Title

Impact of age and comorbidity on treatment of non-small cell lung cancer recurrence following complete resection: A nationally representative cohort study

Authors

Wong, Melisa L
McMurry, Timothy L
Stukenborg, George J
et al.

Publication Date

2016-12-01

DOI

10.1016/j.lungcan.2016.11.002

Peer reviewed

HHS Public Access

Author manuscript

Lung Cancer. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Lung Cancer. 2016 December ; 102: 108–117. doi:10.1016/j.lungcan.2016.11.002.

Impact of age and comorbidity on treatment of non-small cell lung cancer recurrence following complete resection: A nationally representative cohort study

Melisa L. Wong[a], **Timothy L. McMurry**[b], **George J. Stukenborg**[b], **Amanda B. Francescatti**[c], **Carla Amato-Martz**[d], **Jessica R. Schumacher**[e], **George J. Chang**[f], **Caprice C. Greenberg**[e], **David P. Winchester**[g], **Daniel P. McKellar**[h], **Louise C. Walter**[i], and **Benjamin D. Kozower**[j]

[a]Divisions of Hematology/Oncology and Geriatrics, Department of Medicine, University of California San Francisco and San Francisco Veterans Affairs Medical Center. 505 Parnassus Ave, Mailbox 1270, San Francisco, CA 94143, USA

[b]Department of Public Health Sciences, University of Virginia Health System. PO Box 800717, Charlottesville, VA 22908-0717, USA

[c]American College of Surgeons. 633 N. Saint Clair Street, Chicago, IL 60611, USA

[d]Alliance for Clinical Trials in Oncology. 125 S. Wacker Drive, Suite 1600, Chicago, IL 60606, USA

[e]Department of Surgery, University of Wisconsin. 600 Highland Ave, BX7375 Clinical Science Center, Madison, WI 53792-3284, USA

[f]Departments of Surgical Oncology and Health Services Research, The University of Texas MD Anderson Cancer Center. 1515 Holcombe Blvd Unit 444, Houston, TX 77030, USA

[g]Cancer Programs, American College of Surgeons. 633 N. Saint Clair Street, Chicago, IL 60611, USA

[h]Commission on Cancer, American College of Surgeons. 633 N. Saint Clair Street, Chicago, IL 60611, USA

[i]Division of Geriatrics, Department of Medicine, University of California San Francisco and San Francisco Veterans Affairs Medical Center. 4150 Clement (181G), San Francisco, CA 94121, USA

[j]Division of Cardiothoracic Surgery, Department of Surgery, Washington University. One Barnes-Jewish Hospital Plaza, Suite 3108 Queeny Tower, St. Louis, MO 63110-1013, USA

Corresponding author: Benjamin D. Kozower, MD, MPH, Division of Cardiothoracic Surgery, Department of Surgery, Washington University. One Barnes-Jewish Hospital Plaza, Suite 3108 Queeny Tower, St. Louis, MO 63110-1013, USA. Phone: (314) 362-8598 Fax: (314) 362-0328 kozowerb@wudosis.wustl.edu.

Prior presentation: The abstract was previously presented at the 2016 ASCO Annual Meeting. Word count: 3,000

Conflicts of Interest

Timothy L. McMurry has received consulting support from Diffusion Pharmaceuticals. Amanda B. Francescatti has stock ownership in ICAD. George J. Chang has received consulting support from Ethicon. Caprice C. Greenberg has received grant funding from Covidien-Medtronic and consulting support from Johnson and Johnson. The remaining authors have declared no conflicts of interest.

Abstract

Objective—Older patients with non-small cell lung cancer (NSCLC) are less likely to receive guideline-recommended treatment at diagnosis, independent of comorbidity. However, national data on treatment of postoperative recurrence are limited. We evaluated the associations between age, comorbidity, and other patient factors and treatment of postoperative NSCLC recurrence in a national cohort.

Materials and Methods—We randomly selected 9,001 patients with surgically resected stage I-III NSCLC in 2006–2007 from the National Cancer Data Base. Patients were followed for 5 years or until first NSCLC recurrence, new primary cancer, or death, whichever came first. Perioperative comorbidities, first recurrence, treatment of recurrence, and survival were abstracted from medical records and merged with existing registry data. Factors associated with active treatment (chemotherapy, radiation, and/or surgery) versus supportive care only were analyzed using multivariable logistic regression.

Results—Median age at initial diagnosis was 67; 69.7% had ≥1 comorbidity. At 5-year follow-up, 12.3% developed locoregional and 21.5% developed distant recurrence. Among patients with locoregional recurrence, 79.5% received active treatment. Older patients (OR 0.49 for age ≥75 compared with <55; 95% CI 0.27–0.88) and those with substance abuse (OR 0.43; 95% CI 0.23–0.81) were less likely to receive active treatment. Women (OR 0.62; 95% CI 0.43–0.89) and patients with symptomatic recurrence (OR 0.69; 95% CI 0.47–0.99) were also less likely to receive active treatment. Among those with distant recurrence, 77.3% received active treatment. Older patients (OR 0.42 for age ≥75 compared with <55; 95% CI 0.26–0.68) and those with any documented comorbidities (OR 0.59; 95% CI 0.38–0.89) were less likely to receive active treatment.

Conclusion—Older patients independent of comorbidity, patients with substance abuse, and women were less likely to receive active treatment for postoperative NSCLC recurrence. Studies to further characterize these disparities in treatment of NSCLC recurrence are needed to identify barriers to treatment.

Keywords

non-small cell lung cancer; recurrence; treatment; geriatric oncology

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) is a disease of older patients with a median age at diagnosis of 70 [1]. Even when diagnosed early and surgically resected with curative intent, NSCLC recurs in 20–75% of patients depending on patient and tumor characteristics [2–6]. National studies have demonstrated that older patients are less likely to receive guideline-recommended first-line treatment for NSCLC independent of comorbidity, suggesting potential undertreatment based on chronological age [7–9].

However, when fit older patients with minimal comorbidity are treated with guideline-recommended treatment, they derive similar survival benefits as younger patients [10–16]. Accordingly, the American Society of Clinical Oncology and National Comprehensive

Cancer Network recommend a comprehensive assessment of physiologic age, which incorporates comorbidities and functional status, when considering treatment options for older patients [17, 18]. However, there is a paucity of national data on patterns of care for postoperative NSCLC recurrence. As a result, little is known about how age and comorbidity impact the treatment of postoperative recurrence. This critical knowledge gap is largely because cancer registries do not report recurrence or subsequent treatment [19, 20]. This leaves researchers to investigate treatment for recurrent disease in small, single institution studies [3, 21, 22]. For example, active cancer-directed treatment for postoperative NSCLC recurrence ranged from 54% among octogenarians in one Japanese institution [21] to 69% of adult patients in one U.S. institution [3]. Neither study examined factors associated with receipt of treatment for postoperative recurrence.

