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ORIGINAL ARTICLE

Increasing Rates of No Treatment in Advanced-Stage Non–Small Cell Lung Cancer Patients: A Propensity-Matched Analysis

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ABSTRACT

Introduction: Variation in treatment and survival outcomes for NSCLC is high among patients with stage III or IV disease, but patients with untreated NSCLC have not been critically analyzed to evaluate for improvable outcomes. We evaluated treatment trends and their association with oncologic outcomes for NSCLC, hypothesizing that there are a substantial number of untreated patients who are similar to patients who undergo treatment.

Methods: Linear regression was used to calculate trends in utilization of treatment. Kaplan-Meier and Cox regression modeling were used to determine predictors of receiving treatment. Propensity matching was used to compare survival among subsets of treated versus untreated patients.

Results: Patients with primary NSCLC were identified from the National Cancer Data base from 1998 to 2012, and 21% of patients (190,539) received no treatment. For stage IIIA and IV, the proportion of untreated patients increased over the study period by 0.21% and 0.4%, respectively ($p = 0.003$ and $p < 0.0001$). Regardless of stage, untreated patients had significantly shorter overall survival (OS) ($p < 0.0001$). Propensity-matched analyses of 6144 stage IIIA patient pairs treated with chemoradiation versus no treatment confirmed shorter OS for untreated patients (median 16.5 versus 6.1 months, $p < 0.0001$). For 19,046 stage IV patient pairs treated with chemotherapy versus no treatment, similar results were obtained (median OS 9.3 versus 2.0 months, $p < 0.0001$).

Conclusions: The proportion of untreated patients with stage IIIA and IV disease is increasing. Survival outcomes among patients with advanced-stage disease are superior with treatment, independent of selection bias. The benefits and risks of treatment should be carefully assessed before choosing to forego treatment.

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Keywords: NSCLC; Natural history; Untreated; Surgery; Radiation; Chemotherapy

Introduction

NSCLC is the number one cause of cancer-related death in the United States, with an estimated 158,080

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deaths in 2016.[1] Despite the introduction of new systemic treatment approaches, 5-year survival remains dismal at approximately 17%.[2] Despite changing demographics such as greater numbers of women who are younger and have better performance status patients and improvements in systemic therapies and clinical trial enrollment, overall survival (OS) rates have changed slowly and incrementally.[3]

The National Cancer Care Network releases updated guidelines annually for the evaluation and management of NSCLC, and standard therapy regimens are based on stage.[4] For patients with stage I and II disease, local therapy with surgery or radiation is recommended depending on medical operability. In contrast, patients with advanced-stage disease (III or IV), are recognized to be heterogeneous, and greater latitude is acknowledged regarding treatment approaches. As a general rule, however, for stage IIIA and IIIB, chemoradiation is typically considered standard management, with surgery recommended only in specialized settings. For patients with stage IV disease, chemotherapy is typically the recommended treatment, with surgery and radiation being utilized in highly selected circumstances.

Yet, despite these guidelines, a substantial proportion of patients with NSCLC remain untreated, and the number of patients in the United States who undergo no treatment for NSCLC has remained fairly constant since the 1990s. Overall, the proportion of untreated patients with NSCLC varies by stage, ranging from 7% to 45%, but in subsets of older, medically inoperable patients, the untreated population can reach as high as 90%.[5–11] Significantly, untreated patients tend to be older, be black, lack insurance, and have lower income than patients who undergo treatment for NSCLC, underscoring the impact of socioeconomic, racial, and other disparities in treatment decisions.[6] Given the particularly poor survival among untreated patients with NSCLC (reaching a nadir of approximately 7.2 months in the 1990s),[12] we sought to characterize the patient and provider factors of untreated patients with NSCLC in a hospital-based cohort. We hypothesized that patients who are older, poorly educated, without health insurance, and with a higher disease stage would have a higher likelihood of being untreated, but we also hypothesized that there are a substantial number of untreated patients who are statistically similar to patients who undergo treatment.

Methods

We queried the National Cancer Data Base (NCDB) for cases of biopsy-proven NSCLC from 1998 to 2012. The NCDB is a joint program of the Commission on Cancer and the American Cancer Society. Data captured in the NCDB represent 1500 Commission on Cancer–accredited facilities and more than 70% of all newly diagnosed cancer cases in the United States and are used to track treatments and outcomes as well as to provide quality-related performance measures.[13] We abstracted data on key clinical/pathologic characteristics and analyzed the factors associated with patients' untreated status. We used propensity matching to identify untreated patients who were not different from patients who underwent standard of care therapies.

