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Number of Lymph Nodes Associated With Maximal Reduction of Long-Term Mortality Risk in Pathologic Node-Negative Non–Small Cell Lung Cancer

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Background. **Forty-four percent of patients with pathologic node negative (pN0) non–small cell lung cancer (NSCLC) die within 5 years of curative-intent surgical procedures. Heterogeneity in pathologic nodal examination practice raises concerns about the accuracy of nodal staging in these patients. We hypothesized a reciprocal relationship between the number of lymph nodes examined and the probability of missed lymph node metastasis and sought to identify the number of lymph nodes associated with the lowest mortality risk in pN0 NSCLC.**

Methods. **We analyzed resections for first primary pN0 NSCLC in the United States Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2009, with survival updated to December 31, 2009.**

Results. **In 24,650 eligible patients, there was a significant sequential reduction in mortality risk with examination of more lymph nodes. The lowest mortality risk occurred in those with 18 to 21 lymph nodes examined. The hazard ratio for all-cause mortality was 0.65 and the 95% confidence interval (CI) was 0.57 to 0.73; for lung cancer–specific mortality, hazard ratio was 0.62 and CI was 0.53 to 0.73 ($p < 0.001$ for both). The median number of lymph nodes examined was only 6.**

Conclusions. **Lymph node evaluation falls far short of optimal in patients with resected pN0 NSCLC, raising the odds of underestimation of long-term mortality risk and failure to identify candidates for postoperative adjuvant therapy. This represents a major quality gap for which corrective intervention is warranted.**

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With an annual death toll of 1.4 million lives worldwide and 160,000 in the United States, lung cancer is the major oncologic public health burden of the present age [1, 2]. Approximately 85% of patients with lung cancer have non–small cell lung cancer (NSCLC). Although patients with early-stage NSCLC may be cured by surgical intervention, postoperative survival rates are relatively low [3]. Pathologic nodal stage is the strongest predictor of long-term postoperative survival in recipients of surgical procedures; patients without lymph node metastasis have the best survival odds. However, 44% of patients with pathologic node-negative (pN0) NSCLC die within 5 years of resection [4]. The thoroughness with which pathologic staging procedures are applied influences the accuracy of staging, which may affect stage attribution and long-term outcomes [5, 6].

There is evidence of a great deal of heterogeneity in the thoroughness with which lung resection specimens are examined [7–10]. At one extreme, nonexamination of lymph nodes occurs in about 18% of all "node-negative" resections in the United States [11–14]. These so-called pathologic NX cases have a significantly poorer survival than matched pN0 cases [13–15], but pN0 is defined in these analyses as absence of lymph node metastasis in patients with at least 1 lymph node examined, and pN0 cohorts include patients with a wide range of lymph nodes that are examined. However, the probability of identifying lymph node metastasis may be directly

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Dr Osarogiagbon has filed a patent application for a surgical lymph node specimen collection kit.

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proportional to the effort devoted to the search, a surrogate for which may be the number of nodes examined.

We examined the survival of patients with pN0 NSCLC in an effort to elucidate the relationship between the number of lymph nodes examined and survival. We hypothesized that a true correlation between thoroughness of examination and the probability of detecting lymph node metastasis should be manifested as a serial improvement in long-term survival with increasing lymph node number up to a certain point, beyond which there would be little further incremental survival benefit. We sought to determine the number of lymph nodes associated with the largest improvement in survival, which we proposed as the optimal number required to accurately determine the absence of nodal metastasis.

Patients and Methods

Study Design

With the permission of the University of Tennessee Institutional Review Board, we conducted a retrospective analysis of the US Surveillance, Epidemiology, and End Results (SEER) database of patients treated for NSCLC from 1998 to 2009, with survival updated to December 31, 2009.

The SEER Database

SEER is designed to be representative of the US population, with patient-level data abstracted from 18 specific geographically diverse populations representing rural, urban, and regional populations. During the time span included in this study, the SEER data collection sites included up to 28% of the US population [16].

Patient Selection

Eligible patients had initial treatment for a first primary NSCLC in the SEER database from 1998 to 2009. We eliminated patients with bronchioloalveolar carcinoma, small-cell lung cancer, and benign neuroendocrine tumors because nodal status is not as impactful on the prognosis and treatment of these patients. We also eliminated those who did not undergo surgical resection, as well as recipients of radiation therapy, patients with lymph node or distant metastasis, those who did not have nodal examination, and all patients who died within 60 days of operation (Fig 1).

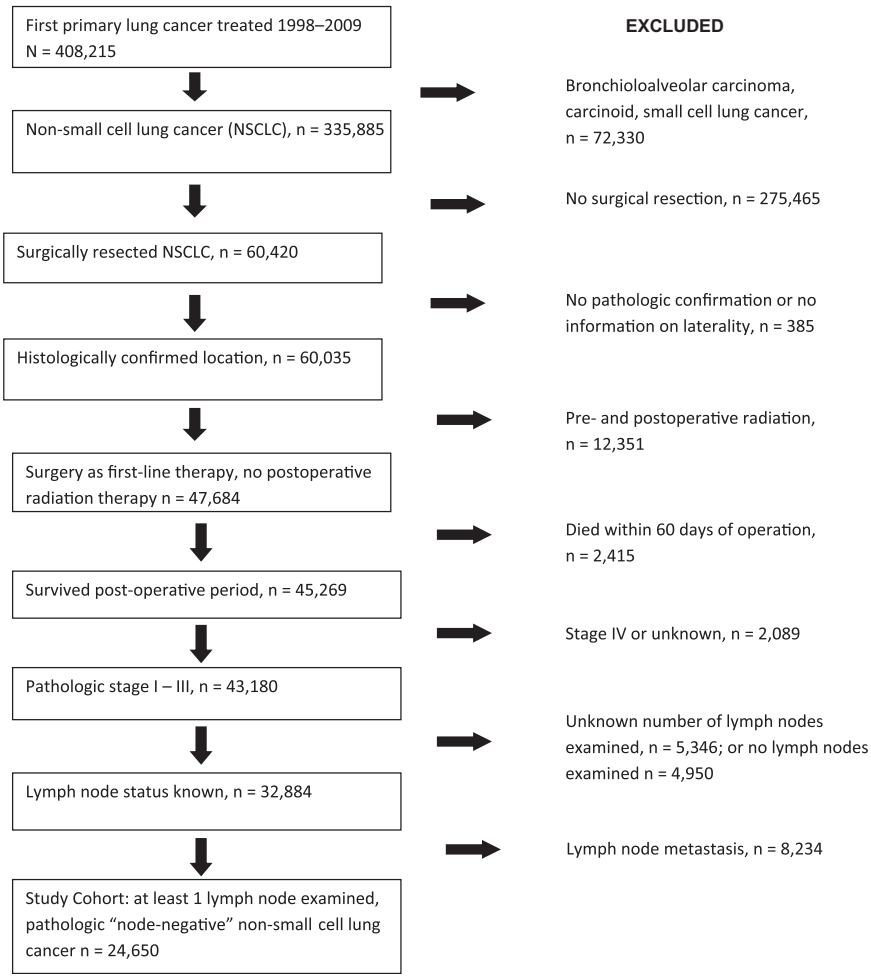

Fig 1. Selection of study cohort.