Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States

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Disparities in receiving lung cancer treatment

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Abstract

Rationale

The level of adherence to lung cancer treatment guidelines in the United States is unclear. Also, it is unclear whether previously identified disparities by racial/ethnic group and by age persist across all clinical subgroups.

Objectives

To assess the level of adherence to the minimal lung cancer treatment recommended by the National Comprehensive Cancer Network guidelines (guideline-concordant treatment) in the United States, and to assess the persistence of disparities by racial/ethnic group and by age across all clinical subgroups.

Methods

We evaluated whether 441,812 lung cancer cases in the National Cancer Database diagnosed between 2010-2014 received guideline-concordant treatment. Multivariable logistic regression models were used to assess possible disparities in receiving guideline-concordant treatment by racial/ethnic group and by age across all clinical subgroups, and whether these persist after adjusting for patient, tumor, and health care provider characteristics.

Results

Overall, 62.1% of subjects received guideline-concordant treatment (range across clinical subgroups: 50.4%-76.3%). However, 21.6% received no treatment (range: 10.3%-31.4%) and 16.3% received less intensive treatment than recommended (range: 6.4%-21.6%). Among the most common less intensive treatments for all subgroups was *conventionally fractionated radiotherapy only* (range: 2.5%-16.0%), as was *chemotherapy only* for non-metastatic subgroups (range: 1.2% to 13.7%), and *conventionally fractionated radiotherapy & chemotherapy* for localized non-small cell lung cancer (5.9%). Guideline-concordant treatment was less likely with increasing age despite adjusting for relevant covariates (age ≥80 compared to <50: adjusted odds ratio [aOR]=0.12, 95% confidence interval [95%CI]=0.12-0.13). This disparity was present in all clinical subgroups. Also, non-Hispanic Blacks were less likely to receive guideline-concordant treatment than non-Hispanic Whites (aOR=0.78, 95%CI=0.76-0.80). This disparity was present in all clinical subgroups, although statistically non-significant for extensive disease small cell lung cancer.

Conclusions

Between 2010-2014, many lung cancer patients in the United States received no treatment or less intensive treatment than recommended. Particularly, elderly lung cancer patients and non-Hispanic Blacks are less likely to receive guideline-concordant treatment. Patterns of care among those receiving less intensive treatment than recommended suggest room for improved uptake of treatments such as Stereotactic Body Radiation Therapy among localized non-small cell lung cancer.

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Introduction

An estimated 142,670 persons will die of lung cancer in the United States in 2019, making it the leading cause of cancer-related deaths (1). Reflecting the large burden to society, lung cancer treatment is an important topic of medical research. A recent bibliometric analysis identified a total of 32,161 studies published on lung cancer between 2004-2013, of which 36% focused on treatments (2). Clinical practice guidelines, which can be considered the basis for measures of quality of care, compile the available evidence and expert consensus (3).

However, literature indicates that the minimal treatment recommended in these guidelines (i.e., guideline-concordant treatment) may not be provided to all lung cancer patients in the United States (4). Furthermore, there is evidence that specific subgroups are less likely than others to receive guideline-concordant treatment. For example, the proportion of cases that receive guideline-concordant treatment is lower for more advanced stages (4). Also, disparities by racial/ethnic group have been described. For example, Black patients are less likely to receive surgical treatment for localized non-small cell lung cancer (L-NSCLC; stages I-II) than White patients (5-10). Additionally, elderly lung cancer patients are less likely to receive guideline-concordant treatment, despite controlling for comorbidity (4, 9, 10). However, comparability and generalizability of the available literature are limited because often only one specific subset of clinical cases is examined (5, 11), relatively small sample sizes are used (8, 10), different methodologies are applied (5, 7), or the data covers different timespans (5, 7). Thus, it is unclear whether disparities in receiving guideline-concordant treatment by racial-ethnic group and by age persist, and whether these are similar across clinical subgroups of lung cancer in the United States.

Therefore, the first aim of this study was to assess the level of adherence to predefined stage-specific guideline-concordant treatment for each clinical subgroup of lung cancer patients in a large US dataset. The second aim was to assess whether previously identified disparities in receiving guideline-concordant treatment by racial/ethnic group and by age persist across all clinical subgroups of lung cancer. Some of the results of this study have been previously reported in the form of an abstract (12).

Methods

Data

We used the US National Cancer Database (NCDB) to extract a cohort of 441,812 patients diagnosed with lung cancer between 2010-2014 (see Figure E1 in the Online Supplement). The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually, from more than 1,500 affiliated facilities. The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Analysis of individual-level NCDB data was performed on site at the University of Michigan Medical School.

To assess the generalizability of the NCDB data to the general US population, we compared baseline characteristics to a cohort of lung cancer patients from the population-based Surveillance, Epidemiology, and End Results (SEER) dataset (13). A detailed version of the methods, including the rationale for case selection, data cleaning, and the analysis of the SEER

dataset is available online (see Supplementary Methods and Tables E1 and E2 in the Online Supplement). This study was deemed exempt by the Institutional Review Board of the University of Michigan.

Definition of Guideline-Concordant Treatment

Two main lung cancer types can be distinguished: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with the majority presenting as NSCLC. Since SCLC is clinically more aggressive than NSCLC, clinical guidelines provide specific treatment recommendations for clinical subgroups of lung cancer type and stage at diagnosis. For each of these clinical subgroups, we assessed whether guideline-concordant treatment was received, defined as the minimal first course treatment these patients should receive according to the National Comprehensive Cancer Network guidelines (14, 15).

While surgery is still recommended as the primary minimal treatment for L-NSCLC (stages I-II), Stereotactic Body Radiation Therapy (SBRT) is now recommended as an alternative treatment to surgery for L-NSCLC patients (14). SBRT delivers high-dose radiation to a specific target in only a few fractions and provides local tumor control rates of up to 90% with moderate toxicity (16, 17). Therefore, both surgery and SBRT were considered guideline-concordant treatment for L-NSCLC. The minimal recommended treatment for locally advanced NSCLC (LA-NSCLC; stage III) and limited disease SCLC (LD-SCLC; stages I-III) depends on operability (14, 15). If operable, the minimal recommendation is surgery combined with chemotherapy. However, the majority of LA-NSCLC and LD-SCLC patients are inoperable, in which case the minimal recommendation is a combination of radiotherapy and chemotherapy.

Therefore, both treatment combinations were considered guideline-concordant for LA-NSCLC and LD-SCLC. For advanced NSCLC (A-NSCLC; stage IV) and extensive disease SCLC (ED-SCLC; stage IV), the minimally recommended treatment is chemotherapy (14, 15). As we assessed the minimal recommended treatment for each clinical subgroup, additional treatments were allowed beside guideline-concordant treatment (e.g. radiotherapy for bone metastases beside chemotherapy in A-NSCLC). A summary of the treatment combinations that were considered guideline-concordant for each clinical subgroup can be found in Table E3 in the Online Supplement.

Since the most frequently used SBRT schemes in the United States comprise a total dose of 45 Gray or more over 1-5 fractions (18-20) and the US billing code for SBRT includes a maximum of 5 fractions (14), SBRT was defined as thoracic radiotherapy with a total radiation dose of 45 Gray or more delivered in 5 fractions or less. There were no restrictions on radiation dose or fractionation for stages other than L-NSCLC. Chemotherapy included the use of targeted therapies. We were not able to separately assess the use of immunotherapy agents in these data because their use was not recommended in the evaluated time-period (see Supplementary Methods in the Online Supplement).

Statistical Analysis

For each clinical subgroup, we assessed the proportion of cases that received guideline-concordant treatment, less intensive treatment than recommended (defined as treatment that was not guideline-concordant), and no treatment. We used clinical stage at diagnosis for creating clinical subgroups because pathological stage can only be known after the outcome of

interest (initial treatment) has occurred. For the groups of patients who received guideline-concordant treatment and less intensive treatment than recommended, we separately assessed which mutually exclusive combinations of surgery, SBRT, conventionally fractionated radiotherapy (CRT; defined as all radiotherapy other than SBRT), chemotherapy (including targeted therapy) and other treatment (including immunotherapy and experimental treatments) were received.

To identify whether previously identified disparities in receiving guideline-concordant treatment by racial/ethnic group and by age persist, we fitted a multivariable logistic regression model with receipt of guideline-concordant treatment as binary outcome and racial/ethnic group and age as independent variables. We further adjusted this model for several covariates that could be associated with racial/ethnic group and age, and also affect receiving guideline-concordant treatment. Based on previous literature, we included sex (9), health insurance status (21), Charlson comorbidity score (22), facility type (11), and stage at diagnosis (4). We further included histology because squamous cell carcinomas are often located centrally (23), potentially making them more difficult to surgically resect. Finally, we included hospital volume because it is a well-established indicator of quality of care (24). The derivation and composition of these variables is detailed in the Supplementary Methods in the Online Supplement.

To identify whether disparities by racial/ethnic group and by age extend across all clinical subgroups, we also fitted a separate model for each clinical subgroup. For clinical subgroups with multiple guideline-concordant treatment combinations, we fitted a separate model for each treatment combination. For example, two separate models were fitted for L-

NSCLC; one with SBRT as binary outcome and one with surgery as binary outcome. These models were adjusted for the same covariates as the overall model.

All analyses were performed using R software version 3.4.1 (25). The base-R glm() function was used to fit the logistic regression models. We used multiple imputation to address missing data, using three imputations (26). Multicollinearity was assessed by calculating generalized variance inflation factors (27).

Results

Patient Characteristics

Baseline characteristics of the 441,812 included patients are shown in Table 1. When comparing these with lung cancer cases in the population-based SEER registry, we found only very small differences in sex, age, racial/ethnic group, health insurance status, histology, and stage at diagnosis (see Table E4 in the Online Supplement).

Adherence to Guideline-Concordant Treatment

The proportion of cases that received guideline-concordant treatment within each clinical subgroup was stable between 2010-2014 (see Figure E2 in the Online Supplement). As shown Table 2, 62.1% of all cases diagnosed between 2010-2014 received guideline-concordant treatment (range: 50.4% in A-NSCLC to 76.3% in L-NSCLC). However, 16.3% received less intensive treatment than recommended (range: 6.4% in ED-SCLC to 21.6% in LA-NSCLC), and 21.6% received no treatment (range: 10.3% in L-NSCLC to 31.4% in A-NSCLC).

Patterns of Care among Patients that Received Guideline-Concordant Treatment

Among L-NSCLC cases that received guideline-concordant treatment, *surgery only* was received most frequently (49.1%), followed by *surgery & chemotherapy* (11.4%), and *SBRT only* (10.0%) (Table 3). In every other clinical subgroup, *CRT & chemotherapy* was most common (range: 25.9% in A-NSCLC to 63.5% in LD-SCLC). Among LA-NSCLC and LD-SCLC, *surgery & CRT & chemotherapy* was also used (7.4% and 2.6%, respectively), as was *surgery & chemotherapy* (4.4% and 2.4%, respectively). Among A-NSCLC and ED-SCLC, *chemotherapy only* was common (19.5% and 35.0%, respectively).

Patterns of Care among Patients that Received Less Intensive Treatment Than Recommended

CRT only was among the most commonly received less-intensive-than-recommended therapies for each clinical subgroup, as was *chemotherapy only* for subgroups other than A-NSCLC and ED-SCLC (see Table 3). Most common among L-NSCLC were *CRT only* (6.1%), *CRT & chemotherapy* (5.9%), and *chemotherapy only* (1.2%). Among LA-NSCLC and LD-SCLC, the most commonly received less-intensive-than-recommended treatments were *CRT only* (8.7% and 2.5%, respectively) and *chemotherapy only* (7.9% and 13.7%, respectively). *CRT only* was the most common among metastatic subgroups A-NSCLC (16.0%) and ED-SCLC (5.8%).

Disparities in Receiving Guideline-Concordant Treatment

As can be seen in Table 4, the odds of receiving guideline-concordant treatment decreased with advancing age (for those aged ≥80 compared to those aged <50: odds ratio[OR]=0.14, 95%

confidence interval [95%CI]=0.13-0.14). This association remained present after adjusting for covariates (for those aged ≥80 compared to those aged <50: adjusted odds ratio[aOR]=0.12, 95%CI=0.12-0.13). Also, the association between age and receiving guideline-concordant treatment was consistent across clinical subgroups, with a notable exception in L-NSCLC (see Table E5 in the Online Supplement). In L-NSCLC, advancing age was associated with a decreased odds of receiving surgery (for those aged ≥80 compared to those aged <50: aOR=0.06, 95%CI=0.05-0.06). However, the odds of receiving SBRT for L-NSCLC increased with advancing age (for those aged ≥80 compared to those aged <50: aOR=18.39, 95%CI=14.09-23.99).

Compared to non-Hispanic Whites, Non-Hispanic Blacks (OR=0.82, 95%CI=0.81-0.84) and Hispanics (OR=0.87, 95%CI=0.84-0.90) were less likely to receive guideline-concordant treatment. This association remained present after adjusting for covariates (non-Hispanic Blacks: aOR=0.78, 95%CI=0.76-0.0.80; Hispanics: aOR=0.94, 95%CI=0.90-0.98). On the other hand, non-Hispanic Asians were more likely to receive guideline-concordant treatment after adjusting for covariates (aOR=1.09, 95%CI=1.04-1.15). However, results for non-Hispanic Asians and Hispanics varied within clinical subgroups (see table E5 in the Online Supplement). For example, within the subgroup of L-NSCLC both non-Hispanic Asians and Hispanics were more likely to receive surgery than non-Hispanic Whites (non-Hispanic Asians: aOR=1.23, 95%CI=1.10-1.37; Hispanics: aOR=1.24, 95%CI=1.13-1.36) but less likely to receive SBRT (non-Hispanic Asians: aOR=0.51, 95%CI=0.43-0.62; Hispanics: aOR=0.47, 95%CI=0.40-0.56). Also, non-Hispanic Asians with A-NSCLC were more likely to receive chemotherapy (aOR=1.25, 95%CI=1.18-1.34).

Discussion

To our knowledge, this study is the first to investigate adherence to guideline-concordant treatment as well as disparities by racial/ethnic group and by age in a uniform manner for all clinical subgroups of lung cancer including SCLC.

Adherence to Guideline-Concordant Treatment

We show that overall, the level of adherence to guideline-concordant treatment among lung cancer patients in the United States is only 62.1%, and varies across clinical subgroups. The rate of guideline-concordant treatment was highest for L-NSCLC. This makes sense as treatment for L-NSCLC is potentially curative and therefore offers the most obvious benefits. The rate of guideline-concordant treatment was lowest for A-NSCLC.

A possible explanation for this finding could be a lack of referral to medical oncologists among A-NSCLC patients. A recent study reported that only 54% of stage IIIB-IV NSCLC cases triaged at the British Columbia Cancer Agency were assessed by a medical oncologist (28). Another study found that one of the most common reasons for not referring patients to a medical oncologist or prescribing chemotherapy was the patient's preference against treatment (29). Some patients with incurable disease fear that chemotherapy side-effects may negatively affect their quality of life (30). Perhaps this could influence their willingness to accept chemotherapy. However, chemotherapy for advanced disease has been shown to improve quality of life, symptom control, and survival compared to best supportive care (31). Therefore,

discussing a patient's possible fears of chemotherapy and the potential health benefits could be an important step towards increasing the uptake of chemotherapy.

Compared to our results, Wang et al. reported even lower rates of guideline-concordant treatment among 20,511 NSCLC cases diagnosed between 2003-2008 (4). In their study, the proportion that received guideline-concordant treatment was 51% among L-NSCLC, 35% among LA-NSCLC, and 27% among A-NSCLC. The difference compared to our study is likely due to patient selection, as Wang et al. included only veterans aged ≥65.

Within the group that received guideline-concordant treatment, our data show that most L-NSCLC cases received surgery, while SBRT and other modalities were used much less frequently. In contrast, most cases in the potentially operable clinical subgroups LA-NSCLC and LD-SCLC did not receive surgery as guideline-concordant treatment. 16.3% of cases in our data received less intensive treatment than recommended. The patterns of care among these cases provide important clues towards improvements in clinical care. For example, the frequent use of *CRT only, CRT & chemotherapy,* and *chemotherapy only* among L-NSCLC suggests that the uptake of SBRT among inoperable cases may still be lagging. Among LA-NSCLC and LD-SCLC the most common forms of less-intensive-than-recommended treatment were *CRT only* and *chemotherapy only*. These findings suggest room for improvement in the uptake of multimodality treatments such as *CRT & chemotherapy* and *surgery & chemotherapy* for these subgroups. The frequent use of *CRT only* among A-NSCLC and ED-SCLC suggests room for an increased uptake of chemotherapy among these metastatic subgroups.

