

# Patterns of care in hilar node-positive (N1) non-small cell lung cancer: A missed treatment opportunity?

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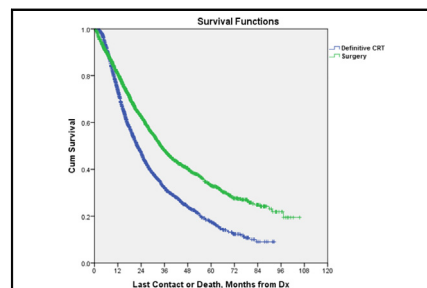
## ABSTRACT

**Background:** For patients with non-small cell lung cancer (NSCLC) metastatic to hilar lymph nodes (N1), guidelines recommend surgery and adjuvant chemotherapy in operable patients and chemoradiation (CRT) for those deemed inoperable. It is unclear how these recommendations are applied nationally, however.

**Methods:** The National Cancer Database was queried to identify patients with a tumor <7 cm (T1/T2) with clinically positive N1 nodes. Patients undergoing CRT (comprising chemotherapy and radiation >45 Gy) or surgical resection were considered adequately treated. Remaining patients were classified as receiving inadequate or no treatment.

**Results:** Of the 20,366 patients who met the study criteria, 63% underwent adequate treatment (48% surgical resection, 15% CRT). The remainder received inadequate treatment (23%) or no treatment (14%). In univariate analysis, the patients receiving inadequate or no treatment were older, tended to be non-Caucasian, had a lower income, and had a higher comorbidity score. Patients undergoing adequate treatment had improved overall survival (OS) compared with those receiving inadequate or no treatment (median OS, 34.0 months vs 11.7 months;  $P < .001$ ). Of those receiving adequate treatment, logistic regression identified several variables associated with surgical resection, including treatment at an academic facility, Caucasian race, and annual income >\$35,000. Increasing age and T2 stage were associated with nonoperative management. Following propensity score matching of 2308 patient pairs undergoing surgery or CRT, resection was associated with longer median OS (34.1 months vs 22.0 months;  $P < .001$ ).

**Conclusions:** Despite the established guidelines, many patients with T1-2N1 NSCLC do not receive adequate treatment. Surgery is associated with prolonged survival in selected patients. Surgical input in the multidisciplinary evaluation of these patients should be mandatory. (*J Thorac Cardiovasc Surg* 2016;151:1549-58)



Propensity-matched survival for patients undergoing surgery versus CRT for N1-positive NSCLC.

### Central Message

Despite the existence of published guidelines, many patients with T1-2N1 NSCLC do not receive adequate treatment. Surgical evaluation should be mandatory in these patients.

### Perspective

Published guidelines recommend surgery as the primary treatment modality for operable patients with hilar node-positive (N1) NSCLC and chemoradiation (CRT) for those deemed inoperable. Our analysis of a large national database shows that adherence to these guidelines is poor. We show that <50% of T1-2N1 patients undergo resection, and that many selected for CRT receive inadequate therapy.

See Editorial Commentary page 1559.

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Node-positive non-small cell lung cancer (NSCLC) is an aggressive disease with high mortality<sup>1</sup>; however, patients with disease limited to pulmonary and hilar lymph nodes (N1) may experience long-term survival with aggressive, multimodal therapy.<sup>2</sup> In patients with acceptable operative

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**Abbreviations and Acronyms**

AJCC	= American Joint Committee on Cancer
CI	= confidence interval
CRT	= chemoradiation
CT	= computed tomography
NCDB	= National Cancer Database
NSCLC	= non–small cell lung cancer
OR	= odds ratio
OS	= overall survival
PET	= positron emission tomography

risk, surgical resection with adjuvant chemotherapy forms the cornerstone of treatment for N1 disease.<sup>3</sup> Although studies directly evaluating treatment of medically inoperable patients with N1 disease are lacking, extrapolation of data from stage III patients suggests that chemoradiation (CRT) is generally the preferred standard of care.<sup>4-7</sup> Despite the existence of established guidelines outlining these treatment paradigms, adherence to these recommendations at the national level is unclear.

The National Cancer Database (NCDB) is a joint program developed in 1989 by the Commission on Cancer, the American College of Surgeons, and the American Cancer Society.<sup>8</sup> The database contains data submitted by more than 1500 accredited cancer centers across the United States and Puerto Rico, and it captures approximately 70% of all new cancer cases diagnosed in the United States annually. To better characterize the treatment of N1 disease nationwide, we queried the NCDB to examine patterns of care regarding N1 (T1 or T2) NSCLC in the United States. We hypothesized that despite the existence of established guidelines, physician practice and surgical referral for this disease would vary considerably.