To address these gaps in understanding treatment patterns for NSCLC recurrence, we examined the associations between age, comorbidities, and other patient factors and treatment of postoperative NSCLC recurrence in a large, nationally representative U.S. cohort. We hypothesized that older patients are less likely to receive active treatment for recurrence, independent of comorbidity. We also hypothesized that comorbidity is associated with decreased receipt of active treatment for recurrence but that this association is weaker than the association with age.

2. MATERIALS AND METHODS

2.1 Data Source

The National Cancer Data Base (NCDB) captures approximately 70% of all newly diagnosed U.S. cancer cases from more than 1,500 Commission on Cancer-accredited (CoC) hospitals [23, 24]. As part of a CoC special study, ten patients with surgically resected NSCLC in 2006–2007 were randomly selected from each facility for data abstraction. Using primary medical records from the initial reporting facility and outside facilities, registrars abstracted perioperative comorbidity, first NSCLC recurrence within 5 years, subsequent treatment of recurrence within 180 days, and updated vital status. Study participation by CoC-accredited facilities with eligible patients was 99.5%. Data were entered into a secure web form and stored at the CoC. Deidentified data were transferred to the University of Virginia and the University of Virginia Institutional Review Board provided an exemption as not human subjects research since data were deidentified and investigators did not have access to the encryption key.

2.2 Patient Population

Patients diagnosed with stage I-III NSCLC between January 1, 2006 and December 31, 2007 and treated with surgical resection with curative intent were eligible for the study. For facilities with fewer than ten eligible patients, data for all eligible patients were abstracted. Randomly selected patients with unavailable medical records, postoperative residual disease (based on pathology report), or who were lost to follow-up within 90 days after surgery were excluded. Excluded patients were replaced with randomly selected eligible patients from the same facility if available (Figure 1). Patients with unknown recurrence status were also excluded but not replaced. Patients were followed for 5 years from the time of initial

definitive surgery or until diagnosis of first NSCLC recurrence, new primary cancer, or death, whichever came first. To classify NSCLC disease as a recurrence versus a second primary lung cancer, we abstracted the treating physician's documentation in the original medical record. For this study, we examined only treatment for NSCLC recurrence and did not examine treatment for second primary lung cancers.

2.3 Data Collection and Measurement

Data collection was conducted from April through July 2015. The hypothesized primary predictors of treatment of recurrence were age at initial diagnosis (categorized as <55 years, 55–64, 65–74, ≥75) and perioperative comorbidities. Comorbid diseases were selected based on the Charlson Comorbidity Index and Adult Comorbidity Evaluation-27, validated measures of comorbidity used for cancer patients [25–28]. Comorbidities included cerebrovascular disease, chronic obstructive pulmonary disease (COPD), congestive heart failure, connective tissue disease, coronary artery disease (CAD), dementia, diabetes with or without end-organ damage, gastrointestinal ulcer disease, hemiplegia or paraplegia, liver disease, morbid obesity, other neurologic conditions, peripheral vascular disease, psychiatric disorder, renal disease, and history of or active substance abuse (including alcohol and/or illicit drugs). Registrars determined the presence of each comorbidity by reviewing medical records for the period within 30 days before and up to 90 days after the patient's initial surgery. Additional demographics included gender, race, zip code area education and median household income, urban versus rural residence [22], and insurance status. Clinical data included pathologic stage at diagnosis, histology, and type of initial surgery (pneumonectomy, lobectomy, segmentectomy, wedge, resection of lung not otherwise specified).

First NSCLC recurrence within 5 years of initial surgery was categorized as locoregional (ipsilateral lung and/or regional lymph nodes) or distant (disease outside the ipsilateral chest). Locoregional and distant recurrences were examined separately because factors associated with treatment of a potentially curable locoregional recurrence may differ from factors associated with treatment of a typically incurable distant recurrence. Patients diagnosed with locoregional and distant recurrences within 90 days of each other were categorized as having distant recurrence. Patients diagnosed with locoregional and distant recurrences who had missing recurrence dates were also categorized as having distant recurrence. Site(s) of recurrence, presence of symptoms at first detection, and subsequent treatment were obtained through medical record review. Treatment for recurrence was categorized as active treatment (chemotherapy including targeted therapy, radiation, and/or surgery) versus supportive care only (no cancer-directed therapy).

2.4 Statistical Analyses

Demographic and clinical characteristics were compared for patients with and without each type of NSCLC recurrence using one-way analysis of variance for continuous variables and Pearson's Chi-square test statistic for categorical variables. For each type of recurrence, demographic and clinical characteristics were compared between patients who received active treatment and those who received supportive care only.

Multivariable generalized estimating equation (GEE) logistic regression models with patient clustering within facilities were developed for each type of recurrence to predict the odds of receiving active treatment versus supportive care only. The primary predictors were age at initial NSCLC diagnosis and perioperative comorbidities that were present in at least 5% of the sample plus an indicator to represent any documented comorbidities. Patients with unavailable comorbidity information were included in the overall patient demographics but excluded from the regression models. Additional predictor variables were selected a priori based on clinical significance and prior literature and included gender, race, stage at diagnosis, histology, type of initial surgery, symptomatic recurrence, and site(s) of recurrence. Zip code area median household income was included in the model for distant recurrence since the larger sample size allowed for the inclusion of more predictor variables. To measure model discrimination, C-statistics were calculated. Results for each predictor variable were reported as adjusted odds ratios (OR) with 95% confidence intervals (CI).

Unadjusted Kaplan-Meier survival curves and log-rank tests were used to compare post-recurrence survival among patients with locoregional recurrence or with distant recurrence by type of treatment received. Of note, we did not perform risk adjustment of the survival estimates because important prognostic factors such as functional status in the period following postoperative NSCLC recurrence were not available to adequately adjust the estimates. The threshold of $P<0.05$ was used to determine statistical significance for all two-sided comparisons. Analyses were performed using R version 3.2.3 (Vienna, Austria).

3. RESULTS

Demographic and clinical characteristics of 9,001 patients from 1,150 CoC-accredited facilities with surgically resected stage I-III NSCLC are shown in Table 1, stratified by recurrence status. Median age at initial NSCLC diagnosis was 67 years (interquartile range 60–74). Approximately half of patients were female (51.3%) and 88.2% were white. The most common comorbidities were COPD, CAD, and diabetes. A majority of patients (69.7%) had at least one documented comorbidity. The most common stage at diagnosis was stage I (67.3%). Lobectomy was performed for 79.5% of the cohort. Compared to patients with no recurrence or locoregional recurrence, those with distant recurrence were more likely to have higher stage initial disease, adenocarcinoma, and have undergone a pneumonectomy.