Finally, 21.6% of cases in our study received no treatment. This is consistent with findings in a smaller study among 6,662 lung cancer cases in the Kaiser Permanente Southern

California tumor registry diagnosed between 2008-2013 (22). In that study, rates of non-treatment ranged from 9% among stage 0-II (compared to 10.3% among L-NSCLC in our study) to 34% among stage IV (compared to 31.4% among A-NSCLC in our study).

Disparities in Receiving Guideline-Concordant Treatment

In our study, advancing age was strongly associated with the odds of receiving guideline-concordant treatment across all clinical subgroups. These findings are in line with the conclusions of an earlier study (4). This association persisted after adjusting for factors that could influence fitness for surgery, such as comorbidity, histology, and stage, as well as health care provider characteristics. Other studies also reported a lower likelihood of lung cancer surgery among older patients, although these findings cannot be directly compared to ours due to the use of different age groups and methods (9, 10, 32). While we confirm the lower likelihood of receiving surgery for elderly L-NSCLC cases, we also show that the likelihood of receiving SBRT strongly increases with advancing age. These results indicate that SBRT is indeed used as an alternative guideline-concordant treatment for L-NSCLC cases which have contraindications for surgery. However, especially in other clinical subgroups efforts should be made to ensure that elderly patients receive the minimal recommended treatment.

Racial/ethnic group was also associated with the odds of receiving guideline-concordant treatment in both the adjusted and unadjusted analyses. Earlier research among US lung cancer patients had already shown that Black patients are less likely to receive surgery for L-NSCLC (5-10, 33) and chemotherapy for A-NSCLC (33, 34). Our current study shows that disparities by racial/ethnic group persist and extend to every clinical subgroup of NSCLC. Furthermore, we

show that Hispanics are also less likely to receive guideline-concordant treatment in general, but more likely to receive surgery for L-NSCLC. In an earlier study, McCann and colleagues offer a possible explanation for racial disparities (35). They reported that while surgery was offered to Black and White lung cancer patients at the same rate, Black patients declined surgery more often. Their study showed no statistically significant difference in insurance between both groups, and results were corrected for preoperative pulmonary function, tumor stage, and comorbidity. Furthermore, Lin and colleagues reported that negative surgical beliefs, fatalism, and mistrust among racial minorities can partly explain why Black patients are less likely to receive guideline-concordant treatment (36). More research is needed to identify the underlying reasons for such beliefs and mistrust and to test strategies to overcome any barriers to delivery of guideline-concordant treatment.

Strengths and Limitations

A major strength of this study is the very large sample size, combined with the extensive treatment data available in the NCDB. The linked SEER-Medicare database, which also contains detailed treatment variables, may be biased towards older individuals as it mainly includes patients aged ≥65 years. In contrast, the NCDB data used for our study included lung cancer patients aged 18 years or older.

There are several potential limitations to our study. The first is the hospital-based nature of the data, which captures only cases diagnosed and treated in Commission on Cancer affiliated hospitals. However, these hospitals together treat 70% of incident cancer cases in the United States. Furthermore, we compared baseline characteristics to a cohort of patients

captured by the smaller but population-based SEER database and found only small differences. Therefore, our results are likely generalizable to the US population.

Second, our data includes only the first course of treatment. Nevertheless, we were able to define guideline-concordant treatment as the minimal recommended treatment. Although the focus of this manuscript was therefore the issue of receiving “less intensive treatment than recommended”, we acknowledge that receiving “more intensive treatment than recommended” could potentially also be an issue. However, for most clinical subgroups the NCDB data does not contain sufficient clinical variables to assess whether each possible combination of surgery, radiotherapy, chemotherapy, and other treatment was “more intensive than recommended”. For example, radiotherapy is not recommended as a minimal treatment for A-NSCLC, but may still be prescribed as symptomatic treatment for painful bone metastases. Nevertheless, we were able to assess that 10.4% of stage I NSCLC cases received adjuvant or neoadjuvant chemotherapy, which could provide an indication of the extent to which overtreatment occurs. Also, 2.9% of A-NSCLC cases received surgery. Future studies should focus more in depth on the severity and consequences of receiving more intensive treatment than recommended for lung cancer.

Third, the data did not include several clinical variables which may affect the choice of treatment. Smoking cessation after the diagnosis of lung cancer has been associated with reduced all-cause mortality (37) and a reduced risk of hospital death and pulmonary complications after surgery (38). Therefore, active smokers may have been less likely to receive surgery. However, guidelines state that surgery should not be denied to patients only due to smoking (14). Pulmonary function and performance score may have also influenced the

likelihood of receiving surgery (39). Although our correction for comorbidities may have partially accounted for these factors, the Charlson score is an aggregate measure that does not account for all possible comorbidities. Another factor that we could not fully account for using the NCDB data is socio-economic status, although we were able to include insurance status. We addressed the absence of these clinical variables by assessing multiple guideline-concordant treatments for some clinical subgroups. For instance, both SBRT and surgery were regarded guideline-concordant treatments for L-NSCLC. However, this carries the implicit assumption that when the non-surgical treatment was given, the patient was indeed medically inoperable.

Fourth, we used the official cut-off of 5 fractions in our definition of SBRT, while some institutions use schemes with up to 10 fractions (19). However, using a cut-off of 10 fractions would only increase the use of SBRT among L-NSCLC in our dataset from 10.4% to 10.9%.

Fifth, hospital-based data such as the NCDB could potentially be clustered by hospital. However, in an exploratory analysis using the data before multiple imputation, incorporating clustering by hospital ID had a negligible effect on the estimates of the overall regression model (data not shown). Given that the effect of clustering by hospital is therefore likely small, we did not incorporate clustering by hospital in our final models.

Finally, we were not able to take patient preferences into account. Hence, we cannot draw firm conclusions on the underlying causes of the identified disparities by racial/ethnic group and by age.

Conclusions

We show that many lung cancer patients in the United States do not receive guideline-concordant treatment. Efforts should be made to decrease the proportion of cases that receive no treatment or less intensive treatment than recommended. Specifically, patterns of care among those receiving less intensive treatment than recommended suggest room for an improved uptake of SBRT among L-NSCLC, multimodality therapy among LA-NSCLC and LD-SCLC, and chemotherapy among metastatic disease (A-NSCLC and ED-SCLC). Furthermore, we show that elderly patients and non-Hispanic Blacks are less likely to receive guideline-concordant treatment across most clinical subgroups of lung cancer despite adjusting for relevant patient, tumor, and health care provider characteristics. This knowledge may be used to target interventions for improving the rate of lung cancer cases that receive guideline-concordant treatment and to reduce disparities.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69: 7-34.
2. Aggarwal A, Lewison G, Idir S, Peters M, Aldige C, Boerckel W, et al. The State of Lung Cancer Research: A Global Analysis. *J Thorac Oncol* 2016; 11: 1040-1050.
3. Benson AB, Brown E. Role of NCCN in Integrating Cancer Clinical Practice Guidelines into the Healthcare Debate. *Am Health Drug Benefits* 2008; 1: 28-33.
4. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. *J Clin Oncol* 2012; 30: 1447-1455.
5. Bach PB, Cramer LD, Warren JL, Begg CB. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 1999; 341: 1198-1205.
6. Fry WA, Menck HR, Winchester DP. The National Cancer Data Base report on lung cancer. *Cancer* 1996; 77: 1947-1955.
7. Esnaola NF, Gebregziabher M, Knott K, Finney C, Silvestri GA, Reed CE, et al. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg* 2008; 86: 220-226.
8. Check DK, Albers KB, Uppal KM, Suga JM, Adams AS, Habel LA, et al. Examining the role of access to care: Racial/ethnic differences in receipt of resection for early-stage non-small cell lung cancer among integrated system members and non-members. *Lung Cancer* 2018; 125: 51-56.

9. Balekian AA, Wisnivesky JP, Gould MK. Surgical Disparities Among Patients With Stage I Lung Cancer in the National Lung Screening Trial. *Chest* 2019; 155: 44-52.

10. Cykert S, Dilworth-Anderson P, Monroe MH, Walker P, McGuire FR, Corbie-Smith G, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *JAMA* 2010; 303: 2368-2376.

11. Bott MJ, Patel AP, Verma V, Crabtree TD, Morgensztern D, Robinson CG, et al. Patterns of care in hilar node-positive (N1) non-small cell lung cancer: A missed treatment opportunity? *J Thorac Cardiovasc Surg* 2016; 151: 1549-1556.

12. Blom EF, Ten Haaf K, Arenberg D, De Koning HJ. MA18.06 Patterns of Lung Cancer Care in the United States: Developments and Disparities [Abstract]. *J Thorac Oncol* 2018; 13: S420.

13. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973-2014 varying) - Linked To County Attributes - Total U.S., 1969-2015 Counties [Internet]. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program [Released 2017 April; Accessed 2017 October 17]. Available from: www.seer.cancer.gov.

14. Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer Version 5.2017 [Internet]. National Comprehensive Cancer Network [Released 2017 March 16; Accessed 2017 April 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. .

15. Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer Version 3.2017 [Internet]. National Comprehensive Cancer Network [Released 2017 February 23; Accessed 2017 April 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. .

16. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; 27: 3290-3296.

17. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303: 1070-1076.

18. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. *Radiother Oncol* 2017; 124: 11-17.

19. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017; 7: 295-301.

20. Pan H, Rose BS, Simpson DR, Mell LK, Mundt AJ, Lawson JD. Clinical practice patterns of lung stereotactic body radiation therapy in the United States: a secondary analysis. *Am J Clin Oncol* 2013; 36: 269-272.

21. Groth SS, Al-Refaie WB, Zhong W, Vickers SM, Maddaus MA, D'Cunha J, et al. Effect of insurance status on the surgical treatment of early-stage non-small cell lung cancer. *Ann Thorac Surg* 2013; 95: 1221-1226.

22. Gould MK, Munoz-Plaza CE, Hahn EE, Lee JS, Parry C, Shen E. Comorbidity profiles and their effect on treatment selection and survival among patients with lung cancer. *Annals of the American Thoracic Society* 2017; 14: 1571-1580.

23. Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis Of Disease. Philadelphia, PA: Elsevier Saunders; 2005.

24. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; 349: 2117-2127.

25. R: A Language and Environment for Statistical Computing [computer program]. Version 3.4.1. Vienna, Austria: R Foundation for Statistical Computing; 2017.

26. Van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. *Journal of statistical software* 2010: 1-68.

27. Fox J, Weisberg S. An R Companion to Applied Regression. Thousand Oaks, CA: SAGE Publications; 2011.

28. Noonan K, Tong KM, Laskin J, Melosky B, Sun S, Murray N, et al. Referral patterns in advanced non-small cell lung cancer: impact on delivery of treatment and survival in a contemporary population based cohort. *Lung Cancer* 2014; 86: 344-349.

29. Ko JJ, Tudor R, Li H, Liu M, Skolnik K, Boland WK, et al. Reasons for lack of referral to medical oncology for systemic therapy in stage IV non-small-cell lung cancer: comparison of 2003-2006 with 2010-2011. *Curr Oncol* 2017; 24: e486-e493.

30. Passik SD, Kirsh KL, Rosenfeld B, McDonald MV, Theobald DE. The changeable nature of patients' fears regarding chemotherapy: implications for palliative care. *J Pain Symptom Manage* 2001; 21: 113-120.

524 31. Non-Small Cell Lung Cancer Collaborative G. Chemotherapy and supportive care versus
525 supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst*
526 *Rev* 2010: CD007309.
527 32. Little AG, Gay EG, Gaspar LE, Stewart AK. National survey of non-small cell lung cancer in the
528 United States: Epidemiology, pathology and patterns of care. *Lung Cancer* 2007; 57:
529 253-260.
530 33. Hardy D, Liu CC, Xia R, Cormier JN, Chan W, White A, et al. Racial disparities and treatment
531 trends in a large cohort of elderly black and white patients with nonsmall cell lung
532 cancer. *Cancer* 2009; 115: 2199-2211.
533 34. Earle CC, Venditti LN, Neumann PJ, Gelber RD, Weinstein MC, Potosky AL, et al. Who gets
534 chemotherapy for metastatic lung cancer? *Chest* 2000; 117: 1239-1246.
535 35. McCann J, Artinian V, Duhaime L, Lewis JW, Jr., Kvale PA, DiGiovine B. Evaluation of the
536 causes for racial disparity in surgical treatment of early stage lung cancer. *Chest* 2005;
537 128: 3440-3446.
538 36. Lin JJ, Mhango G, Wall MM, Lurslurchachai L, Bond KT, Nelson JE, et al. Cultural factors
539 associated with racial disparities in lung cancer care. *Annals of the American Thoracic*
540 *Society* 2014; 11: 489-495.
541 37. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of
542 early stage lung cancer on prognosis: systematic review of observational studies with
543 meta-analysis. *BMJ* 2010; 340: b5569.

38. Mason DP, Subramanian S, Nowicki ER, Grab JD, Murthy SC, Rice TW, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. *Ann Thorac Surg* 2009; 88: 362-370.

39. Zhang R, Lee SM, Wigfield C, Vigneswaran WT, Ferguson MK. Lung function predicts pulmonary complications regardless of the surgical approach. *Ann Thorac Surg* 2015; 99: 1761-1767.

Table 1: Characteristics of Patients in the National Cancer Database Diagnosed with Non-Small Cell Lung Cancer or Small Cell Lung Cancer in Years 2010 – 2014

		Overall (N = 441,812)	**NSCLC** (N = 375,832)	**SCLC** (N = 65,980)
Patient characteristics				
Sex (%)	Male	228,519 (51.7)	196,454 (52.3)	32,065 (48.6)
	Female	213,293 (48.3)	179,378 (47.7)	33,915 (51.4)
Age at diagnosis (%)	<50	22,328 (5.1)	19,224 (5.1)	3,104 (4.7)
	50-54	33,619 (7.6)	27,968 (7.4)	5,651 (8.6)
	55-59	50,955 (11.5)	42,054 (11.2)	8,901 (13.5)
	60-64	62,839 (14.2)	51,902 (13.8)	10,937 (16.6)
	65-69	75,298 (17.0)	62,838 (16.7)	12,460 (18.9)
	70-74	71,798 (16.3)	60,983 (16.2)	10,815 (16.4)
	75-79	58,053 (13.1)	50,616 (13.5)	7,437 (11.3)
	≥80	66,922 (15.1)	60,247 (16.0)	6,675 (10.1)
Racial/ethnic group (%)	Non-Hispanic White	349,842 (79.2)	294,833 (78.4)	55,009 (83.4)
	Non-Hispanic Black	48,060 (10.9)	42,799 (11.4)	5,261 (8.0)
	Non-Hispanic Asian	9,483 (2.1)	8,741 (2.3)	742 (1.1)
	Hispanic	12,081 (2.7)	10,587 (2.8)	1,494 (2.3)
	Other	2,806 (0.6)	2,441 (0.6)	365 (0.6)
	Unknown	19,540 (4.4)	16,431 (4.4)	3,109 (4.7)
Health insurance status (%)	Private	117,168 (26.5)	99,666 (26.5)	17,502 (26.5)
	Medicare	256,740 (58.1)	219,916 (58.5)	36,824 (55.8)
	Medicaid	34,278 (7.8)	28,118 (7.5)	6,160 (9.3)
	Other government insurance	7,023 (1.6)	5,928 (1.6)	1,095 (1.7)
	No insurance	18,112 (4.1)	15,009 (4.0)	3,103 (4.7)
	Unknown	8,491 (1.9)	7,195 (1.9)	1,296 (2.0)
Charlson comorbidity score (%)	0	24,6887 (55.9)	211,483 (56.3)	35,404 (53.7)
	1	130,577 (29.6)	110,304 (29.3)	20,273 (30.7)
	≥2	64,348 (14.6)	54,045 (14.4)	10,303 (15.6)
Health care provider characteristics				
Facility type (%)	Academic	140,344 (31.8)	121,914 (32.4)	18,430 (27.9)
	Non-academic	298,618 (67.6)	251,260 (66.9)	47,358 (71.8)

	Unknown	2,850 (0.6)	2,658 (0.7)	192 (0.3)
Hospital volume	Median (IQR)	524 (302-861)	533 (304-871)	500 (288-837)
Tumor characteristics				
Histology (%)*	Adenocarcinoma	192,943 (43.7)	192,943 (51.3)	-
	Squamous cell	98,848 (22.4)	98,848 (26.3)	-
	Other non-small cell	84,041 (19.0)	84,041 (22.4)	-
	Small cell	65,980 (14.9)	-	65,980 (100.0)
Clinical stage at diagnosis (%)	IA	62,694 (14.2)	61,123 (16.3)	1,571 (2.4)
	IB	26,984 (6.1)	26,049 (6.9)	935 (1.4)
	IIA	17,456 (4.0)	15,898 (4.2)	1,558 (2.4)
	IIB	15,199 (3.4)	14,300 (3.8)	899 (1.4)
	IIIA	57,989 (13.1)	48,881 (13.0)	9,108 (13.8)
	IIIB	34,088 (7.7)	26,941 (7.2)	7,147 (10.8)
	IV	227,402 (51.5)	182,640 (48.6)	44,762 (67.8)

Table legend:
Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer, IQR = interquartile range.
* NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.

