A Model to Predict the Use of Surgical Resection for Advanced-Stage Non-Small Cell Lung Cancer Patients

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Background. For advanced-stage non-small cell lung cancer, chemotherapy and chemoradiotherapy are the primary treatments. Although surgical intervention in these patients is associated with improved survival, the effect of selection bias is poorly defined. Our objective was to characterize selection bias and identify potential surgical candidates by constructing a Surgical Selection Score (SSS).

Methods. Patients with clinical stage IIIA, IIIB, or IV non-small cell lung cancer were identified in the National Cancer Data Base from 1998 to 2012. Logistic regression was used to develop the SSS based on clinical characteristics. Estimated area under the receiver operating characteristic curve was used to assess discrimination performance of the SSS. Kaplan-Meier analysis was used to compare patients with similar SSSs.

Results. We identified 300,572 patients with stage IIIA, IIIB, or IV non-small cell lung cancer without missing data; 6% (18,701) underwent surgical intervention. The surgical cohort was 57% stage IIIA (n = 10,650), 19% stage IIIB (n = 3,483), and 24% stage IV (n = 4,568). The areas under the receiver operating characteristic curve from the best-fit logistic regression model in the training and validation sets were not significantly different, at 0.83 (95% confidence interval, 0.82 to 0.83) and 0.83 (95% confidence interval, 0.82 to 0.83). The range of SSS is 43 to 1,141. As expected, SSS was a good predictor of survival. Within each quartile of SSS, patients in the surgical group had significantly longer survival than nonsurgical patients ($p < 0.001$).

Conclusions. A prediction model for selection of patients for surgical intervention was created. Once validated and prospectively tested, this model may be used to identify patients who may benefit from surgical intervention.

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For patients with advanced-stage (stages IIIA, IIIB, and IV) non-small cell lung cancer (NSCLC), 5-year survival remains very poor despite the introduction of new systemic therapies [1]. Treatment approaches for these patients are very heterogeneous, and a small proportion of these patients undergo surgical intervention alone or combined with other modalities [1]. Overall, in the setting of poor survival outcomes as well as the potential morbidity of an invasive operation, curative-intent treatments, such as surgical resection, are not the primary focus of multimodality therapy because the goals of care remain disease control and palliation [2].

However, the inclusion of surgical intervention into the treatment strategy for advanced-stage NSCLC has been reproducibly associated with improvements in survival [3–8]. Using data from population-based and institutional databases, we and others have demonstrated significantly longer cancer-specific and overall survival in advanced NSCLC patients treated with surgical intervention (alone or in combination) compared with nonsurgical modalities, including chemoradiotherapy, chemotherapy alone, radiotherapy alone, and no treatment ($p < 0.001$) [3–6]. Similarly, in a propensity-matched analysis using data from the National Cancer Data Base (NCDB), stage IIIB patients treated with chemotherapy, radiotherapy, and surgical resection had a median survival of 28.9 months compared with 17.2 months for patients treated with chemoradiotherapy without surgical intervention ($p < 0.001$) [4].

A routine criticism of these analyses is that selection bias (even with advanced statistical techniques such as propensity matching) remains an important

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confounding factor potentially accounting for superior survival outcomes observed for surgical patients [4, 5, 9]. This selection bias may reflect the influence of treatment-related variables that are not independently associated with the outcome variable of interest. Yet, despite an understanding of surgical selection bias as a concept, the measurable effect of surgical selection bias on outcomes has been difficult to quantify, partly because of limited data on clinical and pathologic characteristics related to selection for surgical intervention, particularly in advanced-stage NSCLC. Our objective was to quantify the factors influencing selection of advanced-stage NSCLC patients for operations by generating a predictive model, the Surgical Selection Score (SSS). We hypothesized that the SSS would be independently associated with increased overall survival (OS).