After 5-year follow-up, 1,110 patients (12.3%) developed locoregional recurrence and 1,933 patients (21.5%) developed distant recurrence. By initial stage, the rates of developing locoregional or distant recurrence were: stage I 10.5% and 15.5%, stage II 16.2% and 30.3%, stage III 15.8% and 37.9%. The median time to recurrence overall was 15.9 months. Among patients with locoregional recurrence, 52.0% had ipsilateral lung disease, 29.4% had regional lymph node disease, and 18.6% had both. As shown in Table 2, 79.5% received active treatment for locoregional recurrence while 20.5% received supportive care only. The most common active treatments were chemotherapy (35.7%) and chemotherapy plus radiation (31.2%). Patients were less likely to receive active treatment if they were older ($P<0.001$), had substance abuse ($P=0.01$), symptomatic recurrence ($P=0.01$), or ipsilateral

lung recurrence (P<0.001). In addition, women were less likely to receive active treatment than men, though this difference was not statistically significant (P=0.08).

In the multivariable GEE logistic regression model predicting active treatment for locoregional recurrence versus supportive care only (Figure 2a), older patients, particularly those age ≥75 (OR 0.49 compared to patients age <55; 95% CI 0.27–0.88), and patients with substance abuse (OR 0.43; 95% CI 0.23–0.81) were less likely to receive active treatment. No other individual comorbid diseases were associated with receipt of active treatment for locoregional recurrence. Women (OR 0.62; 95% CI 0.43–0.89) and patients with symptomatic recurrence (OR 0.69; 95% CI 0.47–0.99) or ipsilateral lung recurrence (OR 0.42; 95% CI 0.25–0.71) were also less likely to receive active treatment. The model C-statistic was 0.78, indicating adequate discrimination.

Among patients with distant recurrence, the most common sites of recurrence were brain (29.9%) and bone (26.9%). As shown in Table 3, 77.3% received active treatment for distant recurrence while 22.7% received supportive care only. The most common active treatments were radiation (39.6%) and chemotherapy (30.0%). Patients were less likely to receive active treatment if they were older (P<0.001), had COPD (P=0.004), CAD (P<0.001), diabetes (P=0.01), congestive heart failure (P=0.01), or any documented comorbidities (P<0.001). Stage at diagnosis and site of recurrence were also associated with receipt of active treatment.

In the multivariable GEE logistic regression model predicting active treatment for distant recurrence versus supportive care only (Figure 2b), older patients, particularly those age ≥75 (OR 0.42 compared to patients age <55; 95% CI 0.26–0.68), were less likely to receive active treatment. Patients age 65–74 were also less likely to receive active treatment (OR 0.75 compared to patients age <55; 95% CI 0.49–1.17), but this difference was not statistically significant. In addition, patients with any documented comorbidities were less likely to receive active treatment (OR 0.59; 95% CI 0.38–0.89). There were no statistically significant associations between any individual comorbid diseases and receipt of active treatment for distant recurrence in the multivariable model. Site of recurrence, on the other hand, was associated with receipt of treatment. Patients with liver metastases were less likely to receive active treatment (OR 0.39; 95% CI 0.27–0.58) while patients with bone (OR 1.63; 95% CI 1.11–2.41) or brain metastases (OR 2.30; 95% CI 1.45–3.63) were more likely to receive active treatment. The model C-statistic was 0.75.

Unadjusted post-recurrence survival is shown in Figure 3 for patients with locoregional and distant recurrence by type of treatment received. Among those with locoregional recurrence, median survival after recurrence was 19.9 months (95% CI 18.0–22.0) for those who received active treatment and only 4.0 months (95% CI 2.9–5.7) for those who did not (log-rank P<0.001). Among those with distant recurrence, median survival after recurrence was 11.6 months (95% CI 10.6–12.3) for those who received active treatment and only 3.0 months (95% CI 2.5–3.8) for those who did not (log-rank P<0.001). Five-year post-recurrence survival was relatively poor for all patients (locoregional recurrence: 11.4% for active treatment versus 4.8% for supportive care only; distant recurrence: 6.9% for active treatment versus 2.0% for supportive care only).

4. DISCUSSION

Through this large, nationally representative study of treatment for postoperative NSCLC recurrence, we found that older patients were less likely to receive active treatment for recurrence, independent of comorbidities. In fact, among patients with locoregional recurrence, the only comorbidity that was associated with decreased odds of receiving active treatment was substance abuse. In contrast, patients with distant recurrence with any documented comorbidities were less likely to receive active treatment compared to those with none. However, no specific comorbid diseases were associated with treatment of distant recurrence. We also identified an unexpected gender disparity with women being less likely to receive treatment for locoregional NSCLC recurrence than men.

Differences in the treatment of postoperative NSCLC recurrence by chronological age are not completely explained by the degree of comorbidity among older patients. This finding is similar to prior studies of patterns of care for newly diagnosed NSCLC [7–9]. The increased use of supportive care only among older patients may be due to a combination of inappropriate undertreatment, differences in functional status, or patient preferences [29–32]. Indeed, older patients may be more likely to refuse active treatment for advanced lung cancer [29]. Interestingly, we found that patients with locoregional recurrence that was detected due to symptoms rather than routine surveillance imaging were less likely to receive active treatment. While we would expect symptomatic disease to be an indication for treatment, we hypothesize that these patients may have had more invasive disease making local treatment difficult, aggressive disease that developed between routine surveillance scans, or worse overall functional status and comorbidities making them poor treatment candidates. Decreased receipt of active treatment among patients with symptomatic recurrence may mediate the poor post-recurrence survival associated with the presence of symptoms seen in previous studies [3, 33].

The impact of comorbidity on treatment of recurrence differed for patients with distant metastatic recurrence, which is typically incurable, compared to locoregional recurrence, which may still be curable. Comorbidities can influence treatment decisions by introducing competing causes of morbidity and mortality or by increasing the risks of treatment toxicity. For patients with distant recurrence, those who had any documented comorbidities were 41% less likely to receive active treatment compared to those with no comorbidities. This suggests that any burden of comorbidity is an important factor in the treatment of distant recurrence [34]. Patients with locoregional recurrence and substance abuse, which was the only specific comorbid disease significantly associated with receipt of treatment, were 57% less likely to receive active treatment compared to patients without substance abuse. This finding highlights the potential challenges of managing cancer treatment and addiction simultaneously including concerns about decreased adherence to cancer treatment and increased risk of treatment when combined with the risks of substance abuse. Multidisciplinary interventions are needed to improve cancer care for patients with comorbid substance abuse [35–37].

Women with locoregional recurrence were surprisingly 38% less likely to receive active treatment compared to men. This gender disparity was not present among those with distant

recurrence. Prior studies have shown that when women with NSCLC do receive active treatment in the first-line setting, they experience lower postoperative morbidity and mortality and superior survival compared with men, independent of stage and treatment modality [38–41]. Therefore, this gender disparity for treatment of postoperative locoregional NSCLC recurrence is concerning and warrants further study. Of note, no racial disparities were observed in this study for treatment of NSCLC recurrence, although racial minorities were underrepresented in our sample.