Table 2: Receipt of Guideline-Concordant Treatment among Lung Cancer Patients by Clinical Subgroup

Clinical Subgroup	n	Guideline-Concordant Treatment*	Less Intensive Treatment Than Recommended†	No Treatment
Overall (%)	441,812	274,338 (62.1)	72,155 (16.3)	95,319 (21.6)
L-NSCLC (%)	117,370	89,503 (76.3)	15,741 (13.4)	12,126 (10.3)
LA-NSCLC (%)	75,822	45,774 (60.4)	16,412 (21.6)	13,636 (18.0)
A-NSCLC (%)	182,640	92,119 (50.4)	33,227 (18.2)	57,294 (31.4)
LD-SCLC (%)	21,218	14,765 (69.6)	3,927 (18.5)	2,526 (11.9)
ED-SCLC (%)	44,762	32,177 (71.9)	2,848 (6.4)	9,737 (21.8)

Table legend:
Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV).
* Guideline-concordant treatment was defined as the minimal treatment patients should receive according to the National Comprehensive Cancer Network guidelines. Hence, additional treatment was allowed beside guideline-concordant treatment. We considered guideline-concordant treatment to be either surgery or Stereotactic Body Radiation Therapy for L-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for LA-NSCLC; chemotherapy for A-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for patients with LD-SCLC; and chemotherapy for patients with ED-SCLC.
† Less intensive treatment than recommended was defined as treatment that was not guideline-concordant.

Table 3: Patterns of Care among Lung Cancer Patients by Clinical Subgroup

Clinical Subgroup	Treatment Received*	n (%)
L-NSCLC	Guideline-concordant treatment	
	Surgery only	57,605 (49.1)
	Surgery & chemotherapy	13,359 (11.4)
	SBRT only	11,740 (10.0)
	Surgery & CRT & chemotherapy	4,405 (3.8)
	Surgery & CRT	1,562 (1.3)
	Less intensive treatment than recommended	
	CRT only	7,129 (6.1)
	CRT & chemotherapy	6,953 (5.9)
	Chemotherapy only	1,465 (1.2)
LA-NSCLC	Guideline-concordant treatment	
	CRT & chemotherapy	36,108 (47.6)
	Surgery & CRT & chemotherapy	5,580 (7.4)
	Surgery & chemotherapy	3,335 (4.4)
	Less intensive treatment than recommended	
	CRT only	6,577 (8.7)
	Chemotherapy only	6,008 (7.9)
	Surgery only	2,676 (3.5)
A- NSCLC	Guideline-concordant treatment	
	CRT & chemotherapy	47,370 (25.9)
	Chemotherapy only	35,620 (19.5)
	CRT & chemotherapy & other treatment	2,970 (1.6)
	Chemotherapy & other treatment	2,715 (1.5)
	Less intensive treatment than recommended	
	CRT only	29,219 (16.0)
LD-SCLC	Guideline-concordant treatment	
	CRT & chemotherapy	13,477 (63.5)
	Surgery & CRT & chemotherapy	545 (2.6)
	Surgery & chemotherapy	514 (2.4)
	Less intensive treatment than recommended	
	Chemotherapy only	2,917 (13.7)
	CRT only	534 (2.5)
	Surgery only	340 (1.6)
ED-SCLC	Guideline-concordant treatment	
	CRT & chemotherapy	15,671 (35.0)
	Chemotherapy only	15,658 (35.0)
	Less intensive treatment than recommended	
	CRT only	2,597 (5.8)

Table legend:
Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stage I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiation Therapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions; CRT = conventionally fractionated radiotherapy, defined as all radiotherapy other than Stereotactic Body Radiation Therapy.
* All mutually exclusive combinations of treatment modalities (i.e. all combinations of surgery, Stereotactic Body Radiation Therapy, conventionally fractionated radiotherapy, chemotherapy, and other treatment) were assessed. However, for each clinical subgroup only those treatment combinations that were more prevalent than 1% are reported in this table.

Table 4: Effect of Age and Racial/Ethnic Group on the Odds of Receiving Guideline-Concordant Treatment for Lung Cancer

Age	**<50**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**≥80**
No. of subjects	22,328	33,619	50,955	62,839	75,298	71,798	58,053	66,922
No. events	17,710	25,242	36,765	43,702	50,822	44,959	31,977	23,161
Event risk	0.79	0.75	0.72	0.70	0.67	0.63	0.55	0.35
Crude odds ratio (95% CI) *	Reference	0.79 (0.75-0.82)	0.68 (0.65-0.70)	0.60 (0.57-0.62)	0.54 (0.52-0.56)	0.44 (0.42-0.45)	0.32 (0.31-0.33)	0.14 (0.13-0.14)
Adjusted odds ratio (95%CI) *	Reference	0.76 (0.73-0.79)	0.63 (0.60-0.65)	0.53 (0.51-0.55)	0.48 (0.47-0.50)	0.39 (0.37-0.40)	0.28 (0.27-0.29)	0.12 (0.12-0.13)
Racial/ethnic group	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic**	**Other**			
No. of subjects†	365,922	50,256	9,958	12,682	2,995			
No. events†	229,378	29,206	6,344	7,529	1,881			
Event risk †	0.63	0.58	0.64	0.59	0.63			
Crude odds ratio (95% CI) *	Reference	0.82 (0.81-0.84)	1.04 (1.00-1.09)	0.87 (0.84-0.90)	1.00 (0.93-1.09)			
Adjusted odds ratio (95%CI) *	Reference	0.78 (0.76-0.80)	1.09 (1.04-1.15)	0.94 (0.90-0.98)	0.94 (0.86-1.03)			

Table legend:
Abbreviations: 95% CI = 95% Confidence interval; No. = number.
* The crude and adjusted odds ratios are from the pooled regression model based on all three imputed datasets. Adjusted odds ratios are adjusted for sex, insurance status, Charlson comorbidity score, treating facility type, hospital volume, histology, and clinical stage at diagnosis. Variance inflation factors were ≤2 for all covariates, indicating that multicollinearity was limited.
† The number of subjects, number of events, and event risks for racial/ethnic group are based on the mean values across the three imputed datasets.

Disparities in Receiving ~~Standard of Care~~Guideline-Concordant Treatment for Lung Cancer in the United States

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Running head

Disparities in ~~standard of care for~~receiving lung cancer treatment

Descriptor number

2.9 Racial, Ethnic, or Social Disparities in Lung Disease and Treatment

Keywords (MeSH)

Lung Neoplasms; ~~Standard of Care~~Guideline Adherence; Practice Patterns, Physicians'; Healthcare Disparities.

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Online supplement

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Abstract

Rationale

The level of adherence to lung cancer treatment guidelines in the United States is unclear. Also, it is unclear whether previously identified disparities by ~~race~~racial/ethnic group and by age persist across all clinical subgroups ~~of lung cancer~~.

Objectives

To assess the level of adherence to ~~stage-specific standard of care for~~the minimal lung cancer treatment recommended by the National Comprehensive Cancer Network guidelines (guideline-concordant treatment) in the United States, and to assess the persistence of disparities by ~~race~~racial/ethnic group and by age across all clinical subgroups.

Methods

We evaluated ~~the level of adherence to standard of care according to National Comprehensive Cancer Network guidelines for~~whether 441,812 lung cancer cases in the National Cancer Database diagnosed between 2010-2014~~.~~ received guideline-concordant treatment. Multivariable logistic regression models were used to assess possible disparities in receiving ~~standard of care~~guideline-concordant treatment by ~~race/ethnicity~~racial/ethnic group and by age across all clinical subgroups, and whether these persist after adjusting for patient, tumor, and health care provider characteristics.

Results

Overall, 62.1% of subjects received ~~standard of care~~guideline-concordant treatment (range across clinical subgroups: 50.4%-76.3%). However, 21.6% received no ~~therapy~~treatment (range: 10.3%-31.4%) and 16.3% received ~~non-standard of care~~less intensive treatment than recommended (range: 6.4%-21.6%). Among the most common ~~non-standard of care therapies~~less intensive treatments for all subgroups was *conventionally fractionated radiotherapy only* (range: 2.5%-16.0%), as was *chemotherapy only* for non-metastatic subgroups (range: 1.2% to 13.7%), and *conventionally fractionated radiotherapy & chemotherapy* for ~~early-stage~~ localized non-small cell lung cancer (5.9%). ~~Standard of care~~Guideline-concordant treatment was less likely with increasing age despite adjusting for relevant covariates (age ≥80 compared to <50: adjusted odds ratio [aOR]=0.12, 95% confidence interval [95%CI]=0.12-0.13). This disparity was present in all clinical subgroups. Also, non-Hispanic Blacks were less likely to receive ~~standard of care~~guideline-concordant treatment than non-Hispanic Whites (aOR=0.78, 95%CI=0.76-0.80). This disparity was present in all clinical subgroups, although statistically non-significant for extensive disease small cell lung cancer.

Conclusions

Between 2010-2014, many lung cancer patients in the United States received no ~~therapy~~treatment or ~~non-standard of care.~~less intensive treatment than recommended. Particularly, elderly lung cancer patients and non-Hispanic Blacks are less likely to receive ~~standard of care.~~guideline-concordant treatment. Patterns of ~~non-standard of care~~care among those receiving less intensive treatment than recommended suggest room for improved uptake

of treatments such as Stereotactic Body Radiation Therapy among ~~early-stage~~localized non-small cell lung cancer.

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350

Introduction

An estimated 142,670 persons will die of lung cancer in the United States in 2019, making it the leading cause of cancer-related deaths (1). Reflecting the large burden to society, lung cancer treatment is an important topic of medical research. A recent bibliometric analysis identified a total of 32,161 studies published on lung cancer between 2004-2013, of which 36% focused on treatments (2). Clinical practice guidelines ~~compile the available evidence and expert consensus into a standard of care~~ , which can be considered the basis for measures of quality of care ~~(3). ,~~ compile the available evidence and expert consensus (3).

~~Despite the existence of these clinical practice guidelines~~However, literature indicates that ~~standard of care~~the minimal treatment recommended in these guidelines (i.e., guideline-concordant treatment) may not be provided to all lung cancer patients in the United States (4). Furthermore, there is evidence that specific subgroups are less likely than others to receive ~~standard of care.~~guideline-concordant treatment. For example, the proportion of cases that receive ~~standard of care~~guideline-concordant treatment is lower for more advanced stages (4). Also, ~~racial~~ disparities by racial/ethnic group have been described. For example, Black patients are less likely to receive surgical ~~therapy~~treatment for ~~early-stage~~localized non-small cell lung cancer (~~ES~~L-NSCLC; stages I-II) than White patients (5-10). Additionally, elderly lung cancer patients are less likely to receive ~~standard of care~~guideline-concordant treatment, despite controlling for comorbidity (4, 9, 10). However, comparability and generalizability of the available literature are limited because often only one specific subset of clinical cases is examined (5, 11), relatively small sample sizes are used (8, 10), different methodologies are applied (5, 7), or the data covers different timespans (5, 7). Thus, it is unclear whether

disparities in receiving ~~standard of care by race~~guideline-concordant treatment by racial-ethnic group and by age persist, and whether these are similar across clinical subgroups of lung cancer in the United States.

Therefore, the first aim of this study was to assess the level of adherence to predefined stage-specific ~~standard of care~~guideline-concordant treatment for each clinical subgroup of lung cancer patients in a large US dataset. The second aim was ~~-~~to assess whether previously identified disparities in receiving ~~standard of care~~guideline-concordant treatment by ~~race~~racial/ethnic group and by age persist across all clinical subgroups of lung cancer. Some of the results of this study have been previously reported in the form of an abstract (12).

Methods

Data

We used the US National Cancer Database (NCDB) to extract a cohort of 441,812 patients diagnosed with lung cancer between 2010-2014 (see Figure E1 in the Online Supplement). The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually, from more than 1,500 affiliated facilities. The NCDB records the first course of ~~therapy~~treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Analysis of individual-level NCDB data was performed on site at the University of Michigan Medical School.

To assess the generalizability of the NCDB data to the general US population, we compared baseline characteristics to a cohort of lung cancer patients from the population-based Surveillance, Epidemiology, and End Results (SEER) dataset (13). A detailed version of the methods, including the rationale for case selection, data cleaning, and the analysis of the SEER dataset is available online (see Supplementary Methods and Tables E1 and E2 in the Online Supplement). This study was deemed exempt by the Institutional Review Board of the University of Michigan.

Definition of ~~Standard of Care~~Guideline-Concordant Treatment

Two main lung cancer types can be distinguished: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with the majority presenting as NSCLC. Since SCLC is clinically more aggressive than NSCLC, ~~initial standard of care in~~ clinical guidelines ~~is defined~~provide specific treatment recommendations for clinical subgroups of lung cancer type and stage at diagnosis. ~~We used the National Comprehensive Cancer Network guidelines (14, 15) to determine standard of care for~~For each of these clinical subgroups~~. Standard of care~~, we assessed whether guideline-concordant treatment was received, defined as the minimal first course treatment these patients should receive~~. Hence, other treatments could be given beside the standard of care (e.g. radiotherapy for bone metastases beside chemotherapy in advanced NSCLC (A-NSCLC; stage IV)).~~ according to the National Comprehensive Cancer Network guidelines (14, 15).

While ~~surgical treatment~~ surgery is still recommended as the primary ~~standard of care~~ minimal treatment for ~~ES~~L-NSCLC (~~stage~~stages I-II),~~-~~ Stereotactic Body Radiation Therapy (SBRT)

is now recommended as an alternative ~~standard of care~~treatment to surgery for ~~ES~~L-NSCLC patients (14). SBRT delivers high-dose radiation to a specific target in only a few fractions and provides local tumor control rates of up to 90% with moderate toxicity (16, 17). ~~Standard of care~~Therefore, both surgery and SBRT were considered guideline-concordant treatment for L-NSCLC. The minimal recommended treatment for locally advanced NSCLC (LA-NSCLC; stage III) and limited disease SCLC (LD-SCLC; stages I-III) depends on operability (14, 15). If operable, ~~standard of care for LA-NSCLC~~ the minimal recommendation is surgery combined with chemotherapy. ~~For~~ However, the majority of LA-NSCLC and LD-SCLC patients are inoperable ~~LA-NSCLC~~, in which case the minimal recommendation is a combination of radiotherapy and chemotherapy ~~is standard of care. For~~. Therefore, both treatment combinations were considered guideline-concordant for LA-NSCLC and LD-SCLC. For advanced NSCLC (A-NSCLC~~, chemotherapy is standard of care (14). A small fraction of limited disease SCLC (LD-SCLC; stages I-III) is operable, in which case standard of care is surgery combined with chemotherapy (15). However, concurrent radiotherapy and chemotherapy is standard of care for most LD-SCLC cases, and chemotherapy for~~; stage IV) and extensive disease SCLC (ED-SCLC; stage IV~~) (15). We also summarize the therapies~~), the minimally recommended treatment is chemotherapy (14, 15). As we assessed the minimal recommended treatment for each clinical subgroup, additional treatments were allowed beside guideline-concordant treatment (e.g. radiotherapy for bone metastases beside chemotherapy in A-NSCLC). A summary of the treatment combinations that were considered ~~standard of care~~guideline-concordant for each clinical subgroup can be found in Table E3 in the Online Supplement.

