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

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## 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  $\geq 1$  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  $\geq 75$  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  $\geq 75$  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  $\geq 75$  (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  $\geq 75$  (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.

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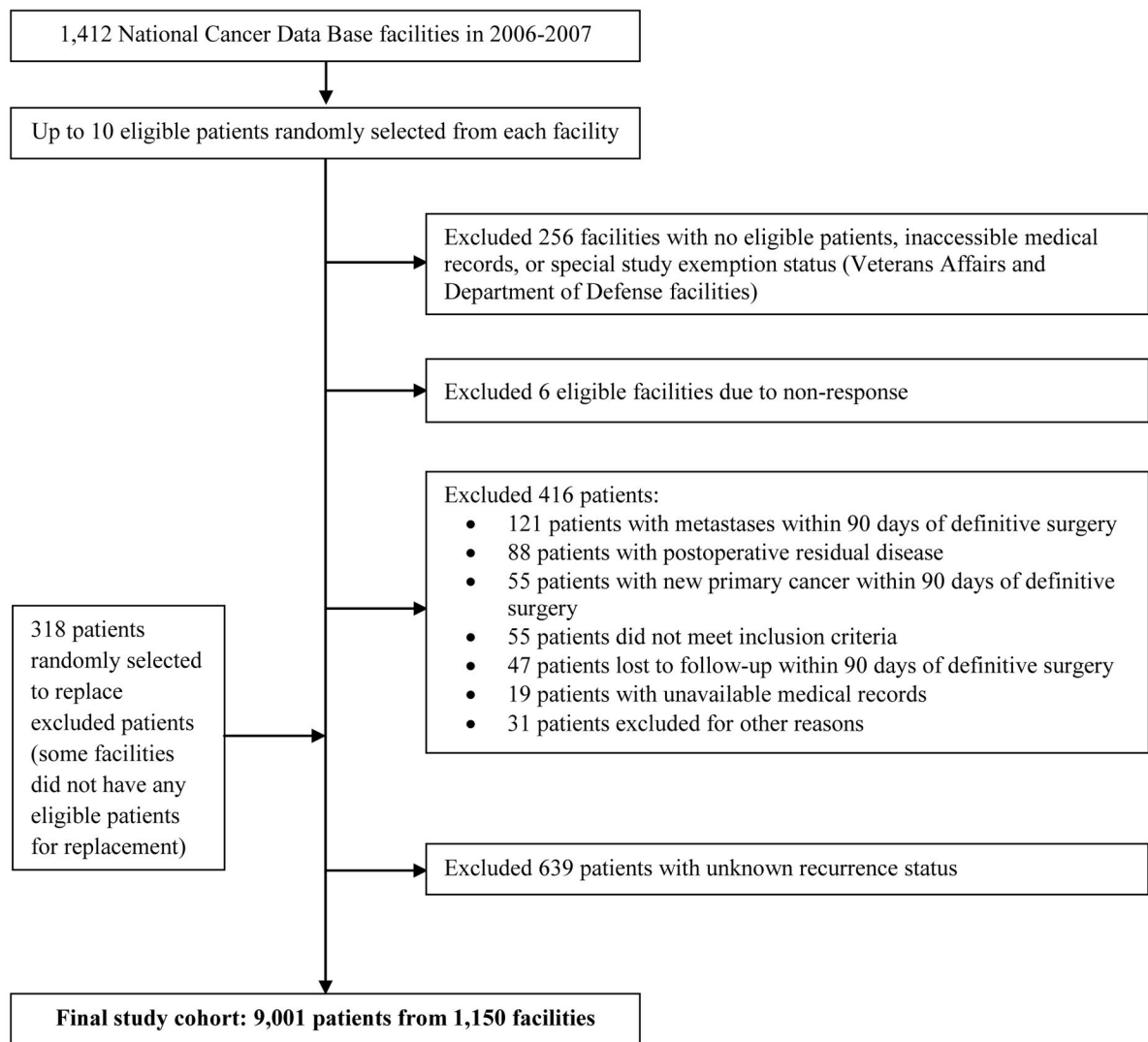
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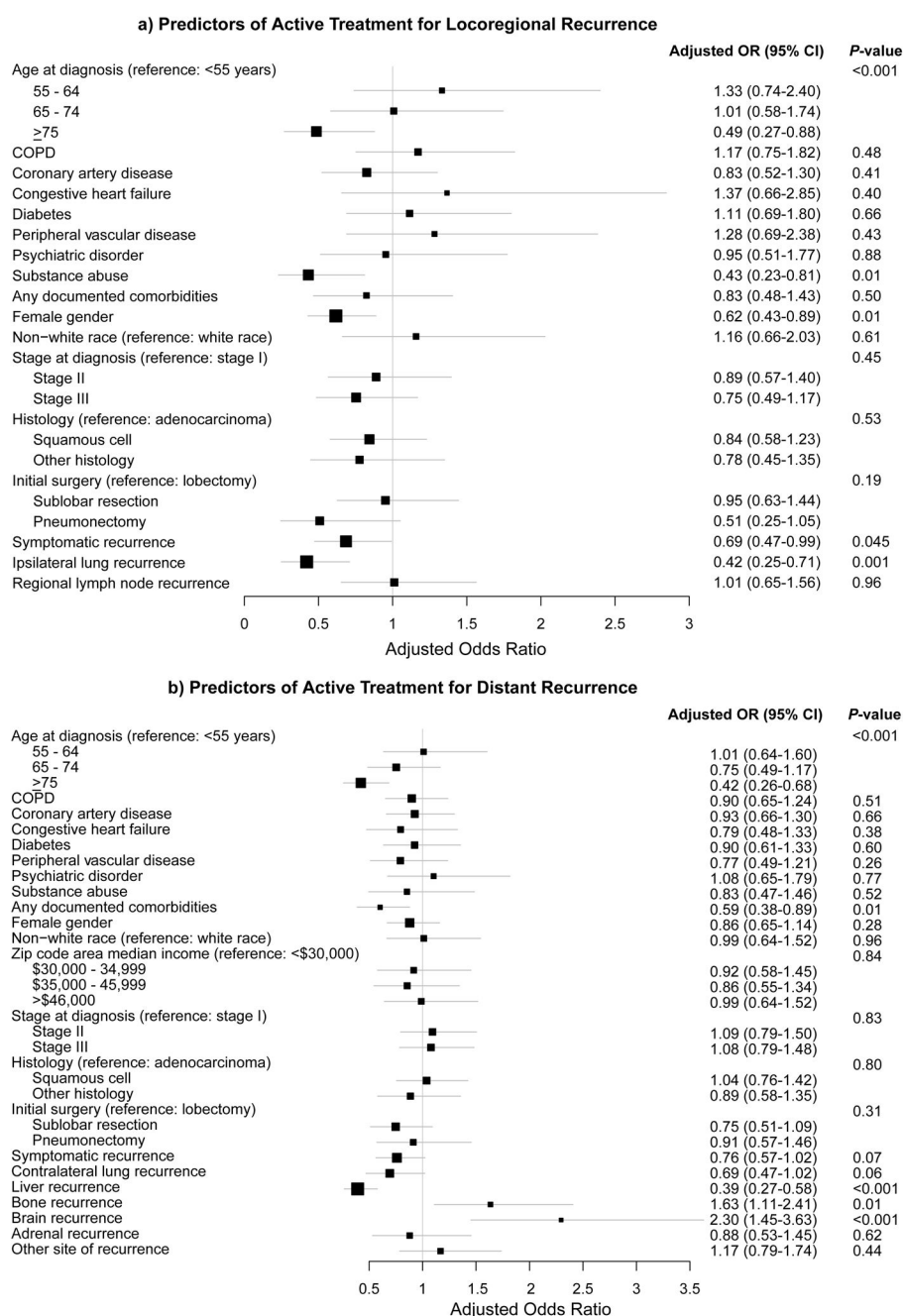
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**Highlights**

- 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.