Active treatment for locoregional and distant NSCLC recurrence was associated with improved unadjusted post-recurrence survival compared to supportive care only, which reflects both differences in patient selection for each group and treatment efficacy. Previous studies have demonstrated an association between poor post-recurrence survival and neoadjuvant chemotherapy, adjuvant radiation, poor performance status, symptomatic recurrence, disease-free interval of less than 1 year [3], initial stage, and site of recurrence [42]. Notably, older age at recurrence was not shown to be associated with post-recurrence survival [3]. In our study, even with active treatment, 5-year post-recurrence survival was relatively poor, which has implications for the optimal timing of post-treatment surveillance imaging. Surveillance guidelines currently vary by professional society [2, 43, 44] and do not incorporate individual patient factors. Research to improve surveillance based on comorbidities, risk of recurrence, and post-recurrence mortality is needed to personalize survivorship care [45].

Our study has several limitations. First, comorbidities were measured at the time of the initial surgery, not at recurrence. While comorbidities measured at recurrence may better reflect patient characteristics that were considered during treatment decision making, our thorough assessment of perioperative comorbidities is likely a reasonable approximation given the short median time to recurrence of 15.9 months. Also, the burden of comorbidity in our cohort is only representative of NSCLC patients fit enough at initial diagnosis to undergo first-line surgery. Finally, we did not collect information on the specific reasons why some patients received supportive care only for their recurrence. Functional decline and decreased quality of life after lung cancer surgery may have limited treatment options for some patients [46–48] while others may have refused cancer-directed therapy. Functional status and patient treatment preferences are important areas for future research on patterns of care for recurrent lung cancer.

In conclusion, older patients independent of comorbidity, patients with substance abuse, and women were less likely to receive active treatment for postoperative NSCLC recurrence. Studies to further characterize these disparities in treatment of NSCLC recurrence are needed to identify barriers to treatment. Since survival after recurrence is relatively limited with or without active treatment, individualized patient assessments are critical to identify those who are most likely to benefit and least likely to be harmed by active treatment. This study also highlights how the addition of complete data on cancer recurrence and subsequent treatment to a national cancer registry can enhance our understanding of important downstream outcomes after first-line treatment.

Acknowledgments

Funding: This work was supported by the Patient-Centered Outcomes Research Institute (PCORI; CE-1306-00727, Kozower) and the National Institute on Aging (T32AG000212, Wong and K24AG041180, Walter).

Role of the Funder: Neither PCORI nor the National Institute on Aging had a role in the design or conduct of the study.

References

1. Howlader, N.; Noone, AM.; Krapcho, M.; Miller, D.; Bishop, K.; Altekruse, SF.; Kosary, CL.; Yu, M.; Ruhl, J.; Tatalovich, Z.; Mariotto, A.; Lewis, DR.; Chen, HS.; Feuer, EJ.; CKA. SEER Cancer Statistics Review, 1975–2013. National Cancer Institute; Bethesda, MD: http://seer.cancer.gov/csr/1975_2013/ [accessed May 1, 2016]
2. Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 Suppl):e437S–54S. [PubMed: 23649451]
3. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, Williams BA, Pairolero PC. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg. 2007; 83(2):409–18. [PubMed: 17257962]
4. Taylor MD, Nagji AS, Bhamidipati CM, Theodosakis N, Kozower BD, Lau CL, Jones DR. Tumor recurrence after complete resection for non-small cell lung cancer. Ann Thorac Surg. 2012; 93(6): 1813–21. [PubMed: 22542070]
5. Ujiie H, Kadota K, Chaft JE, Buitrago D, Sima CS, Lee MC, Huang J, Travis WD, Rizk NP, Rudin CM, Jones DR, Adusumilli PS. Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival. J Clin Oncol. 2015; 33(26):2877–84. [PubMed: 26261257]
6. Lou F, Sima CS, Rusch VW, Jones DR, Huang J. Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung cancer. Ann Thorac Surg. 2014; 98(5):1755–60. discussion 1760–1. [PubMed: 25110337]
7. 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(13):1447–55. [PubMed: 22454424]
8. Nadpara PA, Madhavan SS, Tworek C, Sambamoorthi U, Hendryx M, Almubarak M. Guideline-concordant lung cancer care and associated health outcomes among elderly patients in the United States. J Geriatr Oncol. 2015; 6(2):101–10. [PubMed: 25604094]
9. Ritzwoller DP, Carroll NM, Delate T, Hornbrook MC, Kushi L, Aiello Bowles EJ, Freml JM, Huang K, Loggers ET. Patterns and predictors of first-line chemotherapy use among adults with advanced non-small cell lung cancer in the cancer research network. Lung Cancer. 2012; 78(3):245–52. [PubMed: 23022316]
10. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28(13):2181–90. [PubMed: 20351327]
11. Rocha Lima CM, Herndon JE 2nd, Kosty M, Clamon G, Green MR. Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer. 2002; 94(1):181–7. [PubMed: 11815975]
12. Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, Brindle J, Jatoi A, Jett JR. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol. 2003; 21(17):3201–6. [PubMed: 12874270]
13. Langer CJ, Manola J, Bernardo P, Kugler JW, Bonomi P, Cella D, Johnson DH. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern

Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst. 2002; 94(3):173–81. [PubMed: 11830607]

14. Gridelli C, Balducci L, Ciardiello F, Di Maio M, Felip E, Langer C, Lilenbaum RC, Perrone F, Senan S, de Marinis F. Treatment of Elderly Patients With Non-Small-Cell Lung Cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. Clin Lung Cancer. 2015; 16(5):325–33. [PubMed: 25862554]
15. Ganti AK, deShazo M, Weir AB 3rd, Hurria A. Treatment of non-small cell lung cancer in the older patient. J Natl Compr Canc Netw. 2012; 10(2):230–9. [PubMed: 22308517]
16. Ganti AK, Shostrom V, Alorabi M, Zhen WK, Marr AS, Trujillo K, Islam KM, Lackner RP, Kessinger A. Early Stage Non-Small-Cell Lung Cancer in Octogenarian and Older Patients: A SEER Database Analysis. Clin Lung Cancer. 2016; 17(4):285–91. [PubMed: 26725852]
17. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, Magnuson A, Lichtman SM, Bruinooge SS, Soto-Perez-de-Celis E, Tew WP, Postow MA, Cohen HJ. O. American Society of Clinical. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J Clin Oncol. 2015; 33(32):3826–33. [PubMed: 26195697]
18. National Comprehensive Cancer Network. [accessed May 15, 2016] NCCN Clinical Practice Guidelines in Oncology: Older Adult Oncology. https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf, Version 1.2016
19. In H, Bilimoria KY, Stewart AK, Wroblewski KE, Posner MC, Talamonti MS, Winchester DP. Cancer recurrence: an important but missing variable in national cancer registries. Ann Surg Oncol. 2014; 21(5):1520–9. [PubMed: 24504926]
20. Hiatt RA, Tai CG, Blayney DW, Deapen D, Hogarth M, Kizer KW, Lipscomb J, Malin J, Phillips SK, Santa J, Schrag D. Leveraging state cancer registries to measure and improve the quality of cancer care: a potential strategy for California and beyond. J Natl Cancer Inst. 2015; 107(5)
21. Yasuda M, Nagashima A, Haro A, Saitoh G. Treatment of the postoperative recurrence of lung cancer in octogenarians. Surg Today. 2014; 44(9):1626–32. [PubMed: 24026198]
22. Takahashi Y, Horio H, Hato T, Harada M, Matsutani N, Kawamura M. Predictors of post-recurrence survival in patients with non-small-cell lung cancer initially completely resected. Interact Cardiovasc Thorac Surg. 2015; 21(1):14–20. [PubMed: 25878187]
23. American College of Surgeons. [accessed March 23, 2016] National Cancer Data Base. https://www.facs.org/quality-programs/cancer/ncdb
24. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol. 2008; 15(3):683–90. [PubMed: 18183467]
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–83. [PubMed: 3558716]
26. Kehl KL, Lamont EB, McNeil BJ, Bozeman SR, Kelley MJ, Keating NL. Comparing a medical records-based and a claims-based index for measuring comorbidity in patients with lung or colon cancer. J Geriatr Oncol. 2015; 6(3):202–10. [PubMed: 25662785]
27. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004; 291(20):2441–2447. [PubMed: 15161894]
28. Piccirillo JF, Creech CM, Zequeira R, Anderson S, Johnston AS. Inclusion of comorbidity into oncology data registries. J Registry Manage. 1999; 26:66–70.
29. Ryoo JJ, Ordin DL, Antonio AL, Oishi SM, Gould MK, Asch SM, Malin JL. Patient preference and contraindications in measuring quality of care: what do administrative data miss? J Clin Oncol. 2013; 31(21):2716–23. [PubMed: 23752110]
30. Earle CC, Venditti LN, Neumann PJ, Gelber RD, Weinstein MC, Potosky AL, Weeks JC. Who Gets Chemotherapy for Metastatic Lung Cancer? Chest. 2000; 117(5):1239–1246. [PubMed: 10807806]
31. Girones R, Torregrosa D, Gomez-Codina J, Maestu I, Tenias JM, Rosell R. Lung cancer chemotherapy decisions in older patients: the role of patient preference and interactions with physicians. Clin Transl Oncol. 2012; 14(3):183–9. [PubMed: 22374421]