Since the most frequently used SBRT schemes in the United States comprise a total dose of 45 Gray or more over 1-5 fractions (18-20) and the US billing code for SBRT includes a maximum of 5 fractions (14), SBRT was defined as thoracic radiotherapy with a total radiation dose of 45 Gray or more delivered in 5 fractions or less. There were no restrictions on radiation dose or fractionation for stages other than ~~ES~~L-NSCLC. Chemotherapy included the use of targeted therapies. We were not able to separately assess the use of immunotherapy agents ~~as standard of care~~ in these data because their use was not recommended in the evaluated time-period (see Supplementary Methods in the Online Supplement).

Statistical Analysis

For each clinical subgroup, we assessed ~~adherence to standard of care as~~ the proportion of cases that received ~~standard of care, non-standard of care~~guideline-concordant treatment, less intensive treatment than recommended (defined as treatment that was not ~~standard of care~~guideline-concordant), and no ~~therapy~~treatment. We used clinical stage at diagnosis for creating clinical subgroups because pathological stage can only be known after the outcome of interest (initial treatment) has occurred. For the groups of patients who received ~~standard of care~~guideline-concordant treatment and ~~non-standard of care~~less intensive treatment than recommended, we separately assessed which mutually exclusive combinations of surgery, SBRT, conventionally fractionated radiotherapy (CRT; defined as all radiotherapy other than SBRT), chemotherapy (including targeted therapy) and other ~~therapy~~treatment (including immunotherapy and experimental treatments) were ~~given~~received.

To identify whether previously identified disparities in receiving ~~standard of care~~guideline-concordant treatment by ~~race~~racial/ethnic group and by age persist, we fitted a multivariable logistic regression model with ~~predefined stage-specific standard of care~~receipt of guideline-concordant treatment as binary outcome and ~~race/ethnicity~~racial/ethnic group and age as independent variables. We further adjusted this model ~~with~~for several covariates that could be associated with ~~race/ethnicity~~racial/ethnic group and age, and also affect receiving ~~standard of care~~guideline-concordant treatment. Based on previous literature, we included sex (9), health insurance status (21), Charlson comorbidity score (22), facility type (11), and stage at diagnosis (4). We further included histology because squamous cell carcinomas are often located centrally (23), potentially making them more difficult to surgically resect. Finally, we included hospital volume because it is a well-established indicator of quality of care (24). The derivation and composition of these variables is detailed in the Supplementary Methods in the Online Supplement.

To identify whether disparities by ~~race~~racial/ethnic group and by age extend across all clinical subgroups, we also ~~-~~fitted a separate model for each clinical subgroup. For clinical subgroups with ~~more than one~~multiple guideline-concordant treatment ~~combination as standard of care~~combinations, we fitted a separate model for each ~~specific standard of care~~treatment combination. For example, two separate models were fitted for ~~ES~~L-NSCLC; one with SBRT as binary outcome and one with surgery as binary outcome. These models were adjusted for the same covariates as the overall model.

All analyses were performed using R software version 3.4.1 (25). The base-R glm() function was used to fit the logistic regression models. We used multiple imputation to address

missing data, using three imputations (26). Multicollinearity was assessed by calculating generalized variance inflation factors (27).

Results

Patient Characteristics

Baseline characteristics of the 441,812 ~~-~~included patients are shown in Table 1. When comparing these with lung cancer cases in the population-based SEER registry, we found only very small differences in sex, age, ~~race/ethnicity~~racial/ethnic group, health insurance status, histology, and stage at diagnosis (see Table E4 in the Online Supplement).

Adherence to ~~Standard of Care~~Guideline-Concordant Treatment

The proportion of cases that received ~~standard of care~~guideline-concordant treatment within each clinical subgroup was stable between 2010-2014 (see Figure E2 in the Online Supplement). As shown Table 2, 62.1% of all cases diagnosed between 2010-2014 received ~~standard of care~~guideline-concordant treatment (range: 50.4% in A-NSCLC to 76.3% in ~~E~~SL-NSCLC). However, 16.3% received ~~non-standard of care~~less intensive treatment than recommended (range: 6.4% in ED-SCLC to 21.6% in LA-NSCLC), and 21.6% received no ~~therapy~~treatment (range: 10.3% in ~~E~~SL-NSCLC to 31.4% in A-NSCLC).

Patterns of ~~care~~Care among ~~patients~~Patients that ~~received standard of care~~Received Guideline-Concordant Treatment

Among ~~ES~~L-NSCLC cases that received ~~standard of care~~guideline-concordant treatment, *surgery only* was ~~given~~received most frequently (49.1%), followed by *surgery & chemotherapy* (11.4%), and *SBRT only* (10.0%) (Table 3). In every other clinical subgroup, *CRT & chemotherapy* was most common (range: 25.9% in A-NSCLC to 63.5% in LD-SCLC). Among LA-NSCLC and LD-SCLC, *surgery & CRT & chemotherapy* was also used (7.4% and 2.6%, respectively), as was *surgery & chemotherapy* (4.4% and 2.4%, respectively). Among A-NSCLC and ED-SCLC, *chemotherapy only* was common (19.5% and 35.0%, respectively).

Patterns of ~~care~~Care among ~~patients~~Patients that ~~received non-standard of care~~Received Less Intensive Treatment Than Recommended

CRT only was among the most ~~common non-standard of care~~commonly received less-intensive-than-recommended therapies for each clinical subgroup, as was *chemotherapy only* for subgroups other than A-NSCLC and ED-SCLC (see Table 3). ~~The most~~Most common ~~forms of non-standard of care~~ among ~~ES~~L-NSCLC were *CRT only* (6.1%), *CRT & chemotherapy* (5.9%), and *chemotherapy only* (1.2%). Among LA-NSCLC and LD-SCLC, the most ~~common non-standard of care therapies~~commonly received less-intensive-than-recommended treatments were *CRT only* (8.7% and 2.5%, respectively) and *chemotherapy only* (7.9% and 13.7%, respectively). *CRT only* was the most common ~~form of non-standard of care~~ among metastatic subgroups A-NSCLC (16.0%) and ED-SCLC (5.8%).

Disparities in Receiving ~~Standard of Care~~Guideline-Concordant Treatment

As can be seen in Table 4, the odds of receiving ~~standard of care~~guideline-concordant treatment decreased with advancing age (for those aged ≥80 compared to those aged <50: odds ratio[OR]=0.14, 95% confidence interval [95%CI]=0.13-0.14). This association remained present after adjusting for covariates (for those aged ≥80 compared to those aged <50: adjusted odds ratio[aOR]=0.12, 95%CI=0.12-0.13). Also, the association between age and receiving ~~standard of care~~guideline-concordant treatment was consistent across clinical subgroups, with a notable exception in ~~E~~SL-NSCLC (see Table E5 in the Online Supplement). In ~~E~~SL-NSCLC, advancing age was associated with a decreased odds of receiving surgery (for those aged ≥80 compared to those aged <50: aOR=0.06, 95%CI=0.05-0.06). However, the odds of receiving SBRT for ~~E~~SL-NSCLC increased with advancing age (for those aged ≥80 compared to those aged <50: aOR=18.39, 95%CI=14.09-23.99).

Compared to non-Hispanic Whites, Non-Hispanic Blacks (OR=0.82, 95%CI=0.81-0.84) and Hispanics (OR=0.87, 95%CI=0.84-0.90) were less likely to receive ~~standard of care.~~guideline-concordant treatment. This association remained present after adjusting for covariates (non-Hispanic Blacks: aOR=0.78, 95%CI=0.76-0.0.80; Hispanics: aOR=0.94, 95%CI=0.90-0.98). On the other hand, non-Hispanic Asians were more likely to receive ~~standard of care~~guideline-concordant treatment after adjusting for covariates (aOR=1.09, 95%CI=1.04-1.15). However, results for non-Hispanic Asians and Hispanics varied within clinical subgroups (see table E5 in the Online Supplement). For example, within the subgroup of ~~E~~SL-NSCLC both non-Hispanic Asians and Hispanics were more likely to receive surgery than non-Hispanic Whites (non-Hispanic Asians: aOR=1.23, 95%CI=1.10-1.37; Hispanics: aOR=1.24, 95%CI=1.13-1.36) but less likely to receive SBRT (non-Hispanic Asians: aOR=0.51, 95%CI=0.43-0.62; Hispanics: aOR=0.47,

95%CI=0.40-0.56). Also, non-Hispanic Asians with A-NSCLC were more likely to receive chemotherapy (aOR=1.25, 95%CI=1.18-1.34).

Discussion

To our knowledge, this study is the first to investigate adherence to ~~standard of care and~~guideline-concordant treatment as well as disparities by ~~race~~racial/ethnic group and by age in a uniform manner for all clinical subgroups of lung cancer including SCLC.

Adherence to ~~Standard of Care~~Guideline-Concordant Treatment

We show that overall, the level of adherence to ~~standard of care~~guideline-concordant treatment among lung cancer patients in the United States is only 62.1%, and varies across clinical subgroups. The rate of ~~standard of care~~ guideline-concordant treatment was highest for ~~ES~~L-NSCLC. This makes sense as treatment for ~~ES~~L-NSCLC is potentially curative and therefore offers the most obvious benefits. The rate of ~~standard of care~~guideline-concordant treatment was lowest for A-NSCLC.

A possible explanation for this finding could be a lack of referral to medical oncologists among A-NSCLC patients. A recent study reported that only 54% of stage IIIB-IV NSCLC cases triaged at the British Columbia Cancer Agency were assessed by a medical oncologist (28). Another study found that one of the most common reasons for not referring patients to a medical oncologist or prescribing chemotherapy was the patient's ~~own wish~~preference against treatment (29). Some patients with incurable disease fear that chemotherapy side-effects may

negatively affect their quality of life (30). Perhaps this could influence their willingness to accept chemotherapy. However, chemotherapy for advanced disease has been shown to improve quality of life, symptom control, and survival compared to best supportive care (31). Therefore, discussing~~-~~ a patient's possible fears of chemotherapy and the potential health benefits could be an important step towards increasing the uptake of chemotherapy.

Compared to our results, Wang et al. reported even lower rates of ~~standard of care~~guideline-concordant treatment among 20,511 NSCLC cases diagnosed between 2003-2008 (4). In their study, the proportion that received ~~standard of care~~guideline-concordant treatment was 51% among ~~ES~~L-NSCLC, 35% among LA-NSCLC, and 27% among A-NSCLC. The difference compared to our study is likely due to patient selection~~;~~, as Wang et al. included only veterans aged ≥65.

Within the group that received ~~standard of care~~guideline-concordant treatment, our data show that most ~~ES~~L-NSCLC cases received surgery, while SBRT and other modalities were used much less frequently. In contrast, most cases in the potentially operable clinical subgroups LA-NSCLC and LD-SCLC did not receive surgery as ~~standard of care.~~guideline-concordant treatment. 16.3% of cases in our data received ~~non-standard of care~~less intensive treatment than recommended. The patterns of care among these cases provide important clues towards improvements in clinical care. For example, the frequent use of *CRT only, CRT & chemotherapy,* and *chemotherapy only* among ~~ES~~L-NSCLC suggests that the uptake of SBRT among inoperable cases may still be lagging. Among LA-NSCLC and LD-SCLC the most common forms of ~~non-standard of care~~less-intensive-than-recommended treatment were *CRT only* and *chemotherapy only*. These findings suggest ~~that there is~~ room for improvement in the uptake of multimodality

~~therapies~~treatments such as *CRT & chemotherapy* and *surgery & chemotherapy* for these subgroups. The frequent use of *CRT only* among A-NSCLC and ED-SCLC suggests room for an increased uptake of chemotherapy among these metastatic subgroups.

Finally, 21.6% of cases in our study received no ~~therapy~~treatment. This is consistent with findings in a smaller study among 6,662 lung cancer cases in the Kaiser Permanente Southern California tumor registry diagnosed between 2008-2013 (22). In that study, rates of non-treatment ranged from 9% among stage 0-II (compared to 10.3% among ~~ES~~L-NSCLC in our study) to 34% among stage IV (compared to 31.4% among A-NSCLC in our study).

Disparities in Receiving ~~Standard of Care~~ Guideline-Concordant Treatment

In our study, advancing age was strongly associated with the odds of receiving ~~standard of care~~guideline-concordant treatment across all clinical subgroups. These findings are in line with the conclusions of an earlier study (4). This association persisted after adjusting for factors that could influence fitness for surgery, such as comorbidity, histology, and stage, as well as health care provider characteristics. Other studies also reported a lower likelihood of lung cancer surgery among older patients, although these findings cannot be directly compared to ours due to the use of different age groups and methods (9, 10, 32). While we confirm the lower likelihood of receiving surgery for elderly ~~ES~~L-NSCLC cases, we also show that the likelihood of receiving SBRT strongly increases with advancing age. These results indicate that SBRT is indeed used as an alternative ~~standard of care~~guideline-concordant treatment for ~~ES~~L-NSCLC cases which have contraindications for surgery. However, especially in other clinical subgroups efforts

should be made to ensure that elderly patients receive the minimal ~~standard of care~~recommended treatment.

~~Race/ethnicity~~Racial/ethnic group was also associated with the odds of receiving ~~standard of care~~guideline-concordant treatment in both the adjusted and unadjusted analyses. Earlier research among US lung cancer patients had already shown that Black patients are less likely to receive surgery for ~~ES~~L-NSCLC (5-10, 33) and chemotherapy for A-NSCLC (33, 34). Our current study shows that ~~this~~disparities by racial ~~disparity persists~~/ethnic group persist and ~~extends~~extend to every clinical subgroup of NSCLC. Furthermore, we show that Hispanics are also less likely to receive ~~standard of care~~guideline-concordant treatment in general, but more likely to receive surgery for ~~ES~~L-NSCLC. In an earlier study, McCann and colleagues offer a possible explanation for ~~these~~ racial disparities (35). They reported that while surgery was offered to Black and White lung cancer patients at the same rate, Black patients declined surgery more often. Their study showed no statistically significant difference in insurance between both groups, and results were corrected for preoperative pulmonary function, tumor stage, and comorbidity. Furthermore, Lin and colleagues reported that negative surgical beliefs, fatalism, and mistrust among racial minorities can partly explain why Black patients are less likely to receive ~~standard of care~~guideline-concordant treatment (36). More research is needed to identify the underlying reasons for such beliefs and mistrust and to test strategies to overcome any barriers to delivery of ~~standard of care.~~ guideline-concordant treatment.

Strengths and Limitations

A major strength of this study is the very large sample size, combined with the extensive treatment data available in the NCDB. The linked SEER-Medicare database, which also contains detailed treatment variables, may be biased towards older individuals as it mainly includes patients aged ≥65 years. In contrast, the NCDB data used for our study included lung cancer patients aged 18 years or older.

There are ~~five~~several potential limitations to our study. The first is the hospital-based nature of the data, which captures only cases diagnosed and treated in Commission on Cancer affiliated hospitals. However, these hospitals together treat 70% of incident cancer cases in the United States. Furthermore, we compared baseline characteristics to a cohort of patients captured by the smaller but population-based SEER database and found only small differences. Therefore, our results are likely generalizable to the US population.

Second, our data includes only the first course of treatment. Nevertheless, we were able to define ~~standard of care~~ guideline-concordant treatment as the minimal recommended treatment ~~patients should receive~~. Although the focus of this manuscript was therefore the issue of ~~undertreatment,~~receiving "less intensive treatment than recommended", we acknowledge that ~~overtreatment~~ receiving "more intensive treatment than recommended" could potentially also be an issue. However, for most clinical subgroups the NCDB data does not contain sufficient clinical variables to assess whether each possible combination of surgery, radiotherapy, chemotherapy, and other treatment was "more intensive than recommended". For example, radiotherapy is not recommended as a minimal treatment for A-NSCLC, but may still be prescribed as symptomatic treatment for painful bone metastases. Nevertheless, we were able to assess that 10.4% of stage I NSCLC cases ~~in our data~~ received adjuvant or

neoadjuvant chemotherapy, which could provide an indication of the extent to which overtreatment occurs. Also, 2.9% of A-NSCLC cases received surgery. Future studies should focus more in depth on the severity and consequences of ~~overtreatment of~~receiving more intensive treatment than recommended for lung cancer.