This study received a determination letter from the University of California, Davis, Institutional Review Board. Data for patients with primary NSCLC were obtained from the NCDB participant user file for patients treated from 1998 to 2012. Patients with stage I to IV NSCLC with histologic data available were included. Patients with an additional cancer diagnosis were excluded. Inclusion and exclusion criteria are summarized in Figure 1.

Patient, tumor, and treatment data were extracted and categorized as appropriate. Surgical operations included wedge resection, sublobar resection, lobectomy, bilobectomy, and pneumonectomy. Patient comorbidities were assessed by using the Charlson comorbidity index, described by Deyo et al.[14] Additional categorical variables examined included sex, race, income, education, insurance status, year of diagnosis, clinical stage group, clinical node status, histologic subtype, and treatment facility. Annual income categories were defined as follows: low, less than $38,000; middle, from $38,000 to $47,999; and high, $48,000 or higher. Education categories were defined by the percentage of patients who did not graduate from high school: low, 13% or higher; middle, 7% to lower than 13%; and high, lower than 7%. Continuous variables included age and tumor size. Continuous variables were compared using Kruskal-Wallis tests, and categorical variables were compared using chi-square tests to determine differences in the treatment groups.

Types of treatment included chemotherapy, radiation, and surgery; chemotherapy and surgery; chemoradiation; surgery only; chemotherapy only; radiation only; surgery and radiation; unknown; and no treatment. The unknown treatment group included patients with missing data for chemotherapy, surgery, or radiation, whereas the no-treatment group included patients who did not have an operation, radiation, or chemotherapy. Linear regression analysis was used to determine the trend in treatment over the study period by using the proportion of patients who received treatment in a certain year as a continuous variable as the outcome. OS functions were estimated by the Kaplan-Meier method within treatment groups. Log-rank tests were conducted to examine whether the unadjusted differences in OS

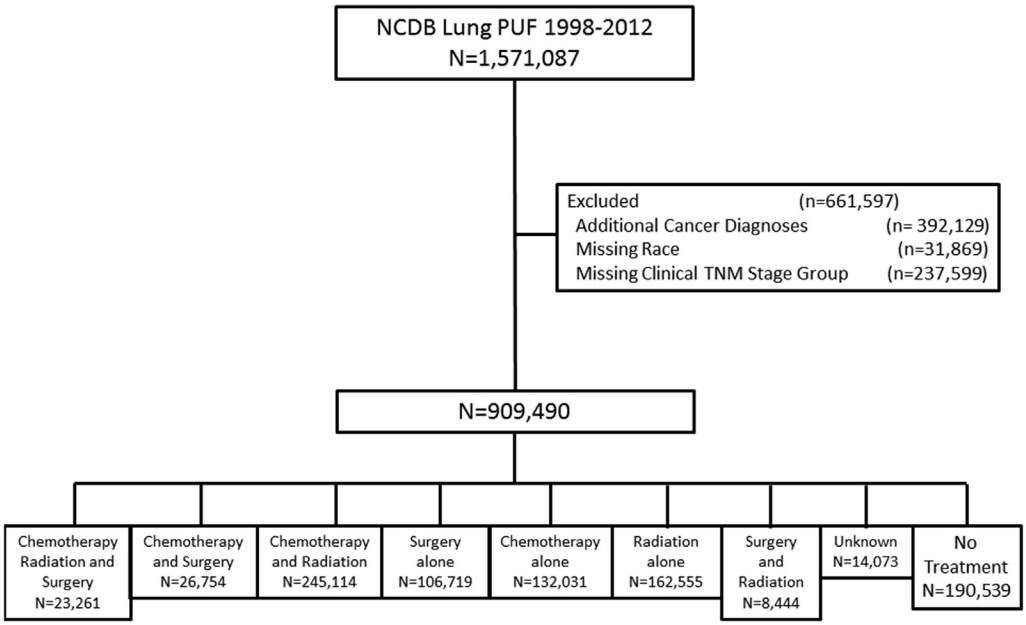

Figure 1. Study population from the National Cancer Data Base participant user file 1998–2012. NCDB, National Cancer Data Base; PUF, participant user file.

between the treatment groups were statistically significant within each stage. The multivariable Cox proportional hazards model was used to study the association of each of the variables with OS.[15] The multivariable logistic regression model was used to study the association of each of the variables with being untreated.