**METHODS**

We queried the NCDB to identify patients treated for clinical N1 node-positive NSCLC (hilar, interlobar, lobar, or segmental nodes) between 1998 and 2010.<sup>9</sup> All information was deidentified, and so the need for Institutional Review Board approval for the study was waived by Washington University. The analysis was limited to patients with T1 or T2 disease (generally representing stage II NSCLC according to the American Joint Committee on Cancer [AJCC] staging manual, 7th edition).<sup>10</sup> Those patients with clinical T3 or T4 tumors, or those with clinically positive mediastinal lymph nodes (N2 disease) were specifically excluded. Patients undergoing either surgical resection or CRT with >45 Gy of radiation were considered adequately treated. Chemotherapy and radiation could be given in any order. Patients not meeting these treatment criteria were classified as receiving inadequate (ie, some chemotherapy and/or radiation but not meeting the previously defined threshold for adequate therapy) or no treatment.

Information regarding patient- and tumor-related variables, treatment details, and short- and long-term outcomes was extracted. Using information on race, income, and population size of the area from which a patient presented, we created dichotomized groups in which a patient was either Caucasian or not Caucasian, had an annual income <\$35,000

or >\$35,000, and presented from a rural location (regional population <250,000) or an urban location, respectively. The Charlson/Deyo score was used as a measure of comorbidity; possible scores were 0, 1, or  $\geq 2$ . Because very few patients have a score  $> 2$ , the NCDB combines patients with scores of  $\geq 2$  into a single group. Treatment facilities were classified as community cancer programs, comprehensive community cancer programs, or academic/research centers. For the analysis, community cancer programs and comprehensive community cancer programs were combined in the category of nonacademic centers.

Last known vital status and the time between the date of diagnosis and the date of follow-up were used to determine survival. The NCDB defines the date of diagnosis as the date of histological confirmation of NSCLC in cases for which that information is available. In cases where the diagnosis was made based on imaging and the patient proceeded directly to resection without biopsy, the date of diagnosis is defined as the date of the radiologic imaging that identified the lesion.

All analyses were performed using SPSS 21.0 for Windows (IBM, Armonk, NY). Descriptive statistics are expressed as mean  $\pm$  standard deviation unless specified otherwise. Independent-samples *t* tests and 1-way analysis of variance were used to compare continuous variables. The  $\chi^2$  test was used to compare categorical data. Overall survival (OS) was estimated by the Kaplan-Meier method. Multivariate logistic regression models were fitted to evaluate variables associated with surgical resection. Factors accounted for in the multivariate analysis included age, tumor size, sex, race, facility type (academic vs nonacademic), income, urban location, Charlson/Deyo score, and clinical T stage.

Propensity score matching was performed to identify 2 equivalent cohorts of patients either undergoing surgery or receiving adequate CRT. The propensity score was the probability of receiving CRT during the study period, estimated using a logistic regression model that included age, race, sex, income, facility type (academic vs nonacademic), Charlson/Deyo score, urban location, clinical T stage, and tumor size. These variables were selected from an initial univariate analysis comparing the surgery and chemotherapy groups, and variables that differed significantly between the 2 groups were chosen for propensity matching. Patients for whom the propensity scores matched to the fourth decimal place were matched in 1:1 fashion. Automated matching was performed using the Fuzzy extension command in SPSS 21.0. For all analyses, a *P* value < .05 was considered statistically significant.

**RESULTS**

A total of 20,366 patients who met the study criteria were identified in the NCDB between 1998 and 2010. These patients were all noted to have NSCLC with clinically positive N1 lymph nodes. Of these, 12,857 patients (63%) received adequate treatment as defined in Methods (surgical resection, *n* = 9719 [48%]; definitive CRT, *n* = 3138 [15%]). The remaining 7509 patients (37%) received either inadequate CRT (*n* = 4640; 23%) or no treatment (*n* = 2869; 14%).

Table 1 compares demographic data and tumor- and treatment-related information in patients receiving adequate therapy and those receiving inadequate or no therapy. In the univariate analyses, compared with the patients receiving adequate treatment, those receiving inadequate or no treatment were older, more likely to be non-Caucasian, had a lower annual income, and had a higher Charlson/Deyo comorbidity score. These patients also were more likely to have slightly larger tumors, as

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