32. Vinod SK, Sidhom MA, Gabriel GS, Lee MT, Delaney GP. Why Do Some Lung Cancer Patients Receive No Anticancer Treatment? J Thorac Oncol. 2010; 5(7):1025–1032. [PubMed: 20453689]
33. Westeel V, Choma D, Clement F, Woronoff-Lemsi MC, Pugin JF, Dubiez A, Depierre A. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. Ann Thorac Surg. 2000; 70(4):1185–90. [PubMed: 11081867]
34. Williams GR, Mackenzie A, Magnuson A, Olin R, Chapman A, Mohile S, Allore H, Somerfield MR, Targia V, Extermann M, Cohen HJ, Hurria A, Holmes H. Comorbidity in older adults with cancer. J Geriatr Oncol. 2016; 7(4):249–57. [PubMed: 26725537]
35. Passik SD, Theobald DE. Managing addiction in advanced cancer patients: why bother? J Pain Symptom Manage. 2000; 19(3):229–34. [PubMed: 10760628]
36. Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients. Part 1: Prevalence and diagnosis. Oncology (Williston Park). 1998; 12(4):517–21. [PubMed: 9575525]
37. Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients. Part 2: Evaluation and treatment. Oncology (Williston Park). 1998; 12(5):729–42. [PubMed: 9597682]
38. Kozower BD, Sheng S, O'Brien SM, Liptay MJ, Lau CL, Jones DR, Shahian DM, Wright CD. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg. 2010; 90(3):875–813. [PubMed: 20732512]
39. Tong BC, Kosinski AS, Burfeind WR Jr, Onaitis MW, Berry MF, Harpole DH Jr, D'Amico TA. Sex differences in early outcomes after lung cancer resection: analysis of the Society of Thoracic Surgeons General Thoracic Database. J Thorac Cardiovasc Surg. 2014; 148(1):13–8. [PubMed: 24726742]
40. Fu JB, Kau TY, Severson RK, Kalemkerian GP. Lung Cancer in Women: Analysis of the National Surveillance, Epidemiology, and End Results Database. Chest. 2005; 127(3):768–777. [PubMed: 15764756]
41. Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? J Clin Oncol. 2007; 25(13):1705–12. [PubMed: 17470862]
42. Consonni D, Pierobon M, Gail MH, Rubagotti M, Rotunno M, Goldstein A, Goldin L, Lubin J, Wacholder S, Caporaso NE, Bertazzi PA, Tucker MA, Pesatori AC, Landi MT. Lung cancer prognosis before and after recurrence in a population-based setting. J Natl Cancer Inst. 2015; 107(6)
43. National Comprehensive Cancer Network. [accessed February 16, 2016] NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, Version 4.2016
44. Saunders M, Sculier JP, Ball D, Capello M, Furuse K, Goldstraw P, Meert AP, Ninane V, Ohe Y, Paesmans M, Park K, Pirker R, Postmus P, Sokolow Y. Consensus: the follow-up of the treated patient. Lung Cancer. 2003; 42(Suppl 1):S17–9.
45. Huang J, Logue AE, Ostroff JS, Park BJ, McCabe M, Jones DR, Bains MS, Rizk NP, Kris MG, Rusch VW. Comprehensive long-term care of patients with lung cancer: development of a novel thoracic survivorship program. Ann Thorac Surg. 2014; 98(3):955–61. [PubMed: 25087931]
46. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. Lung Cancer. 2013; 81(1):11–26. [PubMed: 23562675]
47. Felip E, Rosell R, Maestre JA, Rodriguez-Paniagua JM, Moran T, Astudillo J, Alonso G, Borro JM, Gonzalez-Larriba JL, Torres A, Camps C, Guijarro R, Isla D, Aguilo R, Alberola V, Padilla J, Sanchez-Palencia A, Sanchez JJ, Hermosilla E, Massuti B. G. Spanish Lung Cancer. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol. 2010; 28(19):3138–45. [PubMed: 20516435]
48. Stiles BM, Poon A, Giambrone GP, Gaber-Baylis LK, Wu X, Lee PC, Port JL, Paul S, Bhat AU, Zabih R, Altorki NK, Fleischut PM. Incidence and Factors Associated With Hospital Readmission After Pulmonary Lobectomy. Ann Thorac Surg. 2016; 101(2):434–42. diacussion 442–3. [PubMed: 26718860]

Highlights

- 33.8% of stage I-III NSCLC patients developed postoperative recurrence at 5 years.
- 79.5% of patients with locoregional recurrence received active cancer treatment.
- 77.3% of patients with distant recurrence received active cancer treatment.
- Older patients, independent of comorbidity, were less likely to receive treatment.
- Women and those with substance abuse were also less likely to receive treatment.