Third, the data did not include several clinical variables which may affect the choice of treatment. Smoking cessation after the diagnosis of lung cancer has been associated with reduced all-cause mortality (37) and a reduced risk of hospital death and pulmonary complications after surgery (38). Therefore, active smokers may have been less likely to receive surgery. However, guidelines state that surgery should not be denied to patients only due to smoking (14). Pulmonary function and performance score may have also influenced the likelihood of receiving surgery (39). Although our correction for comorbidities may have partially accounted for these factors, the Charlson score is an aggregate measure that does not account for all possible comorbidities. Another factor that we could not fully account for using the NCDB data is socio-economic status, although we were able to include insurance status. We addressed the absence of these clinical variables by assessing multiple ~~standard of care therapies~~guideline-concordant treatments for some clinical subgroups. For instance, both SBRT and surgery were regarded ~~standard of care~~guideline-concordant treatments for ~~ES~~L-NSCLC. However, this carries the implicit assumption that when the non-surgical ~~standard of care~~treatment was given, the patient was indeed medically inoperable.

Fourth, we used the official cut-off of 5 fractions in our definition of SBRT, while some institutions use schemes with up to 10 fractions (19). However, using a cut-off of 10 fractions would only increase the use of SBRT among ~~ES~~L-NSCLC in our dataset from 10.4% to 10.9%.

Fifth, hospital-based data such as the NCDB could potentially be clustered by hospital. However, in an exploratory analysis using the data before multiple imputation, incorporating clustering by hospital ID had a negligible effect on the estimates of the overall regression model (data not shown). Given that the effect of clustering by hospital is therefore likely small, we did not incorporate clustering by hospital in our final models.

Finally, we were not able to take patient preferences into account. Hence, we cannot draw firm conclusions on the underlying causes of the identified disparities by ~~race/ethnicity~~racial/ethnic group and by age.

Conclusions

We show that many lung cancer patients in the United States do not receive ~~standard of care.~~guideline-concordant treatment. Efforts should be made to decrease the proportion of cases that receive ~~non-standard of care~~no treatment or ~~no therapy.~~less intensive treatment than recommended. Specifically, patterns of ~~non-standard of care~~care among those receiving less intensive treatment than recommended suggest room for an improved uptake of SBRT among ~~ES~~L-NSCLC, multimodality therapy among LA-NSCLC and LD-SCLC, and~~-~~ chemotherapy among metastatic disease (A-NSCLC and ED-SCLC). Furthermore, we show that elderly patients and non-Hispanic Blacks are less likely to receive ~~standard of care~~guideline-concordant treatment across most clinical subgroups of lung cancer despite adjusting for relevant patient, tumor, and health care provider characteristics. This knowledge may be used to target interventions for improving the rate of lung cancer cases that receive ~~standard of care~~guideline-concordant treatment and to reduce disparities.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69: 7-34.

2. Aggarwal A, Lewison G, Idir S, Peters M, Aldige C, Boerckel W, et al. The State of Lung Cancer Research: A Global Analysis. *J Thorac Oncol* 2016; 11: 1040-1050.

3. Benson AB, Brown E. Role of NCCN in Integrating Cancer Clinical Practice Guidelines into the Healthcare Debate. *Am Health Drug Benefits* 2008; 1: 28-33.

4. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. *J Clin Oncol* 2012; 30: 1447-1455.

5. Bach PB, Cramer LD, Warren JL, Begg CB. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 1999; 341: 1198-1205.

6. Fry WA, Menck HR, Winchester DP. The National Cancer Data Base report on lung cancer. *Cancer* 1996; 77: 1947-1955.

7. Esnaola NF, Gebregziabher M, Knott K, Finney C, Silvestri GA, Reed CE, et al. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg* 2008; 86: 220-226.

8. Check DK, Albers KB, Uppal KM, Suga JM, Adams AS, Habel LA, et al. Examining the role of access to care: Racial/ethnic differences in receipt of resection for early-stage non-small cell lung cancer among integrated system members and non-members. *Lung Cancer* 2018; 125: 51-56.

9. Balekian AA, Wisnivesky JP, Gould MK. Surgical Disparities Among Patients With Stage I Lung Cancer in the National Lung Screening Trial. *Chest* 2019; 155: 44-52.

10. Cykert S, Dilworth-Anderson P, Monroe MH, Walker P, McGuire FR, Corbie-Smith G, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *JAMA* 2010; 303: 2368-2376.

11. Bott MJ, Patel AP, Verma V, Crabtree TD, Morgensztern D, Robinson CG, et al. Patterns of care in hilar node-positive (N1) non-small cell lung cancer: A missed treatment opportunity? *J Thorac Cardiovasc Surg* 2016; 151: 1549-1556.

12. Blom EF, Ten Haaf K, Arenberg D, De Koning HJ. MA18.06 Patterns of Lung Cancer Care in the United States: Developments and Disparities [Abstract]. *J Thorac Oncol* 2018; 13: S420.

13. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973-2014 varying) - Linked To County Attributes - Total U.S., 1969-2015 Counties [Internet]. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program [Released 2017 April; Accessed 2017 October 17]. Available from: www.seer.cancer.gov.

14. Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer Version 5.2017 [Internet]. National Comprehensive Cancer Network [Released 2017 March 16; Accessed 2017 April 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. .

15. Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer Version 3.2017 [Internet]. National Comprehensive Cancer Network [Released 2017 February 23; Accessed 2017 April 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. .

16. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; 27: 3290-3296.

17. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303: 1070-1076.

18. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. *Radiother Oncol* 2017; 124: 11-17.

19. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017; 7: 295-301.

20. Pan H, Rose BS, Simpson DR, Mell LK, Mundt AJ, Lawson JD. Clinical practice patterns of lung stereotactic body radiation therapy in the United States: a secondary analysis. *Am J Clin Oncol* 2013; 36: 269-272.

21. Groth SS, Al-Refaie WB, Zhong W, Vickers SM, Maddaus MA, D'Cunha J, et al. Effect of insurance status on the surgical treatment of early-stage non-small cell lung cancer. *Ann Thorac Surg* 2013; 95: 1221-1226.

538 22. Gould MK, Munoz-Plaza CE, Hahn EE, Lee JS, Parry C, Shen E. Comorbidity profiles and their
539 effect on treatment selection and survival among patients with lung cancer. *Annals of*
540 *the American Thoracic Society* 2017; 14: 1571-1580.
541 23. Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis Of Disease. Philadelphia,
542 PA: Elsevier Saunders; 2005.
543 24. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume
544 and operative mortality in the United States. *N Engl J Med* 2003; 349: 2117-2127.
545 25. R: A Language and Environment for Statistical Computing [computer program]. Version
546 3.4.1. Vienna, Austria: R Foundation for Statistical Computing; 2017.
547 26. Van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations
548 in R. *Journal of statistical software* 2010: 1-68.
549 27. Fox J, Weisberg S. An R Companion to Applied Regression. Thousand Oaks, CA: SAGE
550 Publications; 2011.
551 28. Noonan K, Tong KM, Laskin J, Melosky B, Sun S, Murray N, et al. Referral patterns in
552 advanced non-small cell lung cancer: impact on delivery of treatment and survival in a
553 contemporary population based cohort. *Lung Cancer* 2014; 86: 344-349.
554 29. Ko JJ, Tudor R, Li H, Liu M, Skolnik K, Boland WK, et al. Reasons for lack of referral to medical
555 oncology for systemic therapy in stage IV non-small-cell lung cancer: comparison of
556 2003-2006 with 2010-2011. *Curr Oncol* 2017; 24: e486-e493.
557 30. Passik SD, Kirsh KL, Rosenfeld B, McDonald MV, Theobald DE. The changeable nature of
558 patients' fears regarding chemotherapy: implications for palliative care. *J Pain Symptom*
559 *Manage* 2001; 21: 113-120.

31. Non-Small Cell Lung Cancer Collaborative G. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst Rev* 2010: CD007309.

32. Little AG, Gay EG, Gaspar LE, Stewart AK. National survey of non-small cell lung cancer in the United States: Epidemiology, pathology and patterns of care. *Lung Cancer* 2007; 57: 253-260.

33. Hardy D, Liu CC, Xia R, Cormier JN, Chan W, White A, et al. Racial disparities and treatment trends in a large cohort of elderly black and white patients with nonsmall cell lung cancer. *Cancer* 2009; 115: 2199-2211.

34. Earle CC, Venditti LN, Neumann PJ, Gelber RD, Weinstein MC, Potosky AL, et al. Who gets chemotherapy for metastatic lung cancer? *Chest* 2000; 117: 1239-1246.

35. McCann J, Artinian V, Duhaime L, Lewis JW, Jr., Kvale PA, DiGiovine B. Evaluation of the causes for racial disparity in surgical treatment of early stage lung cancer. *Chest* 2005; 128: 3440-3446.

36. Lin JJ, Mhango G, Wall MM, Lurslurchachai L, Bond KT, Nelson JE, et al. Cultural factors associated with racial disparities in lung cancer care. *Annals of the American Thoracic Society* 2014; 11: 489-495.

37. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ* 2010; 340: b5569.

38. Mason DP, Subramanian S, Nowicki ER, Grab JD, Murthy SC, Rice TW, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. *Ann Thorac Surg* 2009; 88: 362-370.

39. Zhang R, Lee SM, Wigfield C, Vigneswaran WT, Ferguson MK. Lung function predicts pulmonary complications regardless of the surgical approach. *Ann Thorac Surg* 2015; 99: 1761-1767.

Table 1: Characteristics of Patients in the National Cancer Database Diagnosed with Non-Small Cell Lung Cancer or Small Cell Lung Cancer in Years 2010 – 2014

		Overall (N = 441,812)	**NSCLC** (N = 375,832)	**SCLC** (N = 65,980)
Patient characteristics				
Sex (%)	Male	228,519 (51.7)	196,454 (52.3)	32,065 (48.6)
	Female	213,293 (48.3)	179,378 (47.7)	33,915 (51.4)
Age at diagnosis (%)	<50	22,328 (5.1)	19,224 (5.1)	3,104 (4.7)
	50-54	33,619 (7.6)	27,968 (7.4)	5,651 (8.6)
	55-59	50,955 (11.5)	42,054 (11.2)	8,901 (13.5)
	60-64	62,839 (14.2)	51,902 (13.8)	10,937 (16.6)
	65-69	75,298 (17.0)	62,838 (16.7)	12,460 (18.9)
	70-74	71,798 (16.3)	60,983 (16.2)	10,815 (16.4)
	75-79	58,053 (13.1)	50,616 (13.5)	7,437 (11.3)
	≥80	66,922 (15.1)	60,247 (16.0)	6,675 (10.1)
~~Race/ethnicity~~Racial/ethnic group (%)	Non-Hispanic White	349,842 (79.2)	294,833 (78.4)	55,009 (83.4)
	Non-Hispanic Black	48,060 (10.9)	42,799 (11.4)	5,261 (8.0)
	Non-Hispanic Asian	9,483 (2.1)	8,741 (2.3)	742 (1.1)
	Hispanic	12,081 (2.7)	10,587 (2.8)	1,494 (2.3)
	Other	2,806 (0.6)	2,441 (0.6)	365 (0.6)
	Unknown	19,540 (4.4)	16,431 (4.4)	3,109 (4.7)
Health insurance status (%)	Private	117,168 (26.5)	99,666 (26.5)	17,502 (26.5)
	Medicare	256,740 (58.1)	219,916 (58.5)	36,824 (55.8)
	Medicaid	34,278 (7.8)	28,118 (7.5)	6,160 (9.3)
	Other government insurance	7,023 (1.6)	5,928 (1.6)	1,095 (1.7)
	No insurance	18,112 (4.1)	15,009 (4.0)	3,103 (4.7)
	Unknown	8,491 (1.9)	7,195 (1.9)	1,296 (2.0)
Charlson comorbidity score (%)	0	24,6887 (55.9)	211,483 (56.3)	35,404 (53.7)
	1	130,577 (29.6)	110,304 (29.3)	20,273 (30.7)
	≥2	64,348 (14.6)	54,045 (14.4)	10,303 (15.6)
Health care provider characteristics				
Facility type (%)	Academic	140,344 (31.8)	121,914 (32.4)	18,430 (27.9)

	Non-academic	298,618 (67.6)	251,260 (66.9)	47,358 (71.8)
	Unknown	2,850 (0.6)	2,658 (0.7)	192 (0.3)
Hospital volume	Median (IQR)	524 (302-861)	533 (304-871)	500 (288-837)
Tumor characteristics				
Histology (%)*****	Adenocarcinoma	192,943 (43.7)	192,943 (51.3)	-
	Squamous cell	98,848 (22.4)	98,848 (26.3)	-
	Other non-small cell	84,041 (19.0)	84,041 (22.4)	-
	Small cell	65,980 (14.9)	-	65,980 (100.0)
Clinical stage at diagnosis (%)	IA	62,694 (14.2)	61,123 (16.3)	1,571 (2.4)
	IB	26,984 (6.1)	26,049 (6.9)	935 (1.4)
	IIA	17,456 (4.0)	15,898 (4.2)	1,558 (2.4)
	IIB	15,199 (3.4)	14,300 (3.8)	899 (1.4)
	IIIA	57,989 (13.1)	48,881 (13.0)	9,108 (13.8)
	IIIB	34,088 (7.7)	26,941 (7.2)	7,147 (10.8)
	IV	227,402 (51.5)	182,640 (48.6)	44,762 (67.8)

Table legend:
Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer, IQR = interquartile range.
* NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.

Table 2: Receipt of ~~Standard of Care Therapy Among~~Guideline-Concordant Treatment among Lung Cancer Patients by Clinical Subgroup

Clinical Subgroup	n	~~Standard of Care*~~ Guideline-Concordant Treatment*	~~Non-Standard of Care~~† Less Intensive Treatment Than Recommended†	No ~~Therapy~~Treatment
Overall (%)	441,812	274,338 (62.1)	72,155 (16.3)	95,319 (21.6)
~~ES~~L-NSCLC (%)	117,370	89,503 (76.3)	15,741 (13.4)	12,126 (10.3)
LA-NSCLC (%)	75,822	45,774 (60.4)	16,412 (21.6)	13,636 (18.0)
A-NSCLC (%)	182,640	92,119 (50.4)	33,227 (18.2)	57,294 (31.4)
LD-SCLC (%)	21,218	14,765 (69.6)	3,927 (18.5)	2,526 (11.9)
ED-SCLC (%)	44,762	32,177 (71.9)	2,848 (6.4)	9,737 (21.8)

Table legend:
Abbreviations: ~~ES~~L-NSCLC = ~~early-stage~~localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV).
* ~~Standard of care is~~Guideline-concordant treatment was defined as the minimal treatment patients should receive~~.~~ according to the National Comprehensive Cancer Network guidelines. Hence, additional treatment ~~could be given~~was allowed beside ~~the standard of care.~~guideline-concordant treatment. We considered ~~standard of care~~guideline-concordant treatment to be either surgery or Stereotactic Body Radiation Therapy for ~~ES~~L-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for LA-NSCLC; chemotherapy for A-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for patients with LD-SCLC; and chemotherapy for patients with ED-SCLC.
† ~~Non-standard of care~~Less intensive treatment than recommended was defined as ~~therapy~~treatment that was not ~~standard of care~~guideline-concordant.

Table 3: Patterns of Care ~~Among~~among Lung Cancer Patients by Clinical Subgroup

Clinical Subgroup	~~Therapy~~Treatment Received*	n (%)
~~ES~~L-NSCLC	~~Standard of care~~Guideline-concordant treatment	
	Surgery only	57,605 (49.1)
	Surgery & chemotherapy	13,359 (11.4)
	SBRT only	11,740 (10.0)
	Surgery & CRT & chemotherapy	4,405 (3.8)
	Surgery & CRT	1,562 (1.3)
	~~Non-standard of care~~Less intensive treatment than recommended	
	CRT only	7,129 (6.1)
	CRT & chemotherapy	6,953 (5.9)
	Chemotherapy only	1,465 (1.2)
LA-NSCLC	~~Standard of care~~Guideline-concordant treatment	
	CRT & chemotherapy	36,108 (47.6)
	Surgery & CRT & chemotherapy	5,580 (7.4)
	Surgery & chemotherapy	3,335 (4.4)
	~~Non-standard of care~~Less intensive treatment than recommended	
	CRT only	6,577 (8.7)
	Chemotherapy only	6,008 (7.9)
	Surgery only	2,676 (3.5)
A- NSCLC	~~Standard of care~~Guideline-concordant treatment	
	CRT & chemotherapy	47,370 (25.9)
	Chemotherapy only	35,620 (19.5)
	CRT & chemotherapy & other ~~therapy~~treatment	2,970 (1.6)
	Chemotherapy & other ~~therapy~~treatment	2,715 (1.5)
	~~Non-standard of care~~Less intensive treatment than recommended	
	CRT only	29,219 (16.0)
LD-SCLC	~~Standard of care~~Guideline-concordant treatment	
	CRT & chemotherapy	13,477 (63.5)
	Surgery & CRT & chemotherapy	545 (2.6)
	Surgery & chemotherapy	514 (2.4)
	~~Non-standard of care~~Less intensive treatment than recommended	
	Chemotherapy only	2,917 (13.7)
	CRT only	534 (2.5)
	Surgery only	340 (1.6)
ED-SCLC	~~Standard of care~~Guideline-concordant treatment	

CRT & chemotherapy	15,671 (35.0)
Chemotherapy only	15,658 (35.0)
~~Non-standard of care~~Less intensive treatment than recommended	
CRT only	2,597 (5.8)

Table legend:
Abbreviations: ~~ES~~L-NSCLC = ~~early-stage~~localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stage I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiation Therapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions; CRT = conventionally fractionated radiotherapy, defined as all radiotherapy other than Stereotactic Body Radiation Therapy.
* All mutually exclusive combinations of treatment modalities (i.e. all combinations of surgery, Stereotactic Body Radiation Therapy, conventionally fractionated radiotherapy, chemotherapy, and other ~~therapy~~treatment) were assessed. However, for each clinical subgroup only those treatment combinations that were more prevalent than 1% are reported in this table.