Propensity score matching was used to identify two similar groups of patients for the stages (stage IIIA and IV) in which the proportion of untreated patients increased over the study period. Propensity score matching of patients with stage IIIA disease who were treated with chemoradiation versus no treatment was used to identify two comparable groups of patients.[16] Similarly, propensity score matching of patients with stage IV disease who were treated with chemotherapy only versus no treatment was used to identify two comparable groups. Patients in these analyses were matched for age, sex, race, income, education, clinical tumor size, clinical node status, Charlson/Deyo score, and facility type. p Values less than 0.05 were considered statistically significant. All statistical analyses were conducted with SAS for Windows, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

The distribution of the treatment group by stage is shown in Figure 2 and Supplementary Figure 1. Overall, 21% of patients (190,539) received no treatment (by stage: I, 13.5%; II, 15.4%; IIIA, 16.5%; IIIB, 22.2%; and IV, 25.5%). For each stage, treatment groups varied significantly by age, Charlson-Deyo score, sex, race, insurance status, income, education, year of diagnosis, facility type, histologic subtype, tumor size, and clinical N status (data not shown, but available upon request). Across all stages, untreated patients were more likely to be older and have Medicare rather than private insurance.

When considered as a continuous variable, the proportion of patients in each treatment group for each year was used to calculate the trends in changes in treatment patterns. The results are shown in Supplementary Tables 1 to 5. For stages I and II, the proportion of untreated patients decreased by 0.66% and 0.23%, respectively, over the 14-year study period ($p < 0.0001$ and $p = 0.022$). For stages IIIA and IV, the proportion of untreated patients increased over the study period by 0.21% and 0.4%, respectively ($p = 0.003$ and $p < 0.0001$) (Fig. 3). For stage IIIB there was no significant change in the proportion of untreated patients.

Factors associated with OS (Supplementary Table 6) and receiving no treatment were analyzed and are shown in Table 1. A subset of the cohort with complete data was used for these analyses, secondary to missing and unavailable data within the NCDB participant user file. Type of treatment, age, sex, race, insurance status, income, education, Charlson-Deyo score, year of diagnosis, clinical stage, tumor size, clinical nodal status, histologic subtype, and type of treatment facility were all significantly associated with OS ($p < 0.0001$). As expected, older age, female sex, nonwhite race, no insurance, low income, low education, higher Charlson-Deyo score, earlier year of diagnosis, higher clinical

