood socioeconomic status (SES) was based on US Census characteristics combined into the summary Yost index, categorized into quintiles [13].

Only patients for whom NSCLC was the first or only cancer diagnosis were included, and patients diagnosed

Table 1. Characteristics of Patients With Stage I to III Non-Small Cell Lung Cancer Treated With Surgery in California, 2004 to 2011

Variables	Frequency (n = 16,393)	Percentage
Age, years		
<65	5,572	33.99
65–74	6,181	37.71
75+	4,640	28.30
Sex		
Male	7,743	47.32
Female	8,650	52.77
Race		
Non-Hispanic white	11,927	72.76
Non-Hispanic black	1,029	6.28
Hispanic	1,477	9.01
Asian/Pacific Islander	1,852	11.30
Other/unknown	108	0.66
Socioeconomic status		
Lowest	2,024	12.77
Lower-middle	3,114	19.65
Middle	3,485	21.99
Higher-middle	3,631	22.91
Highest	3,594	22.68
SEER stage		
IA	6,071	37.03
IB	4,700	28.67
IIA	923	5.63
IIB	1,616	9.86
IIIA	2,028	12.37
IIIB	1,055	6.44
Grade		
I, or well differentiated	2,574	15.70
II, or moderately well differentiated	6,393	39.00
III, or poor differentiated	5,683	34.67
IV, or undifferentiated/analytic	454	2.77
Grade and differentiation not stated	1,289	7.86
Tumor size, mm		
<20	4,174	25.46
20–29	4,515	27.54
30–49	4,781	29.16
50–69	1,725	10.52
70+	1,198	7.31
Surgery types		
Sublobar resection	2,439	14.88
Lobectomy	13,167	80.32
Pneumonectomy	787	4.80
Number of lymph nodes		
0	1,464	8.93
1–3	2,700	16.47
4–10	6,564	40.04
10+	4,467	27.25
Unknown	1,198	7.31

SEER = Surveillance, Epidemiology, and End Results.