Patients and Methods

This study received a determination letter from the University of California, Davis Institutional Review Board. We queried the NCDB for cases of NSCLC proven on biopsy specimens from 1998 to 2012. The NCDB is a joint program of the Commission on Cancer and the American Cancer Society. Data from the NCDB represent 1,500 Commission on Cancer–accredited facilities including more than 70% of all newly diagnosed cancer cases in the United States. These data are used to track treatments and outcomes as well as provide quality-related performance measures [10].

Patients with stage IIIA, IIIB, and IV NSCLC with histologic data available were included. The study cohort is summarized in Figure 1. Standard patient, tumor, and treatment data were extracted and categorized as appropriate. Operations included wedge resection, sublobar resection, lobectomy, bilobectomy, and pneumonectomy. Patient comorbidities were assessed using the Charlson Comorbidity Index, described by Deyo and colleagues [11]. Additional categoric variables examined included clinical tumor group, clinical tumor size, clinical node group, clinical metastases group, histology, age, sex, race, income, education, insurance status, and treatment facility. Age was categorized by percentile (10th, 25th, 50th, 75th, and 90th). Income categories were defined low, less than $38,000; middle, $38,000 to 47,999; and high, more than $48,000. Education categories were defined by the percentage of adults in the patients' zip code who did not graduate from high school: low, 13% or more; middle, 7% to less than 13%; and high, less than 7%. Patients with an additional cancer diagnosis, missing TNM stage group, stage I or II, or missing Charlson-Deyo Index or other demographic data were excluded.

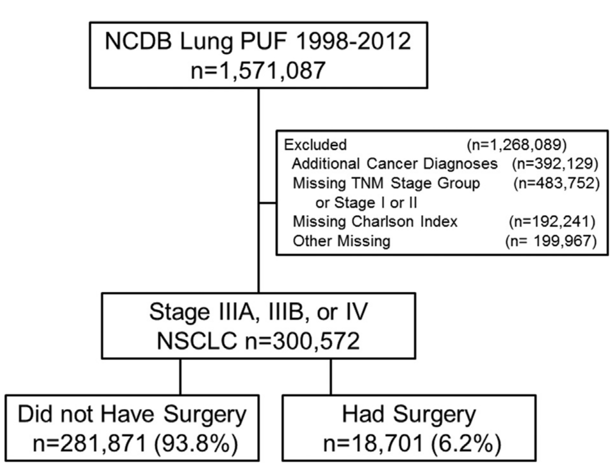

Fig 1. Cohort of stage IIIA, IIIB, and IV patients from the National Cancer Database (NCDB) Participant Use Files (PUF). (NSCLC = non-small cell lung cancer; TNM = tumor-node-metastasis.)

Statistical Analyses

Categorical variables were compared using χ^2 tests to determine differences among the treatment groups (Table 1). Logistic regression was used to create the SSS using models containing increasing numbers of clinical and tumor characteristics, as shown in Figure 2, with the outcome variable representing inclusion of surgical intervention in the treatment regimen [12]. The models were developed in a nested fashion with a simple model initially, and then complexity increased as clinical factors were added. The SSS was developed on a training data set and was validated using a separate validation data set. These training and validation sets were generated using stratified randomization to maintain the proportion of surgical patients in each data set. The entire cohort was split 50/50 into two sets, one for training and one for validation. The ability of each model to predict selection for surgical intervention was assessed and validated by calculating the area under the receiver operating characteristic curve (AUROC) [13]. The equality of the AUROCs from the training and validation sets was compared using the χ^2 test. The final model was determined using the Bayesian information criterion [14].

SSS Creation

The SSS was created by multiplying the logarithm of the odds ratios from the logistic regression model by 100 and adding the total to generate one numeric score for each patient. The probability of undergoing surgical therapy was calculated for the entire cohort and separately by stage. OS functions were estimated using Kaplan-Meier method within treatment groups. Log-rank tests were conducted to examine whether the differences in OS between the treatment groups were statistically significant within quartiles of the SSS. Statistical significance was considered at p values of less than 0.05. Statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC).

Results

We identified 300,572 patients with specimen-proven stage IIIA, IIIB, or IV NSCLC without missing data, and 18,701 of these patients (6.2%) underwent surgical