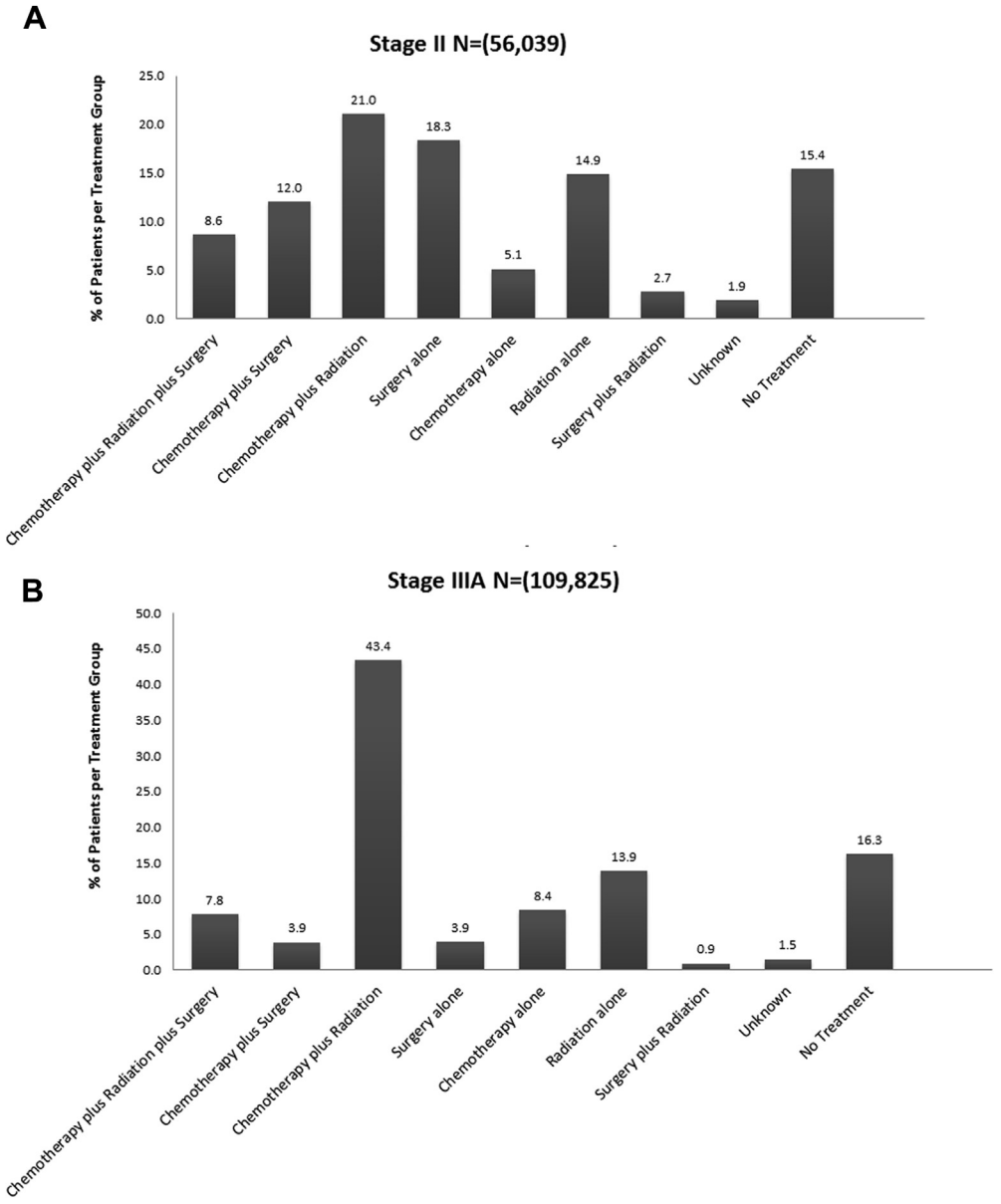

Figure 2. Distribution of treatment group by stage: stage II (*A*), stage IIIA (*B*), stage IIIB (*C*), and stage IV (*D*). (Stage I available in Supplementary Fig. 1)

stage, larger tumor size, and higher nodal status were all significantly associated with receiving no treatment.

In the stages of disease at which the number of untreated patients increased (stages IIIA and IV), propensity score matching was used to identify comparable groups of patients treated with standard of care approaches (chemotherapy and radiation for stage IIIA and chemotherapy only for stage IV) versus untreated patients. We were able to identify 6144 matched pairs of patients with stage IIIA disease (Supplementary Table 7) and 19,046 matched pairs of patients with stage IV disease (Supplementary Table 8). Significant differences in OS were observed between the matched pairs. For stage IIIA disease, median OS was 16.5 versus 6.1 months ($p < 0.0001$) (Fig. 4*A*), and for stage IV, median OS was 9.3 versus 2.0 months ($p < 0.0001$) (Fig. 4*B*).

Discussion

It is unrealistic to expect that all patients with lung cancer will be candidates for and choose to undergo treatment for NSCLC, especially those with advanced-stage NSCLC. However, as novel therapies offering improved survival have been introduced, there have also been improvements in supportive care and side effect management that have also improved patient tolerance of standard cytotoxic therapies such as chemotherapy, radiotherapy, and even surgery.[17] Consequently, a