Table 4: Effect of Age and ~~Race/Ethnicity~~Racial/Ethnic Group on the Odds of Receiving ~~Standard of Care~~Guideline-Concordant Treatment for Lung Cancer

Age	**<50**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**≥80**
No. of subjects	22,328	33,619	50,955	62,839	75,298	71,798	58,053	66,922
No. events	17,710	25,242	36,765	43,702	50,822	44,959	31,977	23,161
Event risk	0.79	0.75	0.72	0.70	0.67	0.63	0.55	0.35
Crude odds ratio (95% CI) *	Reference	0.79 (0.75-0.82)	0.68 (0.65-0.70)	0.60 (0.57-0.62)	0.54 (0.52-0.56)	0.44 (0.42-0.45)	0.32 (0.31-0.33)	0.14 (0.13-0.14)
Adjusted odds ratio (95%CI) *	Reference	0.76 (0.73-0.79)	0.63 (0.60-0.65)	0.53 (0.51-0.55)	0.48 (0.47-0.50)	0.39 (0.37-0.40)	0.28 (0.27-0.29)	0.12 (0.12-0.13)
~~Race/ethnicity~~Racial/ethnic group	**Non-Hispanic White**	**Non-Hispanic Black**	**Non-Hispanic Asian**	**Hispanic**	**Other**			
No. of subjects†	365,922	50,256	9,958	12,682	2,995			
No. events†	229,378	29,206	6,344	7,529	1,881			
Event risk †	0.63	0.58	0.64	0.59	0.63			
Crude odds ratio (95% CI) *	Reference	0.82 (0.81-0.84)	1.04 (1.00-1.09)	0.87 (0.84-0.90)	1.00 (0.93-1.09)			
Adjusted odds ratio (95%CI) *	Reference	0.78 (0.76-0.80)	1.09 (1.04-1.15)	0.94 (0.90-0.98)	0.94 (0.86-1.03)			

Table legend:
Abbreviations: 95% CI = 95% Confidence interval; No. = number.
* The crude and adjusted odds ratios are from the pooled regression model based on all three imputed datasets. Adjusted odds ratios are adjusted for sex, insurance status, Charlson comorbidity score, ~~-~~treating facility type, hospital volume, histology, and clinical stage at diagnosis. Variance inflation factors were ≤2 for all covariates, indicating that multicollinearity was limited.
† The number of subjects, number of events, and event risks for ~~race/ethnicity~~racial/ethnic group are based on the mean values across the three imputed datasets.

Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States

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Online Supplement

Supplementary Methods

Data

We used the National Cancer Database (NCDB) to extract a cohort of patients diagnosed with lung cancer between 2010-2014. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually, from more than 1500 affiliated facilities. The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Analysis of individual-level NCDB data was performed on site at the University of Michigan Medical School. This study was deemed exempt by the Institutional Review Board of the University of Michigan.

Case selection

Only cases with International Classification of Diseases for Oncology 3rd edition (ICD-0-3) malignant behavior code were selected (E1). Stages 0, occult, and unknown were excluded as guidelines provide no treatment recommendations for these patients. We further removed cases without a known stage subcategory (e.g. stage I rather than IA) because these do not provide sufficient detail. We selected only those cases staged using the American Joint Committee on Cancer (AJCC) 7th edition Cancer Staging Manual, which was effective from 2010-2017 (E2). In accordance with NCDB instructions, we further excluded the following: cases with

a history of multiple primary tumors of which lung cancer wasn't the first; cases with a date of diagnosis before the reporting facility's reference date (i.e. the date from which the facility guarantees the accuracy of data); and cases that did not receive any treatment at the reporting facility. Also, we excluded cases with unknown treatment. Finally, we selected only cases with less than four months (122 days) between diagnosis and onset of therapy because the NCDB uses the principle that initial treatment must begin within four months of the date of initial diagnosis.

Data cleaning

Baseline characteristics

Baseline characteristics of included patients were derived and included sex, age at diagnosis, racial/ethnic group, insurance status, Charlson comorbidity score, tumor histology, clinical stage at diagnosis, treating facility type, and treating hospital volume. The derivation of these variables is detailed below.

Deriving sex

The standard coding of sex was used.

Deriving age at diagnosis

Age at diagnosis was collapsed into categories under 50, 80 or over, and 5-year intervals in between.

Deriving racial/ethnic groups

Available Race codes were recoded to categories White, Black, Asian, Other (and Unknown) using definitions from the Census 2000 Technical Documentation (E3) as shown in Table E1. The variable for Spanish/Hispanic origin was collapsed into categories Non-Hispanic, Hispanic and Unknown. Cases in which the only evidence of the person's Hispanic origin was surname or maiden name were explicitly assigned the category Unknown. Cases with Hispanic origin could be of any Race. Therefore, recoded variables Race and Spanish/Hispanic origin were combined into a new variable with categories non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, Other, and unknown.

Deriving insurance status

The standard coding of insurance status was used. According to the NCDB codebook, the first recorded payer or insurer was used if multiple forms of insurance are recorded on the patient's admission page.

Deriving Charlson comorbidity score

The Charlson comorbidity score is the sum of the scores for each of the comorbid conditions as mapped from the Charlson Comorbidity Score Mapping Table in the online NCDB Data Dictionary (E4). Individual comorbidities were not available in the data. The Charlson score in the NCDB is only available aggregated into scores 0, 1 and 2 or higher. A Charlson score of 0

does not mean that no comorbidities are present, but that none of the comorbidities from the mapping table were present.

Deriving tumor histology

ICD-0-3 morphological codes were assigned to categories adenocarcinoma (including bronchioalveolar carcinoma and large cell carcinoma), squamous cell carcinoma, other non-small cell and small cell lung cancer (SCLC), as shown in Table E2. The classification was based on an earlier publication (E5). In accordance with the ICD-0-3 coding manual, morphological codes that were not listed in that classification or that were accompanied by a lung cancer-specific site code despite not being typically associated with lung cancer were not discarded but were assigned the histological category other (E1).

Deriving stage at diagnosis

We used clinical stage at diagnosis because pathological stage is only available after the outcome of interest (initial treatment) has taken place. As is customary in clinical guidelines, clinical stage for SCLC was collapsed to limited disease SCLC (LD-SCLC; stages I-III) and extensive disease SCLC (ED-SCLC; stage IV). For the analysis of NSCLC cases, we collapsed stages IA, IB, and II into localized NSCLC (L-NSCLC), stages IIIA and IIIB into locally advanced NSCLC (LA-NSCLC), and stage IV into advanced NSCLC (A-NSCLC).

Deriving facility type

Treating facility type was derived by combining Commission on Cancer accreditation categories into academic (includes Academic Comprehensive Cancer Programs and National Cancer Institute-designated Comprehensive Cancer Centers) and non-academic (all other reported program types). Commission on Cancer programs categories are based on type of facility, program structure, services provided, and the volume of patients. Key characteristics of the category "Academic Comprehensive Cancer Program" are the annual accession of at least 500 newly diagnosed cancer cases, the availability of a full range of diagnostic and therapeutic services, the participation in research, and the participation in postgraduate medical education in at least four programs including internal medicine and surgery (E6). The category National Cancer Institute-Designated Comprehensive Cancer Center Program only requires the availability of a full range of diagnostic and treatment facilities (E6).

Deriving hospital volume

Hospital volume was calculated by determining how many lung cancer cases (both NSCLC and SCLC) were treated at the reporting (and therefore treating) facility, using the unique facility identifier. Hospital volume was aggregated in quartiles and used as a categorical variable.

Extracting a cohort from the Surveillance, Epidemiology, and End Results dataset

Applying a case selection process similar to that of the studied NCDB cohort, we extracted a cohort from the Surveillance, Epidemiology, and End Results (SEER) 18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases November 2016 data submission using proprietary SEER*Stat software (E7). First, only cases with ICD-0-3 topography codes for lung

cancer (C340 - C343, C348 and C349) and malignant behavior code were selected. We only selected cases staged using the AJCC 7th Edition Cancer Staging Manual (E2). Stages 0 and occult and cases with unspecified substage (i.e. stage I rather than IA) were excluded. For full comparability of baseline characteristics between the NCDB and the SEER database, we did not exclude cases with an unknown stage in this comparison. Only cases with "one primary only" or "1st of 2 or more primaries" were selected. Finally, only cases with known age diagnosed in years 2010 through 2014 were selected.

To assess the generalizability of NCDB data to the general US population, we compared baseline characteristics of the cohort from the SEER database to the cohort of lung cancer patients from the NCDB database. Where possible, ICD-0-3 morphological codes were assigned to histology categories using the same classification that we used for the NCDB cohort, as shown in Table E2. The following histologies were available in the NCDB cohort, but not in the SEER cohort: 8143, 8572, 8573 (classified as adenocarcinoma); 8005, 8040, 8080, 8090, 8094, 8120, 8154, 8160, 8210, 8211, 8243, 8262, 8280, 8313, 8380, 8401, 8453, 8503, 8510 (classified as other non-small cell). The following histologies were available in the SEER cohort, but not in the NCDB cohort and were classified as follows: 8201, 8571 (adenocarcinoma); 8034, 8300, 8410, 9590, 9591, 9650, 9651, 9663, 9671, 9673, 9680, 9687, 9690, 9699, 9714 (other non-small cell). We recoded and categorized racial/ethnic groups in the exact same way as for the NCDB cohort, as described elsewhere in the Supplementary Methods. As the insurance status variable in the SEER database is less granular than in the NCDB, we recoded insurance status in both datasets to categories insured (NCDB: private, Medicare, Medicaid, other government insurance; SEER: insured, insured with no specifics, any Medicaid), uninsured, and unknown.

The treatment facility type variable that we used in the NCDB analysis is NCDB-specific and was therefore unavailable for the SEER database. Finally, the Charlson comorbidity score was also not available in the SEER database.

Constructing treatment variables

The NCDB records the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. We were not able to distinguish whether multiple therapies were given concurrently or sequentially. Available treatment modalities in the dataset were surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy and other treatment (including experimental treatments).

The use of each of these modalities was coded in one or several variables. For each modality, crosstables were constructed between the available variables to check the internal consistency of the dataset. If possible based on these crosstables, unknown values were recoded (e.g. for n=43 cases, the variable RX_SUMM_SURG_PRIM_SITE indicated that it was unknown whether surgery was given while the variable REASON_FOR_NO_SURGERY indicated that surgery was not given. These were recoded as not having received surgery). Based on these crosstables, we constructed a set of binary variables to indicate whether surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy and other treatment were administered.

The names of individual systemic agents are not recorded by the NCDB. The NCDB uses the SEER*Rx Interactive Antineoplastic Drugs Database (E8) to determine whether systemic

agents are to be coded as chemotherapy, hormone therapy, or immunotherapy. We investigated the targeted therapy agents that are most commonly used in lung cancer care (i.e. EGFR-inhibitors erlotinib, afatinib and gefitinib and ALK-inhibitors crizotinib and ceritinib) in the SEER*Rx database and found that these were all coded as chemotherapy. Therefore, we were not able to separately report on the use of targeted agents.

When investigating other novel treatment agents used in lung cancer care in the SEER*Rx database, we found that Vascular Endothelial Growth Factor (VEGF) inhibitor bevacizumab has been coded as immunotherapy for cases diagnosed after January 1st 2013 only. For cases diagnosed prior to that date, bevacizumab had been coded as chemotherapy. Protein Programmed Cell Death 1 (PD-1) inhibitors pembrolizumab, nivolumab and Protein Programmed Cell Death-Ligand 1 (PD-L1) inhibitor atezolizumab were coded as immunotherapy for all cases. The recommendation and clinical use of these agents in lung cancer therapy is very recent though, and is unlikely to be captured in the available dataset with cases diagnosed between 2010-2014. To our knowledge, there are no hormone therapy agents that have an accepted role in the treatment of lung cancer. As a result, hormone therapy and immunotherapy were aggregated with the other treatment category.

Radiotherapy was further divided into Stereotactic Body Radiotherapy (SBRT) and conventionally fractionated radiotherapy (CRT). SBRT delivers high-dose radiation to a specific target in only a few fractions and provides local tumor control rates of up to 90% with moderate toxicity (E9, E10). Since the most frequently used SBRT schemes in the US comprise a total dose of 45 Gray or more over 1-5 fractions (E11-E13) and the US billing code for SBRT includes a maximum of 5 fractions (E14), SBRT was defined as thoracic radiotherapy with a total

radiation dose of 45 Gray or more delivered in 5 fractions or less. CRT was defined as all radiotherapy that was not SBRT.

The remaining treatment variables were: surgery, SBRT, CRT, chemotherapy (including targeted therapies), and other treatment (including experimental treatments and immunotherapy). Cases that received none of these therapies were coded as having received no therapy.

Definition of Guideline-Concordant Treatment

Two main lung cancer types can be distinguished: NSCLC and SCLC, with the majority presenting as NSCLC. Since SCLC is clinically more aggressive than NSCLC, clinical treatment guidelines provide specific recommendations for clinical subgroups of lung cancer type and stage at diagnosis. For each of these clinical subgroups, we assessed whether guideline-concordant treatment was received, defined as the minimal first course treatment these patients should receive according to the National Comprehensive Cancer Network guidelines (E14, E15).

While surgical treatment is still recommended as the primary minimal treatment for L-NSCLC, SBRT is now recommended as an alternative treatment to surgery for L-NSCLC patients (E14). Therefore, both surgery and SBRT were considered guideline-concordant treatment for L-NSCLC. The minimal recommended treatment for LA-NSCLC and LD-SCLC depends on operability (E14, E15). If operable, the minimal recommendation is surgery combined with chemotherapy. However, the majority of LA-NSCLC and LD-SCLC patients are inoperable, in

which case the minimal recommendation is a combination of radiotherapy and chemotherapy. Therefore, both treatment combinations were considered guideline-concordant for LA-NSCLC and LD-SCLC. For A-NSCLC and ED-SCLC, the minimal recommended treatment is chemotherapy (E14, E15). As we assessed the minimal recommended treatment for each clinical subgroup, additional treatments were allowed beside guideline-concordant treatment (e.g. radiotherapy for bone metastases beside chemotherapy in A-NSCLC). There were no restrictions on radiation dose or fractionation for stages other than L-NSCLC. A summary of the treatment combinations that were considered guideline-concordant for each clinical subgroup can be found in Table E3 in the Online Supplement.

Statistical Analysis

For each clinical subgroup, we assessed the proportion of cases that received guideline-concordant treatment, less treatment than recommended (defined as treatment that was not guideline-concordant), and no treatment. We used clinical stage at diagnosis for creating clinical subgroups because pathological stage can only be known after the outcome of interest (initial treatment) has occurred. For the groups of patients who received guideline-concordant treatment and less intensive treatment than recommended, we separately assessed which mutually exclusive combinations of surgery, SBRT, CRT, chemotherapy (including targeted therapy) and other treatment (including immunotherapy and experimental treatments) were received.