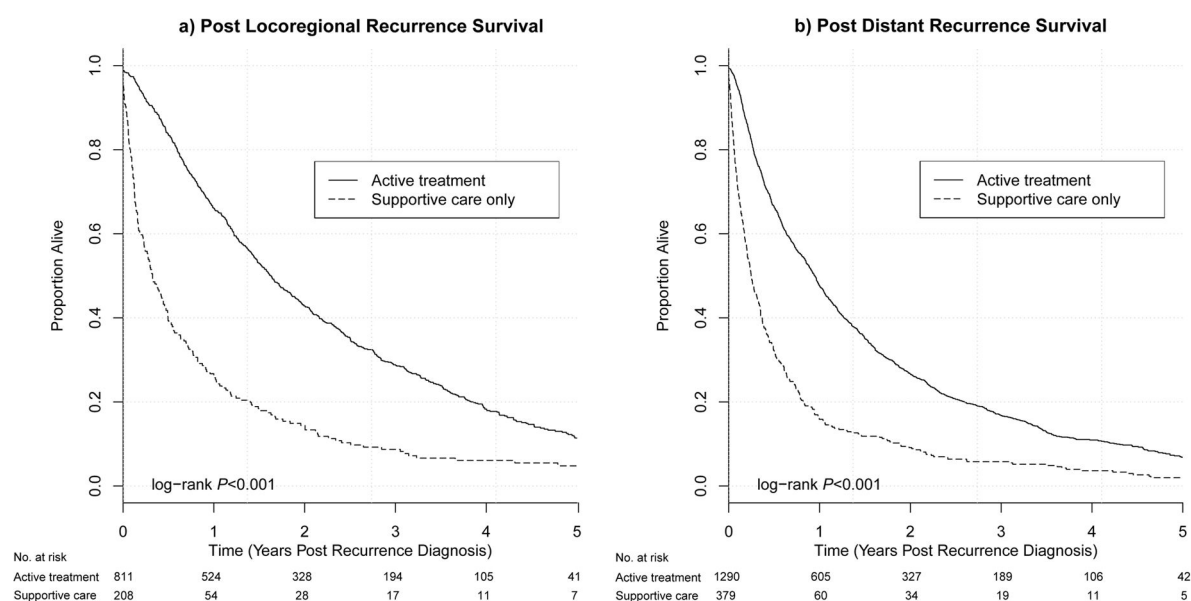
**Figure 1.**  
Non-small cell lung cancer National Cancer Data Base study flow chart.

**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)                                  | <0.001  |
| Histology              |                                        |                                                  |                                             |         |
| 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)                                  | <0.001  |
| Initial surgery        |                                        |                                                  |                                             |         |
| 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<sup>\*</sup>).

| Characteristic <sup>†</sup>     | Active treatment <sup>‡</sup> (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 <sup>§</sup> | 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 <sup>  </sup>   |                                                      |                                             |         |

| Characteristic <sup>†</sup> | Active treatment <sup>‡</sup> (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.

<sup>†</sup> 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.

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

<sup>§</sup> 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 <sup>†</sup>     | Active treatment <sup>‡</sup> (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 <sup>§</sup> | 143 (11.1)                                             | 59 (15.5)                                   |         |
| Pneumonectomy                   | 123 (9.5)                                              | 35 (9.2)                                    |         |
| Symptomatic recurrence          | 679 (55.8)                                             | 190 (52.3)                                  | 0.26    |

| Characteristic <sup>†</sup>   | Active treatment <sup>‡</sup> (n = 1,294, 77.3%) n (%) | Supportive care only (n = 381, 22.7%) n (%) | P-value |
|-------------------------------|--------------------------------------------------------|---------------------------------------------|---------|
| Recurrence site <sup>//</sup> |                                                        |                                             |         |
| 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.

<sup>†</sup> 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.

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

<sup>§</sup> Sublobar resection includes wedge resection, segmentectomy, and resection of lung NOS.

<sup>//</sup> 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,  $P=0.96$ ).