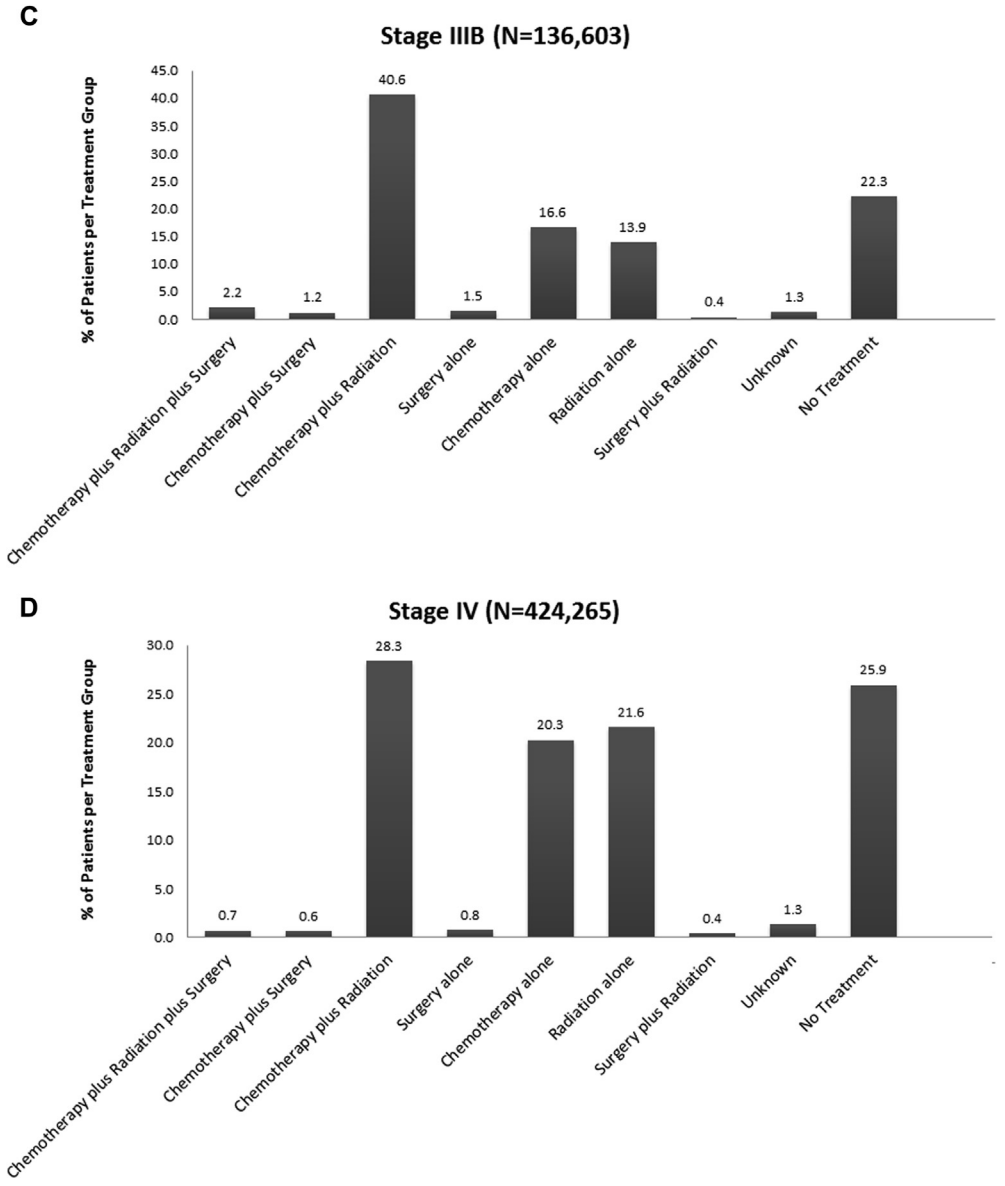

Figure 2. (*continued*).

plausible hypothesis would be that the number of untreated patients with an advanced stage of NSCLC would decrease over time, as we observed for patients with stage I and II disease. However, when we used the NCDB hospital-based data set, we observed the opposite; namely, there was a significant increase in the prevalence of patients receiving no treatment in stage IIIA and IV disease. Among stage IIIA patients tracked in the California Cancer Registry, a similar trend was identified for increased numbers of patients being untreated between 2004 and 2012 (0.9% [$p < 0.001$]).[9] Additionally, among stage IIIA, IIIB, and IV patients, there was a trend of significantly decreased use of multimodality regimens in the California Cancer Registry.

By using a propensity matching analysis, we attempted to assess the number of untreated patients who were statistically similar to patients who received standard of care treatments as outlined in National Comprehensive Cancer Network guidelines.[4] We identified 8457 untreated stage IIIA patients and were able to match 73% (6144) to comparable treated patients. Among the stage IV patients, we were able to match 55% of the untreated cohort (19,046) to patients who underwent chemotherapy. The substantial fraction of matched patients receiving no treatment is evidence that other factors besides selection bias are affecting decisions to forego treatment in advanced-stage NSCLC.