To identify whether previously identified disparities in receiving guideline-concordant treatment by racial/ethnic group and by age persist, we fitted a multivariable logistic regression

model with receipt of guideline-concordant treatment as binary outcome and racial/ethnic group and age as independent variables. We further adjusted this model for several covariates that could be associated with racial/ethnic group and age, and also affect receiving guideline-concordant treatment. Based on previous literature, we included sex (E16), health insurance status (E17), Charlson comorbidity score (E18), facility type (E19), and stage at diagnosis (E20). We further included histology because squamous cell carcinomas are often located centrally (E21), potentially making them more difficult to surgically resect. Finally, we included hospital volume because it is a well-established indicator of quality of care (E22).

To identify whether disparities by racial/ethnic group and by age extend across all clinical subgroups, we also fitted a separate model for each clinical subgroup. For clinical subgroups with multiple guideline-concordant treatment combinations, we fitted a separate model for each treatment combination. For example, two separate models were fitted for L-NSCLC; one with SBRT as binary outcome and one with surgery as binary outcome. These models were adjusted for the same covariates as the overall model.

All analyses were performed using R software version 3.4.1 (E23). The base-R glm() function was used to fit the logistic regression models. We used multiple imputation (m=3) to address missing data (E24). Multicollinearity was assessed by calculating generalized variance inflation factors (E25).

References

E1. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International Classification of Diseases for Oncology. 3rd ed. Geneva, Switzerland: World Health Organization; 2013.

E2. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.

E3. U.S. Census Bureau. Census 2000 Summary File 2 Technical Documentation. Available from: https://www.census.gov/prod/cen2000/doc/sf2.pdf

E4. American College of Surgeons. National Cancer Data Base - Data Dictionary PUF 2014. http://ncdbpuf.facs.org/node/259. Accessed April 25, 2017.

E5. Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev. 2015;24(1):154-61.

E6. American College of Surgeons. About Cancer Program Categories. https://www.facs.org/quality-programs/cancer/coc/apply/categories. Accessed October 10, 2018.

E7. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973-2014 varying) - Linked To County Attributes - Total U.S., 1969-2015 Counties. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program; Released April 2017. www.seer.cancer.gov . Accessed October 17, 2017.

E8. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Rx Interactive Antineoplastic Drugs Database. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program. https://seer.cancer.gov/seertools/seerrx/. Accessed July 28, 2018.

E9. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27(20):3290-6.

E10. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070-6.

E11. Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017;124(1):11-7.

E12. Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017;7(5):295-301.

E13. Pan H, Rose BS, Simpson DR, Mell LK, Mundt AJ, Lawson JD. Clinical practice patterns of lung stereotactic body radiation therapy in the United States: a secondary analysis. Am J Clin Oncol. 2013;36(3):269-72.

E14. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer Version 5.2017. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 20, 2017.

E15. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed April 20, 2017.

E16. Balekian AA, Wisnivesky JP, Gould MK. Surgical Disparities Among Patients With Stage I Lung Cancer in the National Lung Screening Trial. Chest 2019; 155: 44-52.

E17. Groth SS, Al-Refaie WB, Zhong W, Vickers SM, Maddaus MA, D'Cunha J, et al. Effect of insurance status on the surgical treatment of early-stage non-small cell lung cancer. Ann Thorac Surg 2013; 95: 1221-1226.

E18. Gould MK, Munoz-Plaza CE, Hahn EE, Lee JS, Parry C, Shen E. Comorbidity profiles and their effect on treatment selection and survival among patients with lung cancer. Annals of the American Thoracic Society 2017; 14: 1571-1580.

E19. Bott MJ, Patel AP, Verma V, Crabtree TD, Morgensztern D, Robinson CG, et al. Patterns of care in hilar node-positive (N1) non-small cell lung cancer: A missed treatment opportunity? J Thorac Cardiovasc Surg 2016; 151: 1549-1556.

E20. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. J Clin Oncol 2012; 30: 1447-1455.

E21. Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis Of Disease. Philadelphia, PA: Elsevier Saunders; 2005.

E22. Von Meyenfeldt EM, Gooiker GA, van Gijn W, Post PN, van de Velde CJ, Tollenaar RA, et al. The relationship between volume or surgeon specialty and outcome in the surgical

treatment of lung cancer: a systematic review and meta-analysis. J Thorac Oncol 2012; 7: 1170-1178.

E23. R: A Language and Environment for Statistical Computing [computer program]. Version 3.4.1. Vienna, Austria: R Foundation for Statistical Computing; 2017.

E24. Van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. Journal of statistical software 2010: 1-68.

E25. Fox J, Weisberg S. An R Companion to Applied Regression. 2nd ed. Thousand Oaks, CA: SAGE Publications; 2011.

Supplementary Tables and Figures

Supplementary Table E1: Recoding Race Categories from the National Cancer Database Participant User File

Recoded race category	Original race categories
White	White
Black	Black
Asian	Chinese; Japanese; Filipino; Hawaiian; Korean; Vietnamese; Laotian; Hmong; Kampuchean (including Khmer and Cambodian); Thai; Asian Indian or Pakistani NOS; Asian Indian; Pakistani; Other Asian (including Asian NOS and Oriental NOS)
Other	American Indian, Aleutian or Eskimo; Micronesian NOS; Chamorran; Guamanian NOS; Polynesian NOS; Tahitian; Samoan; Tongan; Melanesian NOS; Fiji Islander; New Guinean; Pacific Islander NOS; Other

Supplementary Table E2: Assigning International Classification of Diseases for Oncology 3rd Edition Histological Codes to Histology Categories

Histology category	ICD-0-3 histological codes included
Adenocarcinoma	
Adenocarcinoma	8140; 8141; 8143; 8200; 8230; 8260; 8310; 8323; 8480; 8481; 8490; 8550; 8570; 8572; 8573; 8574; 8575; 8576
Bronchioalveolar carcinoma	8250; 8251; 8252; 8253; 8254; 8255
Large cell carcinoma	8012; 8013; 8014
Squamous cell carcinoma	
Squamous Cell Carcinoma	8052; 8070; 8071; 8072; 8073; 8074; 8075; 8076; 8083; 8084
Other non-small cell lung cancer	
Other	8000; 8001; 8003; 8004; 8005; 8010; 8011; 8020; 8021; 8022; 8030; 8031; 8032; 8033; 8035; 8040; 8046; 8050; 8051; 8080; 8082; 8090; 8094; 8120; 8123; 8144; 8154; 8160; 8210; 8211; 8240; 8241; 8243; 8244; 8245; 8246; 8247; 8249; 8262; 8280; 8290; 8313; 8320; 8333; 8341; 8380; 8401; 8430; 8441; 8453; 8470; 8500; 8503; 8507; 8510; 8551; 8560; 8562; 8940; 8980
Small cell lung cancer	
Small cell lung cancer	8002; 8041; 8042; 8043; 8044; 8045

Table legend:
Abbreviations: ICD-0-3 = International Classification of Diseases for Oncology 3rd Edition.

Supplementary Table E3: Overview of Therapy That Was Considered Guideline-Concordant Treatment for Each Clinical Subgroup

Clinical Subgroup	Guideline-Concordant Treatment*
L-NSCLC (%)	Surgery ± additional treatments AND/OR SBRT ± additional treatments
LA-NSCLC (%)	Surgery + chemotherapy ± additional treatments AND/OR Radiotherapy (any regimen) + chemotherapy ± additional treatments
A-NSCLC (%)	Chemotherapy ± additional treatments
LD-SCLC (%)	Surgery + chemotherapy ± additional treatments AND/OR Radiotherapy (any regimen) + chemotherapy ± additional treatments
ED-SCLC (%)	Chemotherapy ± additional treatments

Table legend:
Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiation Therapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions.
* Guideline-concordant treatment was defined as the minimal treatment patients should receive. Hence, ± sign indicates that additional treatment was allowed beside the minimal recommended treatment. Available treatment modalities were surgery, radiotherapy (further specified as Stereotactic Body Radiotherapy or conventional radiotherapy), chemotherapy (including targeted therapies), and other treatment (including experimental treatments and immunotherapy).

Supplementary Table E4: Comparison of Baseline Characteristics of Non-Small Cell Lung Cancer and Small Cell Lung Cancer Patients Diagnosed Between Years 2010 – 2014 in the National Cancer Database and the Surveillance, Epidemiology, and End Results Database

Database		**NCDB**	**SEER**	**NCDB**	**SEER**
Lung cancer type		**NSCLC** (N = 399,682)*	**NSCLC** (N = 163,141)	**SCLC** (N = 68,740)	**SCLC** (N = 23,285)
Patient characteristics					
Sex (%)	Male	208,212 (52.1)	85,944 (52.7)	33,316 (48.5)	11,742 (50.4)
	Female	191,470 (47.9)	77,197 (47.3)	35,424 (51.5)	11,543 (49.6)
Age at diagnosis (%)	< 50	20,455 (5.1)	7,201 (4.4)	3,203 (4.7)	922 (4.0)
	50 - 54	29,459 (7.4)	10,187 (6.2)	5,872 (8.5)	1,771 (7.6)
	55 - 59	44,363 (11.1)	16,236 (10)	9,228 (13.4)	2,902 (12.5)
	60 - 64	54,899 (13.7)	21,446 (13.1)	11,363 (16.5)	3,806 (16.3)
	65 - 69	66,778 (16.7)	26,578 (16.3)	12,973 (18.9)	4,505 (19.3)
	70 - 74	64,950 (16.3)	25,777 (15.8)	11,276 (16.4)	3,817 (16.4)
	75 - 79	54,016 (13.5)	22,870 (14.0)	7,776 (11.3)	2,892 (12.4)
	≥ 80	64,762 (16.2)	32,846 (20.1)	7,049 (10.3)	2,670 (11.5)
Racial/ethnic group (%)	Non-Hispanic White	31,3067 (78.3)	120,577 (73.9)	57,227 (83.3)	19,038 (81.8)
	Non-Hispanic Black	45,403 (11.4)	19,357 (11.9)	5,500 (8.0)	2,124 (9.1)
	Non-Hispanic Asian	9,330 (2.3)	11,072 (6.8)	771 (1.1)	804 (3.5)
	Hispanic	11,523 (2.9)	8,731 (5.4)	1,582 (2.3)	896 (3.8)
	Other	2,645 (0.7)	1,348 (0.8)	376 (0.5)	177 (0.8)
	Unknown	17,714 (4.4)	2,056 (1.3)	3,284 (4.8)	246 (1.1)
Health insurance status (%)	Insured	375,267 (93.9)	146,763 (90.0)	64,075 (93.2)	21,771 (93.5)
	Uninsured	15,778 (3.9)	5,108 (3.1)	3,222 (4.7)	927 (4.0)
	Unknown	8,637 (2.2)	11,270 (6.9)	1,443 (2.1)	587 (2.5)
Tumor characteristics					
Histology (%)[†]	Adenocarcinoma	204,865 (51.3)	79,549 (48.8)	-	-
	Squamous cell carcinoma	104,537 (26.2)	37,549 (23.0)	-	-
	Other non-small cell	90,280 (22.6)	46,043 (28.2)	-	-
Stage at diagnosis (%)[‡]	IA	61,123 (15.3)	19,091 (11.7)	1,571 (2.3)	420 (1.8)
	IB	26,049 (6.5)	10,967 (6.7)	935 (1.4)	310 (1.3)
	IIA	15,898 (4.0)	6,171 (3.8)	1,558 (2.3)	396 (1.7)
	IIB	14,300 (3.6)	6,437 (3.9)	899 (1.3)	256 (1.1)
	IIIA	48,881 (12.2)	19,212 (11.8)	9,108 (13.2)	2,724 (11.7)
	IIIB	26,941 (6.7)	8,846 (5.4)	7,147 (10.4)	2,239 (9.6)
	IV	18,2640 (45.7)	79,230 (48.6)	44,762 (65.1)	16,304 (70)
	Unknown	23,850 (6.0)	13,187 (8.1)	2,760 (4.0)	636 (2.7)

Table legend:
Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; NCDB = National Cancer Database; SEER = Surveillance, Epidemiology, and End Results.
* Other analyses in this study exclude cases with unknown stage. For full comparability of baseline characteristics between the National Cancer Database and the Surveillance, Epidemiology, and End Results database, this table does include unknown stages. Therefore, the total number of cases in this table is different from other tables in the manuscript.
† NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.
‡ In our main analysis for the NCDB data, we used clinical stage because pathological stage can only be known after the outcome of interest has taken place (i.e. treatment). Clinical stage is not available in the SEER database. Instead, the SEER database uses an algorithm based on Collaborative Stage variables to derive AJCC 7th edition stages. This algorithm occasionally uses pathological data if available.

Supplementary Table E5: Effect of Patient, Health Care Provider, and Tumor Characteristics on the Odds of Receiving Guideline-Concordant Treatment for Lung Cancer by Clinical Subgroup

	Overall	L-NSCLC		LA-NSCLC		A-NSCLC	LD-SCLC		ED-SCLC
	Guideline-Concordant Treatment*	Surgery	SBRT	Radiotherapy & Chemotherapy	Surgery & Chemotherapy	Chemotherapy	Radiotherapy & Chemotherapy	Surgery & Chemotherapy	Chemotherapy
Patient characteristics									
Sex									
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.01 (0.99-1.02)	0.97 (0.95-1.00)	1.07 (1.02-1.11)	0.94 (0.91-0.97)	1.05 (1-1.1)	1.04 (1.02-1.06)	1.05 (0.99-1.12)	0.78 (0.68-0.89)	0.98 (0.94-1.02)
Age									
<50	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
50-54	0.76 (0.73-0.79)	0.49 (0.43-0.55)	2.78 (2.07-3.73)	0.99 (0.9-1.08)	0.78 (0.7-0.87)	0.76 (0.72-0.8)	0.78 (0.64-0.96)	0.65 (0.43-0.98)	0.74 (0.64-0.87)
55-59	0.63 (0.6-0.65)	0.35 (0.32-0.39)	4.57 (3.48-6.01)	0.87 (0.8-0.95)	0.68 (0.62-0.76)	0.63 (0.59-0.66)	0.65 (0.54-0.79)	0.75 (0.52-1.08)	0.61 (0.53-0.7)
60-64	0.53 (0.51-0.55)	0.28 (0.26-0.32)	5.82 (4.46-7.61)	0.75 (0.69-0.82)	0.62 (0.56-0.68)	0.53 (0.5-0.56)	0.53 (0.44-0.64)	0.8 (0.56-1.14)	0.52 (0.45-0.6)
65-69	0.48 (0.47-0.5)	0.27 (0.24-0.30)	6.66 (5.10-8.70)	0.64 (0.59-0.7)	0.58 (0.52-0.65)	0.5 (0.47-0.52)	0.49 (0.4-0.59)	0.86 (0.6-1.24)	0.46 (0.4-0.53)
70-74	0.39 (0.37-0.4)	0.21 (0.19-0.24)	8.55 (6.55-11.16)	0.53 (0.48-0.58)	0.43 (0.38-0.48)	0.39 (0.37-0.42)	0.39 (0.32-0.47)	0.65 (0.45-0.95)	0.35 (0.3-0.41)
75-79	0.28 (0.27-0.29)	0.15 (0.14-0.17)	11.44 (8.76-14.94)	0.37 (0.34-0.4)	0.27 (0.24-0.31)	0.28 (0.27-0.3)	0.25 (0.21-0.31)	0.54 (0.36-0.8)	0.26 (0.23-0.3)
≥80	0.12 (0.12-0.13)	0.06 (0.05-0.06)	18.39 (14.09-23.99)	0.15 (0.14-0.17)	0.09 (0.08-0.11)	0.12 (0.11-0.13)	0.12 (0.1-0.15)	0.22 (0.14-0.34)	0.12 (0.1-0.14)
Racial/ethnic group									
Non-Hispanic White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Non-Hispanic Black	0.78 (0.76-0.8)	0.62 (0.59-0.64)	1.03 (0.95-1.1)	0.87 (0.83-0.91)	0.62 (0.58-0.68)	0.85 (0.82-0.87)	0.97 (0.87-1.08)	0.6 (0.45-0.79)	0.93 (0.86-1.01)
Non-Hispanic Asian	1.09 (1.04-1.15)	1.23 (1.1-1.37)	0.51 (0.43-0.62)	0.84 (0.75-0.94)	1.12 (0.95-1.32)	1.25 (1.18-1.34)	0.98 (0.75-1.28)	0.75 (0.34-1.67)	1.02 (0.83-1.25)
Hispanic	0.94 (0.9-0.98)	1.24 (1.13-1.36)	0.47 (0.4-0.56)	0.81 (0.73-0.89)	0.99 (0.85-1.14)	1.02 (0.96-1.08)	0.67 (0.55-0.83)	0.75 (0.44-1.29)	0.92 (0.8-1.07)
Other	0.94 (0.86-1.03)	0.96 (0.81-1.15)	1.03 (0.79-1.33)	0.72 (0.6-0.87)	0.79 (0.59-1.06)	1.04 (0.91-1.18)	0.79 (0.53-1.17)	0.8 (0.32-2.05)	1.18 (0.88-1.58)
Health Insurance status									