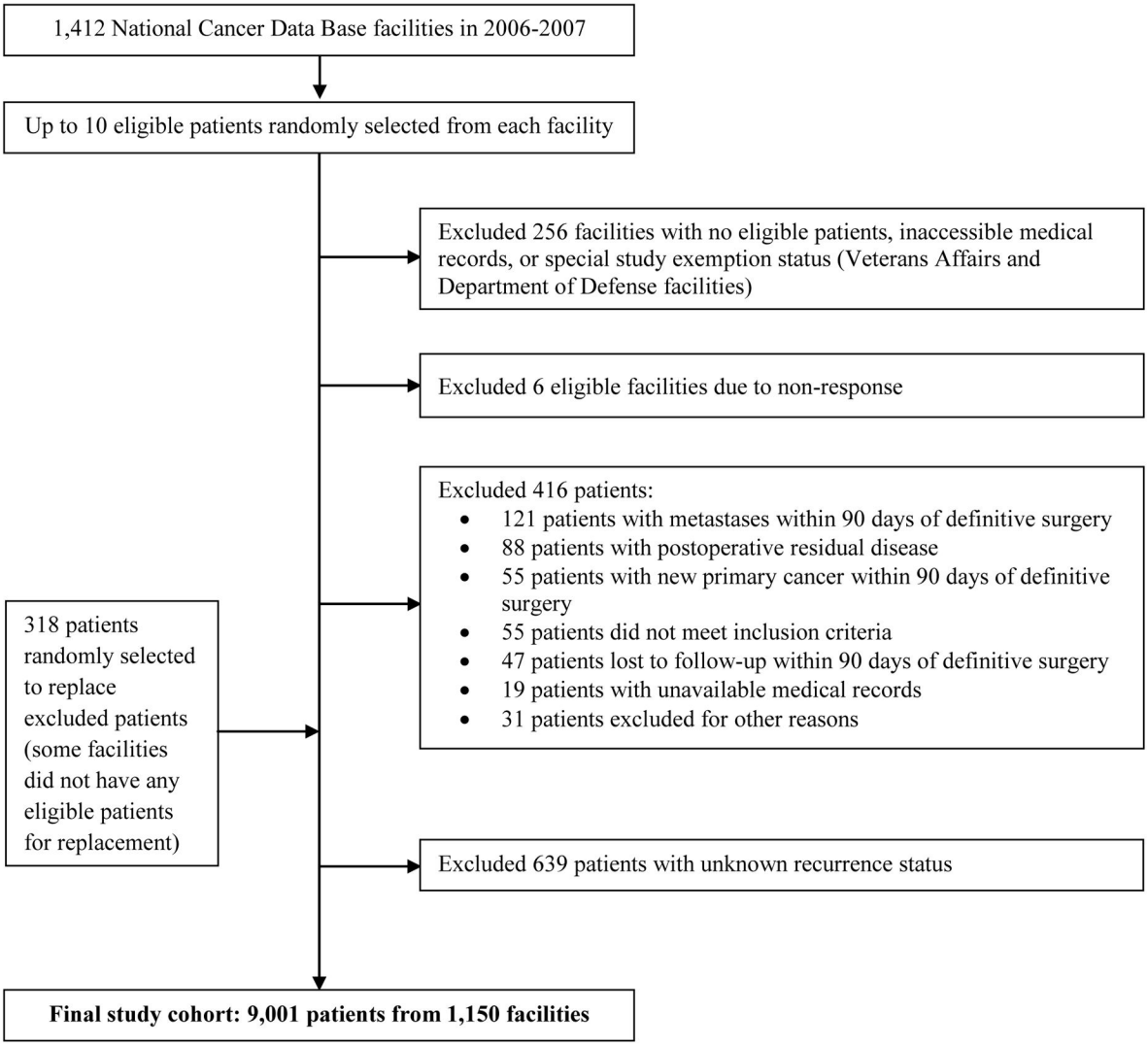

Figure 1.
Non-small cell lung cancer National Cancer Data Base study flow chart.

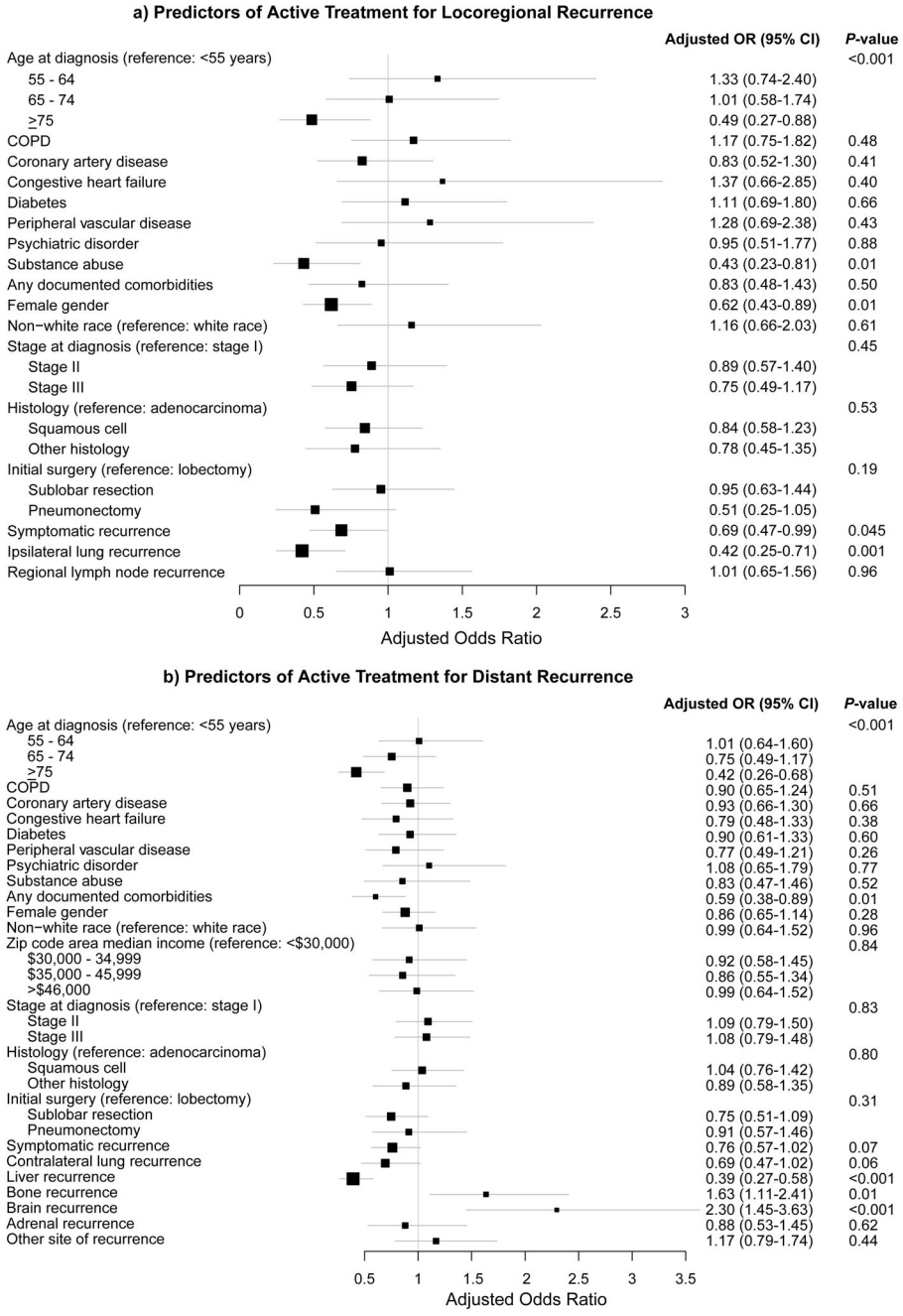

Figure 2.