There are many factors that influence the decision not to undergo treatment for NSCLC, including patient and disease characteristics, as well as physician factors. Wassenaar et al. found that primary care physicians are

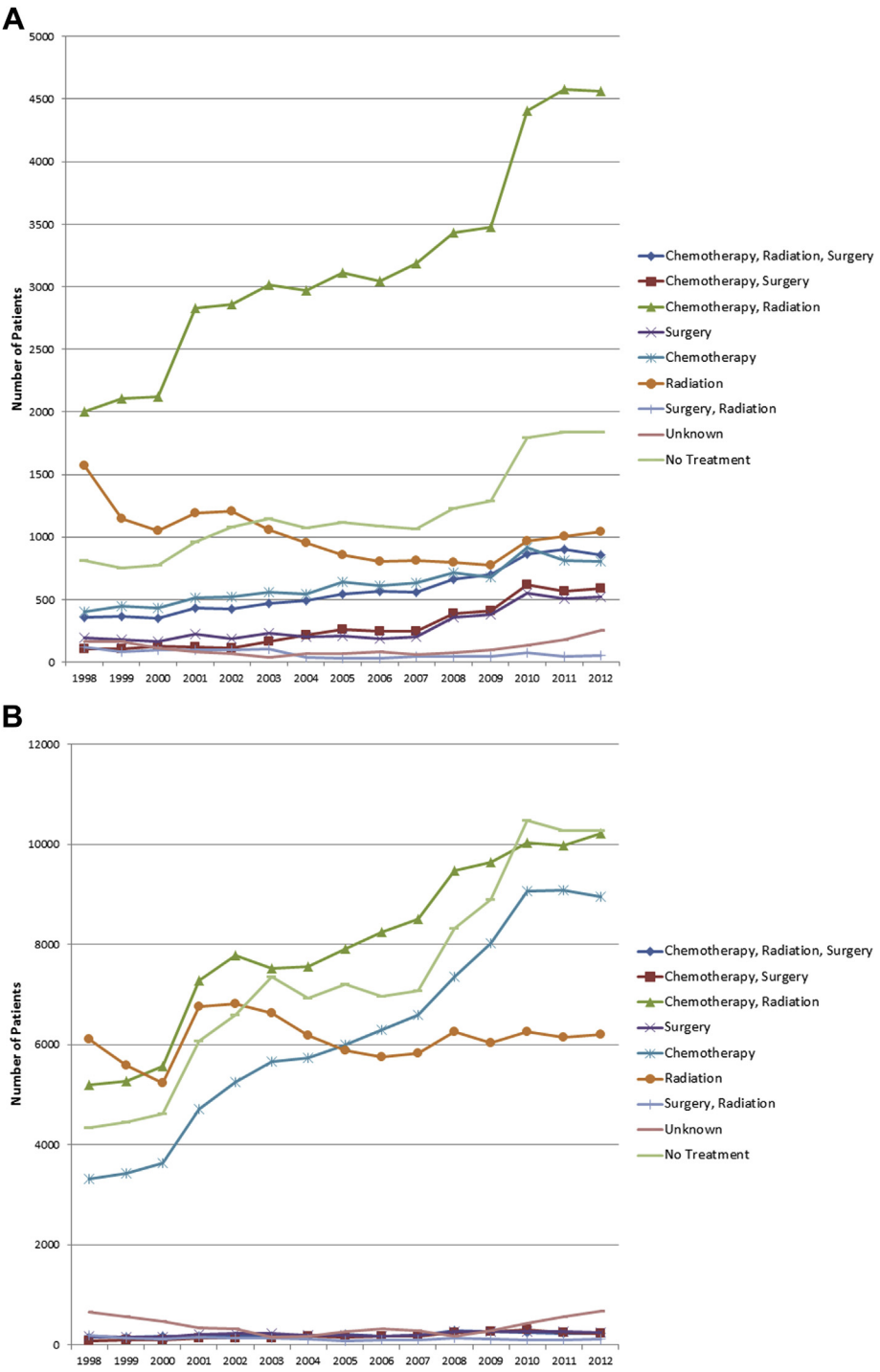

Figure 3. (*A*) Trends in number of patients in each treatment group for stage IIIA. (*B*) Trends in number of patients in each treatment group for stage IV.

less likely to refer patients with advanced NSCLC to an oncologist than to refer patients with breast cancer.[18] Similarly, Goulart et al. observed that family practice physicians were less likely to refer patients with advanced-stage NSCLC to medical oncologists than were general internists.[19] Thus, it is possible that physician referral patterns and preferences influence treatment patterns and outcomes, as Goulart et al. also found that practice patterns influenced the delivery of guideline-based therapy. It should also be noted that patient factors such as rural location and insurance status likely influence physician referral patterns as well, which may not only limit options for care but also raise barriers to receiving treatment.