Private insurance	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Medicare	0.72 (0.7-0.73)	0.63 (0.6-0.65)	1.55 (1.45-1.65)	0.83 (0.8-0.87)	0.67 (0.63-0.72)	0.71 (0.69-0.73)	0.76 (0.7-0.84)	0.79 (0.65-0.95)	0.74 (0.69-0.79)
Medicaid	0.58 (0.56-0.59)	0.42 (0.39-0.45)	1.92 (1.7-2.16)	0.78 (0.73-0.83)	0.55 (0.5-0.6)	0.56 (0.54-0.58)	0.64 (0.57-0.73)	0.54 (0.39-0.74)	0.65 (0.59-0.71)
Other government insurance	0.6 (0.57-0.64)	0.25 (0.23-0.28)	4.46 (3.91-5.08)	1.04 (0.93-1.17)	0.51 (0.42-0.61)	0.51 (0.47-0.56)	0.94 (0.73-1.2)	0.63 (0.36-1.1)	0.71 (0.6-0.86)
No insurance	0.48 (0.46-0.49)	0.43 (0.39-0.47)	1.13 (0.9-1.41)	0.66 (0.61-0.72)	0.42 (0.37-0.48)	0.46 (0.44-0.48)	0.58 (0.49-0.68)	0.53 (0.33-0.85)	0.49 (0.44-0.54)
Charlson comorbidity score									
0	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1	0.83 (0.82-0.84)	1.29 (1.25-1.33)	0.77 (0.73-0.8)	0.74 (0.72-0.77)	1.14 (1.09-1.2)	0.73 (0.71-0.74)	0.75 (0.7-0.81)	1.47 (1.27-1.71)	0.85 (0.81-0.89)
≥2	0.59 (0.58-0.6)	0.88 (0.85-0.92)	0.97 (0.92-1.02)	0.55 (0.53-0.58)	0.82 (0.76-0.89)	0.5 (0.49-0.52)	0.61 (0.56-0.66)	1.09 (0.89-1.33))	0.61 (0.58-0.65)
Health care provider characteristics									
Facility type									
Academic	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Non-academic	0.91 (0.89-0.92)	0.89 (0.86-0.92)	0.76 (0.72-0.79)	1.1 (1.06-1.14)	0.75 (0.71-0.79)	0.94 (0.92-0.96)	1.11 (1.03-1.2)	0.73 (0.62-0.85)	0.97 (0.92-1.03)
Hospital volume[†]									
861-3596 (Q4)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
524-861 (Q3)	0.96 (0.94-0.98)	0.94 (0.9-0.97)	0.98 (0.93-1.03)	1.1 (1.05-1.15)	0.84 (0.79-0.9)	0.93 (0.91-0.96)	1.11 (1.02-1.22)	0.69 (0.57-0.84)	0.96 (0.9-1.02)
302-524 (Q2)	0.86 (0.85-0.88)	0.93 (0.9-0.97)	0.77 (0.73-0.81)	1.04 (0.99-1.08)	0.84 (0.79-0.9)	0.86 (0.84-0.89)	1.01 (0.92-1.1)	0.66 (0.55-0.8)	0.85 (0.79-0.9)
1-302 (Q1)	0.77 (0.76-0.79)	0.89 (0.86-0.93)	0.44 (0.41-0.48)	0.96 (0.92-1.01)	0.76 (0.7-0.81)	0.81 (0.79-0.83)	0.93 (0.85-1.02)	0.62 (0.5-0.76)	0.73 (0.68-0.77)
Tumor characteristics									
Histology[‡]									
Adenocarcinoma	Reference	Reference	Reference	Reference	Reference	Reference	-	-	-
Squamous cell	0.83 (0.81-0.84)	0.51 (0.5-0.53)	1.52 (1.45-1.59)	1.22 (1.17-1.26)	0.58 (0.55-0.61)	0.85 (0.83-0.87)			
Other non-small cell	0.44 (0.43-0.45)	0.26 (0.25-0.27)	1.92 (1.83-2.02)	0.66 (0.63-0.69)	0.39 (0.37-0.43)	0.48 (0.47-0.5)	-	-	-
Small cell	1.61 (1.58-1.65)	-	-	-	-	-	-	-	-
Clinical stage at diagnosis[§]									

IA	Reference	Reference	Reference	-	-	-	Reference	Reference	-
IB	0.51 (0.49-0.53)	0.78 (0.75-0.81)	0.64 (0.61-0.68)	-	-	-	1.42 (1.19-1.68)	0.41 (0.33-0.51)	-
IIA	0.25 (0.24-0.26)	0.57 (0.55-0.6)	0.16 (0.14-0.17)	-	-	-	2.7 (2.32-3.15)	0.2 (0.16-0.25)	-
IIB	0.15 (0.15-0.16)	0.35 (0.34-0.37)	0.17 (0.16-0.19)	-	-	-	1.98 (1.66-2.36)	0.17 (0.12-0.22)	-
IIIA	0.22 (0.21-0.23)	-	-	Reference	Reference	-	2.71 (2.42-3.04)	0.04 (0.04-0.05)	-
IIIB	0.19 (0.19-0.2)	-	-	1.13 (1.09-1.16)	0.19 (0.17-0.20)	-	2.33 (2.07-2.62)	0.01 (0.01-0.02)	-
IV	0.15 (0.14-0.15)	-	-	-	-	-	-	-	-

Table legend:

Abbreviations: L-NSCLC = localized non-small cell lung cancer (stages I-II); LA-NSCLC = locally-advanced non-small cell lung cancer (stage III); A-NSCLC = advanced non-small cell lung cancer (stage IV); LD-SCLC = limited disease small cell lung cancer (stages I-III); ED-SCLC = extensive disease small cell lung cancer (stage IV); SBRT = Stereotactic Body Radiotherapy, defined as thoracic radiotherapy with a dose of ≥45 Gray in ≤5 fractions.

* A separate multivariable logistic regression model was fitted to a subset of patients for each clinical subgroup. The binary dependent variable in each model was receipt of guideline-concordant treatment for that clinical subgroup, defined as the minimal treatment those patients should receive according to the National Comprehensive Cancer Network guidelines. Hence, additional treatment was allowed beside guideline-concordant treatment. Guideline-concordant treatment was either surgery or SBRT for L-NSCLC; either radiotherapy and chemotherapy or surgery and chemotherapy for LA-NSCLC; chemotherapy for A-NSCLC; either surgery and chemotherapy or radiotherapy and chemotherapy for patients with LD-SCLC; and chemotherapy for patients with ED-SCLC. In clinical subgroups with multiple guideline-concordant treatment combinations, each of these treatment combinations was assessed in a separate model. Results are presented as adjusted odds ratio (95% confidence interval).

† Hospital volume (i.e. the number of unique cases treated at the treating facility) was categorized in quartiles (Q1-Q4).

‡ NSCLC is subdivided into three distinct histology categories, while SCLC is considered a separate disease category.

§ As clinical subgroups are defined by stage and lung cancer type, different stages are used as the reference category across the different models.

Supplementary Figure E1: Selection of Lung Cancer Cases from the National Cancer Database

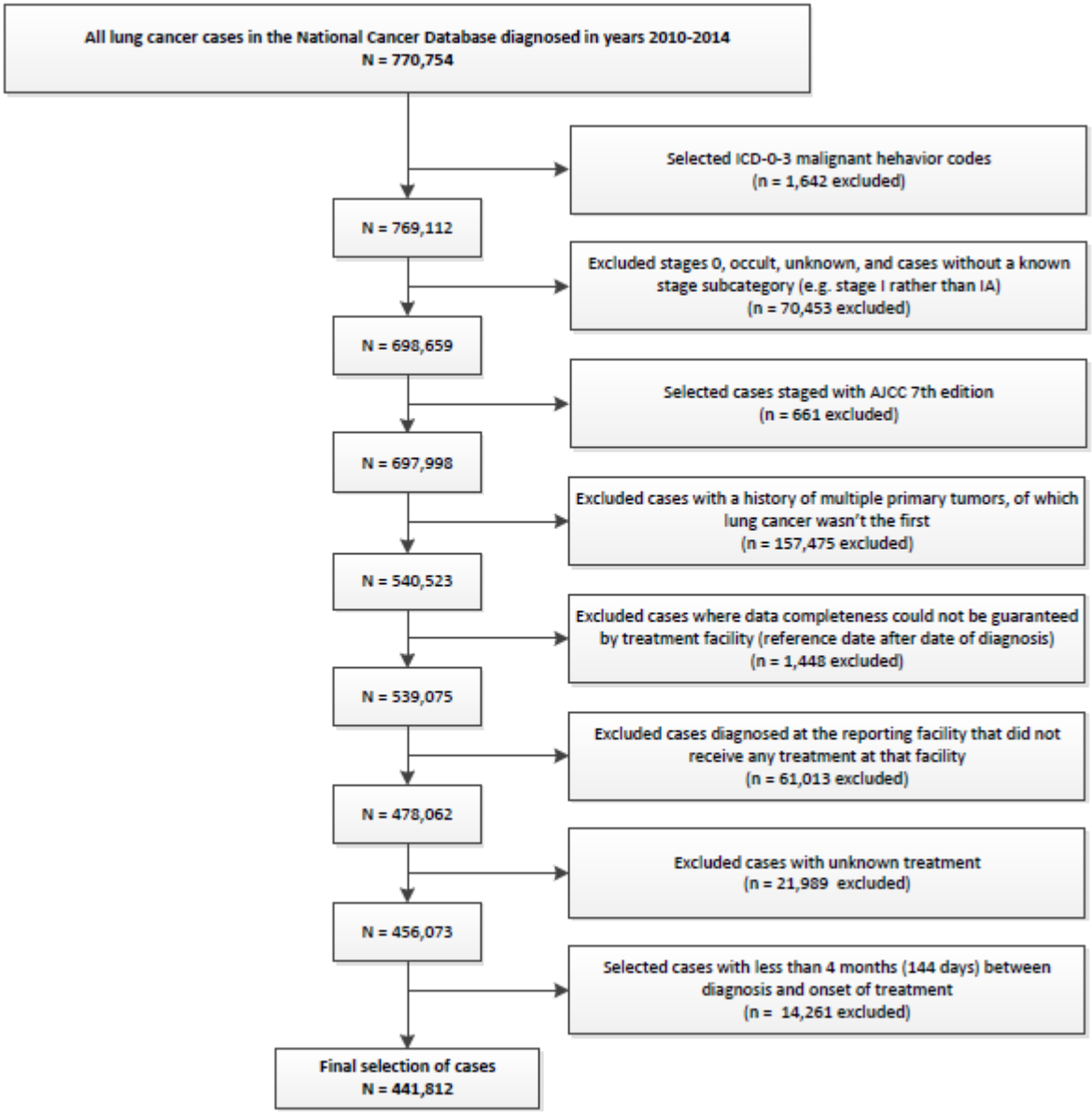

Figure legend:
Abbreviations: ICD-0-3 = International Classification of Diseases for Oncology 3rd Edition; AJCC = American Joint Committee on Cancer.

Supplementary Figure E2: Time Trends for Therapy Received by Lung Cancer Patients in the National Cancer Database

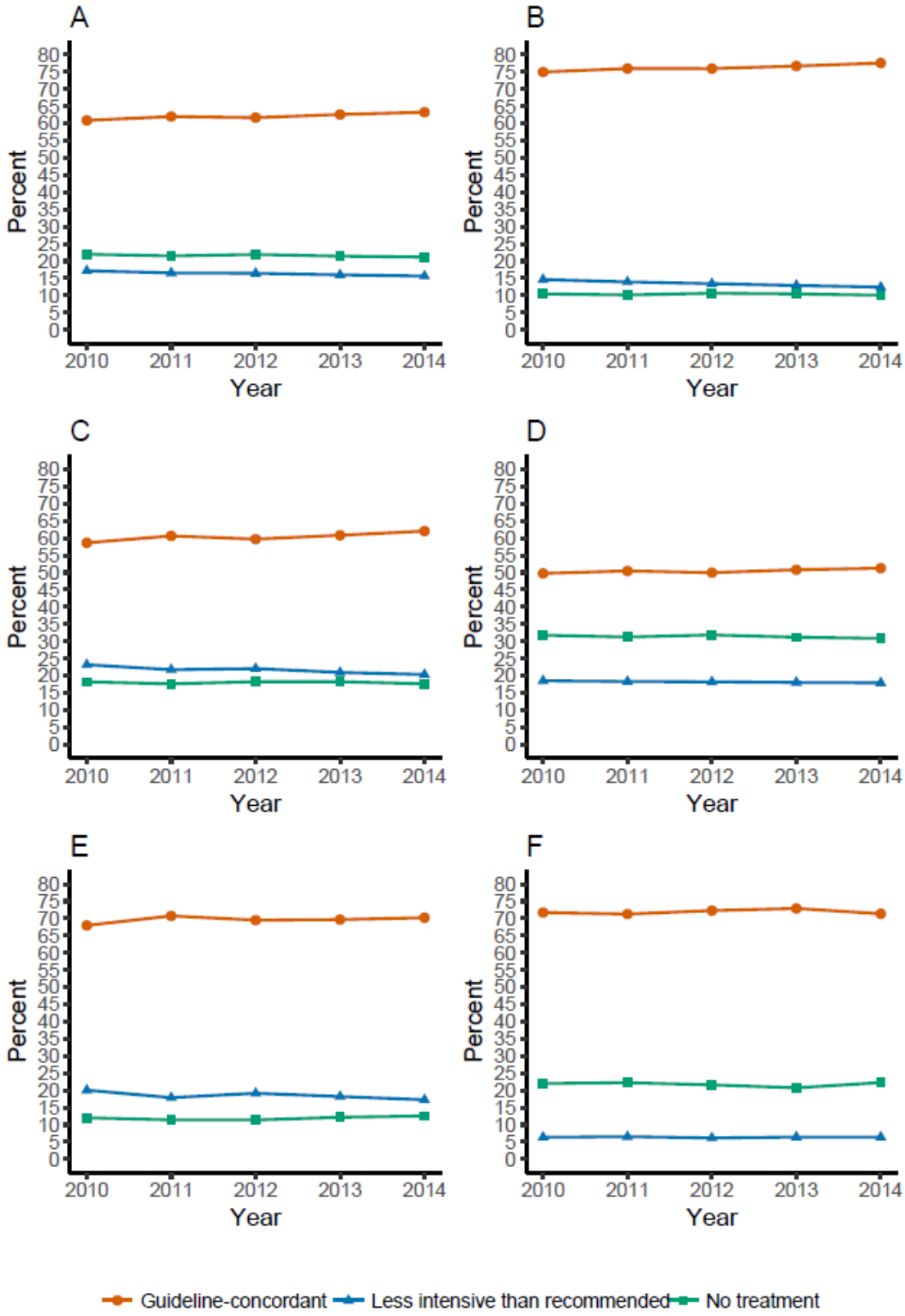

Figure legend:
Time trend for therapy received among [A] All cases; [B] localized non-small cell lung cancer cases (stages I-II); [C] locally-advanced non-small cell lung cancer cases (stage III); [D] advanced non-small cell lung cancer cases (stage IV); [E] limited disease small cell lung cancer cases (stages I-III); and [F] extensive disease small cell lung cancer cases (stage IV). We considered guideline-concordant treatment to be either surgery or stereotactic body radiotherapy for localized non-small cell lung cancer; either a combination of radiotherapy and chemotherapy or a combination of surgery and chemotherapy for locally advanced non-small cell lung cancer; chemotherapy for advanced non-small cell lung cancer; a combination of radiotherapy and chemotherapy or surgery and chemotherapy for patients with limited disease small cell lung cancer; and chemotherapy for patients with extensive disease small cell lung cancer. For each year, the proportion of cases that received guideline-concordant treatment, less intensive treatment than recommended, and no treatment add up to 100%.