Multivariable generalized estimating equation logistic regression models of predictors of active treatment versus supportive care only for a) locoregional recurrence and b) distant recurrence.

Model C-statistic for locoregional recurrence is 0.78.

Model C-statistic for distant recurrence is 0.75.

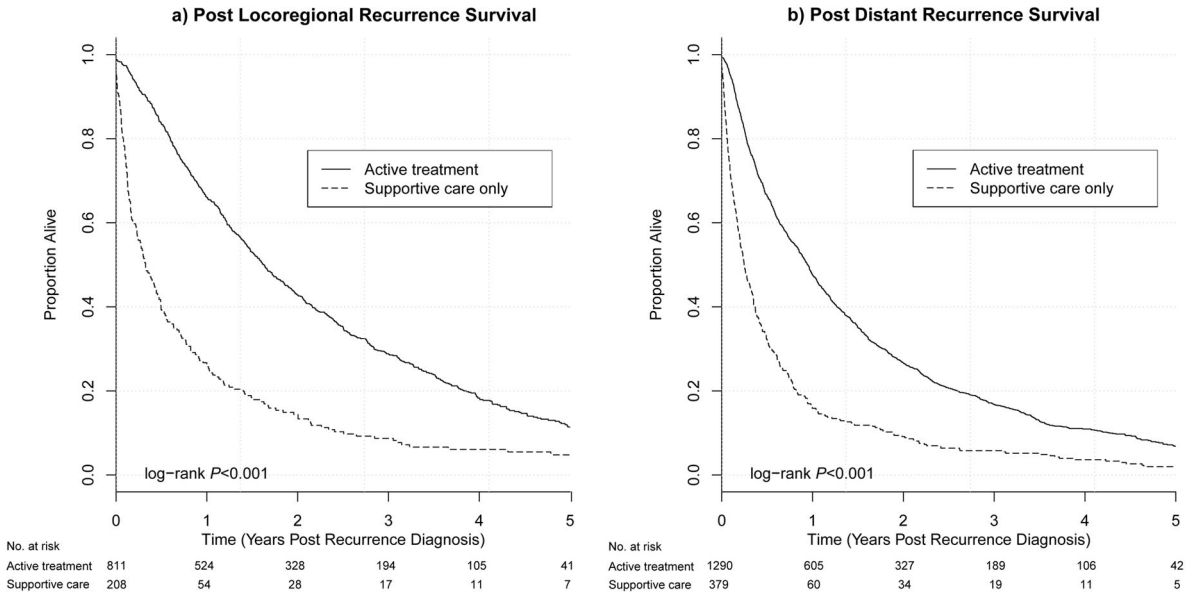

Figure 3.

Kaplan-Meier post-recurrence survival curves for non-small cell lung cancer patients with a) locoregional recurrence and b) distant recurrence by type of treatment received.

Table 1

Demographic and clinical characteristics (N = 9,001).

Characteristic	No Recurrence (n = 5,958, 66.2%) n (%)	Locoregional Recurrence (n = 1,110, 12.3%) n (%)	Distant Recurrence (n = 1,933, 21.5%) n (%)	*P*-value
Age at diagnosis, years				0.06
<55	787 (13.2)	154 (13.9)	310 (16.0)	
55 – 64	1,569 (26.3)	274 (24.7)	500 (25.9)	
65 – 74	2,235 (37.5)	409 (36.8)	698 (36.1)	
≥75	1,367 (22.9)	273 (24.6)	425 (22.0)	
Comorbidities				
COPD	2,449 (41.1)	476 (42.9)	761 (39.4)	0.15
Coronary artery disease	1,246 (20.9)	243 (21.9)	398 (20.6)	0.69
Diabetes	966 (16.2)	176 (15.9)	264 (13.7)	0.03
Peripheral vascular disease	522 (8.8)	95 (8.6)	148 (7.7)	0.32
Psychiatric disorder	475 (8.0)	86 (7.7)	145 (7.5)	0.79
Congestive heart failure	335 (5.6)	71 (6.4)	114 (5.9)	0.58
Substance abuse	325 (5.5)	63 (5.7)	109 (5.6)	0.93
Any documented comorbidities	4,168 (70.0)	783 (70.5)	1,325 (68.5)	0.41
Gender				0.08
Male	2,851 (47.9)	553 (49.8)	979 (50.6)	
Female	3,106 (52.1)	557 (50.2)	954 (49.4)	
Race				0.53
White	5,266 (88.4)	970 (87.4)	1,701 (88.0)	
Black	495 (8.3)	100 (9.0)	169 (8.7)	
Asian/Pacific Islander	123 (2.1)	29 (2.6)	47 (2.4)	
Other	74 (1.2)	11 (1.0)	16 (0.8)	
Zip code area education (% of adults who did not graduate from high school)				0.12
<14%	1,873 (32.6)	332 (31.7)	597 (32.6)	
14 – 19.9%	1,594 (27.7)	266 (25.4)	468 (25.6)	
20 – 28.9%	1,358 (23.6)	249 (23.8)	458 (25.0)	
≥29%	922 (16.0)	201 (19.2)	306 (16.7)	
Zip code area median household income				0.49
<$30,000	724 (12.6)	147 (14.0)	261 (14.3)	
$30,000 – 34,999	1,117 (19.4)	204 (19.5)	349 (19.1)	
$35,000 – 45,999	1,700 (29.6)	317 (30.2)	525 (28.7)	
>$46,000	2,206 (38.4)	380 (36.3)	694 (37.9)	
Urban	5,573 (97.6)	1,011 (96.7)	1,773 (98.0)	0.09
Insured	5,740 (97.7)	1,076 (98.2)	1,860 (97.1)	0.18
Stage at diagnosis				<0.001
Stage I	4,477 (75.1)	638 (57.5)	940 (48.6)	
Stage II	877 (14.7)	265 (23.9)	497 (25.7)	

Characteristic	No Recurrence (n = 5,958, 66.2%) n (%)	Locoregional Recurrence (n = 1,110, 12.3%) n (%)	Distant Recurrence (n = 1,933, 21.5%) n (%)	*P*-value
Stage III	604 (10.1)	207 (18.6)	496 (25.7)	
Histology				<0.001
Adenocarcinoma	3,277 (55.0)	636 (57.3)	1,229 (63.6)	
Squamous cell	1,925 (32.3)	343 (30.9)	452 (23.4)	
Other	756 (12.7)	131 (11.8)	252 (13.0)	
Initial surgery				<0.001
Lobectomy	4,802 (80.6)	833 (75.0)	1,520 (78.6)	
Wedge	688 (11.5)	182 (16.4)	174 (9.0)	
Pneumonectomy	307 (5.2)	58 (5.2)	182 (9.4)	
Segmentectomy	144 (2.4)	35 (3.2)	48 (2.5)	
Resection of lung, NOS	17 (0.3)	2 (0.2)	9 (0.5)	

Abbreviations: COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified.