Table 1. Multivariable Logistic Regression Analysis for Predictors of Receiving No Treatment (N = 446,383)

Effect	OR Estimates			
	Point Estimate	95% Wald Confidence Limits		*p* Value
Age	1.053	1.052	1.054	**<0.0001**
Sex				**0.0038**
Male vs. female	0.976	0.961	0.992	
Race				**<0.0001**
Black vs. white	1.245	1.214	1.277	
Other vs. white	1.337	1.184	1.509	
Unknown vs. white	1.538	1.415	1.671	
Insurance status				**<0.0001**
Unknown vs. not insured	0.674	0.627	0.723	
Medicaid vs. not Insured	0.784	0.746	0.825	
Medicare vs. not Insured	0.504	0.482	0.526	
Other government insurance vs. not insured	0.466	0.428	0.508	
Private insurance vs. not insured	0.453	0.433	0.473	
Income				**<0.0001**
High vs. low	0.907	0.884	0.930	
Middle vs. low	0.919	0.897	0.941	
Education				**<0.0001**
High vs. low	0.827	0.807	0.847	
Middle vs. low	0.885	0.866	0.904	
Charlson-Deyo score				**<0.0001**
1 vs. 0	1.176	1.155	1.198	
2 vs. 0	1.582	1.546	1.620	
Year of diagnosis	0.991	0.988	0.994	**<0.0001**
Stage				**<0.0001**
II vs. I	1.302	1.252	1.354	
IIIA vs. I	1.727	1.666	1.790	
IIIB vs. I	2.207	2.133	2.283	
IV vs. I	3.069	2.985	3.155	
Histologic subtype				**<0.0001**
Other vs. adenocarcinoma	1.052	1.033	1.073	
Squamous vs. adenocarcinoma	1.008	0.987	1.029	
Facility Type				**<0.0001**
Academic/research program vs. community cancer program	0.772	0.752	0.793	
Comprehensive community cancer program vs. community cancer program	0.862	0.842	0.883	
Other specified types of cancer programs vs. community cancer program	1.088	0.903	1.311	
Tumor size, mm	1.000	1.000	1.001	**<0.0001**
Clinical N status				**<0.0001**
cN1 vs. cN0	0.915	0.887	0.944	
cN2 vs. CN0	0.934	0.912	0.957	
cN3 vs. CN0	0.789	0.766	0.813	

Note: Boldface indicates statistical significance.

Socioeconomic disparities are strongly linked with differences in treatment and poor outcomes for NSCLC. Berglund et al. identified a decreased likelihood of treatment with chemotherapy for patients with advanced-stage NSCLC as economic status declined ($p < 0.01$) and as age ($p < 0.01$) and comorbidities increased ($p < 0.01$).[20] Survival was the longest among the patients in the highest quintile of economic status. Racial differences in rates of surgery between black and white patients in the Surveillance, Epidemiology, and End Results Program have also been identified, and an analysis of Surveillance, Epidemiology, and End Results data suggests that an additional 44 lives could have been saved if surgery had been used equally along racial lines for early-stage NSCLC.[21] Insurance status also significantly affects treatment decisions. Groth et al. found that patients with stage I NSCLC and private insurance were more likely to undergo treatment with lobectomy than patients with Medicare, Medicaid, or no insurance (p value not specified).[22] Similarly, geographic factors