Table 2

Characteristics of patients with locoregional recurrence by type of treatment received (n = 1,022 patients[*]).

Characteristic[†]	Active treatment[‡] (n = 812, 79.5%) n (%)	Supportive care only (n = 210, 20.5%) n (%)	*P*-value
Active treatment type			
Chemotherapy	290 (35.7)	--	
Chemotherapy and radiation	253 (31.2)	--	
Radiation	165 (20.3)	--	
Any surgery	104 (12.8)	--	
Age at diagnosis, years			<0.001
<55	112 (13.8)	27 (12.9)	
55 – 64	218 (26.8)	38 (18.1)	
65 – 74	317 (39.0)	65 (31.0)	
≥75	165 (20.3)	80 (38.1)	
Comorbidities			
COPD	358 (44.1)	89 (42.4)	0.71
Coronary artery disease	178 (21.9)	51 (24.3)	0.52
Diabetes	129 (15.9)	33 (15.7)	1.00
Peripheral vascular disease	70 (8.6)	19 (9.0)	0.95
Psychiatric disorder	64 (7.9)	18 (8.6)	0.85
Congestive heart failure	50 (6.2)	15 (7.1)	0.72
Substance abuse	41 (5.0)	21 (10.0)	0.01
Any documented comorbidities	566 (69.7)	157 (74.8)	0.18
Gender			0.08
Male	417 (51.4)	93 (44.3)	
Female	395 (48.6)	117 (55.7)	
Race			0.20
White	706 (86.9)	190 (90.5)	
Non-white	106 (13.1)	20 (9.5)	
Stage at diagnosis			0.47
Stage I	473 (58.3)	116 (55.2)	
Stage II	195 (24.0)	49 (23.3)	
Stage III	144 (17.7)	45 (21.4)	
Histology			0.40
Adenocarcinoma	474 (58.4)	112 (53.3)	
Squamous cell	246 (30.3)	73 (34.8)	
Other	92 (11.3)	25 (11.9)	
Initial surgery			0.17
Lobectomy	622 (76.6)	152 (72.4)	
Sublobar resection[§]	153 (18.8)	42 (20.0)	
Pneumonectomy	37 (4.6)	16 (7.6)	
Symptomatic recurrence	237 (31.0)	80 (41.5)	0.01
Recurrence site[//]			

Characteristic†	Active treatment‡ (n = 812, 79.5%) n (%)	Supportive care only (n = 210, 20.5%) n (%)	*P*-value
Ipsilateral lung	525 (67.2)	170 (83.7)	<0.001
Regional lymph node	389 (49.8)	82 (40.4)	0.02

Abbreviations: COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified.

*88 patients with locoregional recurrence were excluded from Table 2 due to missing treatment information.

†There were no differences in zip code area education, zip code area median household income, urban status, or insurance status between patients who received active treatment and those who did not.

‡Active treatment includes chemotherapy, radiation, and/or surgery.

§Sublobar resection includes wedge resection, segmentectomy, and resection of lung NOS.

//182 patients had both ipsilateral lung and regional lymph node recurrence (133 patients in the active treatment group versus 49 patients in the supportive care only group).

Table 3

Characteristics of patients with distant recurrence by type of treatment received (n = 1,675 patients [*]).

Characteristic[†]	Active treatment[‡] (n = 1,294, 77.3%) n (%)	Supportive care only (n = 381, 22.7%) n (%)	*P*-value
Active treatment type			
Chemotherapy	388 (30.0)	--	
Chemotherapy and radiation	213 (16.5)	--	
Radiation	512 (39.6)	--	
Any surgery	181 (14.0)	--	
Age at diagnosis, years			<0.001
<55	229 (17.7)	44 (11.5)	
55 – 64	366 (28.3)	75 (19.7)	
65 – 74	458 (35.4)	139 (36.5)	
≥75	241 (18.6)	123 (32.3)	
Comorbidities			
COPD	500 (38.6)	179 (47.0)	0.004
Coronary artery disease	243 (18.8)	103 (27.0)	<0.001
Diabetes	168 (13.0)	69 (18.1)	0.01
Peripheral vascular disease	94 (7.3)	35 (9.2)	0.26
Psychiatric disorder	98 (7.6)	33 (8.7)	0.56
Congestive heart failure	66 (5.1)	34 (8.9)	0.01
Substance abuse	70 (5.4)	21 (5.5)	1.00
Any documented comorbidities	850 (65.7)	298 (78.2)	<0.001
Gender			0.89
Male	656 (50.7)	191 (50.1)	
Female	638 (49.3)	190 (49.9)	
Race			
White	1,138 (87.9)	335 (87.9)	1.00
Non-white	156 (12.1)	46 (12.1)	
Stage at diagnosis			0.03
Stage I	585 (45.2)	201 (52.8)	
Stage II	354 (27.4)	93 (24.4)	
Stage III	355 (27.4)	87 (22.8)	
Histology			0.34
Adenocarcinoma	838 (64.8)	231 (60.6)	
Squamous cell	293 (22.6)	96 (25.2)	
Other	163 (12.6)	54 (14.2)	
Initial surgery			0.07
Lobectomy	1,028 (79.4)	287 (75.3)	
Sublobar resection[§]	143 (11.1)	59 (15.5)	
Pneumonectomy	123 (9.5)	35 (9.2)	
Symptomatic recurrence	679 (55.8)	190 (52.3)	0.26

Characteristic[†]	Active treatment[‡] (n = 1,294, 77.3%) n (%)	Supportive care only (n = 381, 22.7%) n (%)	*P*-value
Recurrence site[//]			
Brain	438 (33.8)	63 (16.5)	<0.001
Bone	364 (28.1)	86 (22.6)	0.04
Contralateral lung	262 (20.3)	118 (31.1)	<0.001
Liver	146 (11.3)	92 (24.1)	<0.001
Adrenal	92 (7.1)	30 (7.9)	0.69
Other	229 (17.7)	68 (17.8)	1.00

Abbreviations: COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified.

[*]258 patients with distant recurrence were excluded from Table 3 due to missing treatment information.

[†]There were no differences in zip code area education, zip code area median household income, urban status, or insurance status between patients who received active treatment and those who did not.

[‡]Active treatment includes chemotherapy, radiation, and/or surgery.

[§]Sublobar resection includes wedge resection, segmentectomy, and resection of lung NOS.

[//]254 patients had more than one site of recurrence (197 patients in the active treatment group versus 57 patients in the supportive care only group, *P*=0.96).