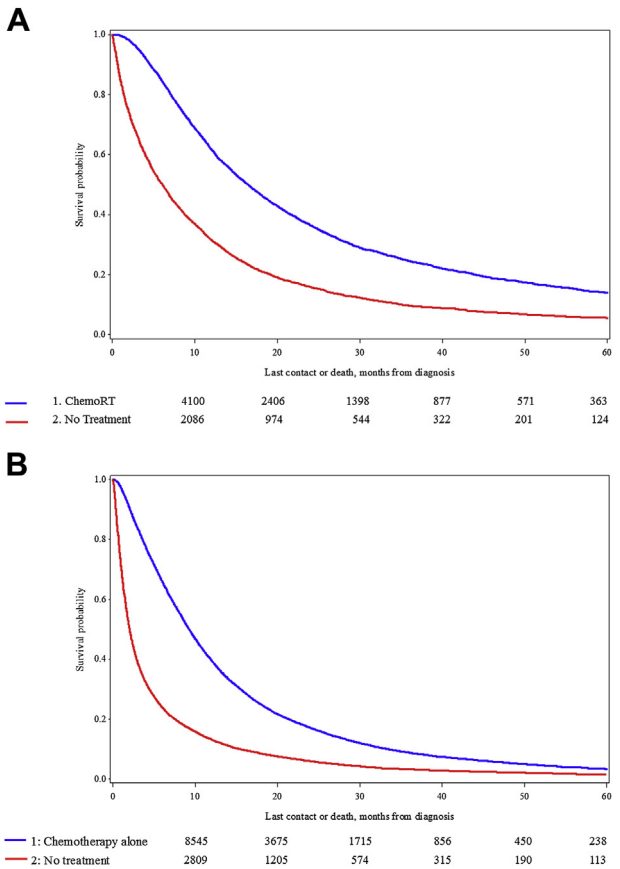

Figure 4. (*A*) Kaplan-Meier curve for overall survival in patients at stage IIIA undergoing chemotherapy plus radiation versus no treatment after propensity score matching of 6144 patient pairs (log-rank test $p < 0.0001$). (*B*) Kaplan-Meier curve for overall survival in patients at stage IV undergoing chemotherapy versus no treatment after propensity score matching of 19,046 patient pairs (log-rank test $p < 0.0001$). RT, radiotherapy.

have been associated with oncologic outcomes. For example, Johnson et al. found that rural patients with NSCLC in Georgia were more likely than urban patients to have unstaged disease (OR = 1.63, 95% confidence interval [CI]: 1.45–1.83) and less likely than urban patients to receive radiation (OR = 0.89, 95% CI: 0.82–0.96) or chemotherapy (OR = 0.92, 95% CI: 0.85–0.99).[23]

In our analysis, older patients were also less likely to undergo treatment, and previous studies have suggested that this contributes to marked survival disparities. An analysis by Nanda et al. used the NCDB to evaluate patients older than 70 years with early-stage NSCLC and compared outcomes between stereotactic radiotherapy (SBRT) and no treatment.[10] Despite having similar Charlson-Deyo scores, untreated patients had a median survival of 10.1 months, compared with 29 months for patients who had been treated with SBRT ($p < 0.001$). This survival benefit to SBRT was consistently observed across all age groups, including those patients aged 85 and older, suggesting that a substantial proportion of older patients may be undertreated.

Nevertheless, it is important to consider our analysis within the context of its strengths and limitations. The large sample size in the NCDB allows for identification of patterns of treatment, but it does not allow for a granular assessment of individual subsets of patients. Despite our attempts to create distinct subsets of patients, it is not possible to fully account for the heterogeneity seen within each stage for patients with NSCLC when an administrative data set is used. Additionally, we are unable to assess the extent of multidisciplinary evaluation or the role of a tumor board in treatment decisions using this data set, which would enhance our analysis.

Ultimately, our analysis could be interpreted as yet another article demonstrating a selection bias for treated patients. However, it is important to underscore the significant numbers of untreated patients who were able to be matched with treated patients in both stage IIIA or IV NSCLC. This identifies a potentially notable area for improvement to develop innovative ways to improve access to care for patients with higher-stage NSCLC, especially those from groups with lower socioeconomic status, lower education, lower income, and nonprivate insurance. Future studies will need to investigate additional factors that influence treatment decisions for patients with NSCLC, including regional treatment variations, proximity to treatment, and presence of regional treatment resources, as these may all be areas that can be improved with targeted interventions to overcome barriers to treatment.

Conclusion

Substantial numbers of patients remain untreated for NSCLC in the United States, but high percentages of these patients are statistically similar to treated patients when compared by age, sex, race, income, education, tumor size, nodal status, Charlson-Deyo score, and type of treatment facility. Physicians should endeavor to ensure that patients from disparate populations are evaluated and counseled thoroughly by multidisciplinary teams before choosing to forego treatment for NSCLC.

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the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.11.2221.

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