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Treatment Toxicity in Elderly Patients with Advanced Non-Small Cell Lung Cancer

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Abstract

Objectives—Toxicity is a main concern limiting the use of chemotherapy and radiotherapy (RT) for elderly patients with non-small cell lung cancer (NSCLC). The objective of this study was to assess the rates of treatment-related toxicity among elderly stage IIIB and IV NSCLC patients.

Materials and Methods—We used the Surveillance, Epidemiology and End Results registry linked to Medicare records to identify 2,596 stage IIIB and 14,803 stage IV NSCLC patients ≥70 years of age, diagnosed in 2000 or later. We compared rates of toxicity requiring hospitalization according to treatment (chemotherapy, RT, or chemoradiation [CRT]) in unadjusted and adjusted models controlling for selection bias using propensity scores.

Results—Among stage IIIB patients, rates of any severe toxicity were 10.1%, 23.8%, 30.4%, and 39.2% for patients who received no treatment, RT, chemotherapy alone, and CRT, respectively. In stage IV patients, rates of any severe toxicity were 31.5 % vs. 13.5% among those treated with and without chemotherapy, respectively. In stage IIIB patients treated with CRT, the most common toxicities was esophagitis (odds ratio [OR]:48.5, 95% confidence interval [CI]:6.7–350.5). Among stage IV patients treated with chemotherapy, the risk of toxicity was highest for neutropenia (OR: 8.4, 95% CI: 6.1–11.5).

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Conclusion—Toxicity was relatively common among stage IIIB patients with up to a 6 fold increase in elderly individuals treated with CRT and a 4 fold increase in toxicities among stage IV patients. This information should be helpful to guide discussions about the risk-benefit ratio of chemotherapy and RT in elderly patients with advanced NSCLC.

Keywords

non-small cell lung cancer; chemotherapy; radiotherapy; toxicity; outcomes research

Introduction

Non-small cell lung cancer (NSCLC) predominantly affects elderly individuals and is the leading cause of cancer-related mortality in this age group [1]. Despite this high prevalence, elderly patients are underrepresented in lung cancer clinical trials, particularly those evaluating chemotherapy, radiotherapy (RT), or their combination for advanced disease [2–3]. Limited life expectancy, comorbidities, and a unique physiology limit the generalizability of results from randomized controlled trials (RCTs) of younger adults, which create challenges when attempting to use evidence-based data to guide treatment decisions for older patients. These uncertainties contribute to undertreatment and subsequently, worse NSCLC outcomes in the elderly [5–7].

A main concern limiting the use of chemotherapy and RT for elderly patients with NSCLC is the occurrence of treatment-associated toxicity, possibly due to age-associated organ function decline [8–10]. Although data from some phase III RCTs suggests that elderly NSCLC patients benefit and can tolerate these treatments, there is limited evidence regarding toxicities among community elders, the majority of whom do not fulfill the strict inclusion criteria for these trials.

In this study, we used population-based cancer data to examine the rates and predictors of severe toxicities associated with different treatment modalities in elderly patients with stage IIIB and IV NSCLC.

Methods

The study was conducted using data from the Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare claims. SEER collects detailed cancer information from 20 regional registries, and has been linked to Medicare enrollment and claims data [11–12].

From the registry, we identified all patients ≥70 years with primary cases of histologically confirmed, unresected Stage IIIB or IV NSCLC, diagnosed between 2000 and 2007 to limit the analyses to more recent treatment regimens. We limited the cohort to those Medicare patients with both Parts A (inpatient) and B (outpatient) coverage, and excluded patients participating in a health maintenance organization, as Medicare does not collect claims for these individuals. We further excluded patients who received hospice or were in a nursing home within 30 days of diagnosis, as they would be unlikely candidates for treatment with chemotherapy or RT due to poor functional status.

Sociodemographic information (age, sex, race, ethnicity, and marital status) was obtained from SEER. Socioeconomic status was estimated based on the median income for the census tract of the zip code of the patient's residence. We estimated comorbidity burden using the Deyo adaptation of the Charlson comorbidity index applying lung cancer-specific weights [13–14]. We used Medicare data to identify patients with claims for home services that are restricted to homebound individuals [15]. Thus, these claims may be used as a proxy for poor functional status.

We used Medicare claims to determine the diagnostic and staging work-up of patients including the use of positron emission tomography and mediastinoscopy. Tumor characteristics were determined using information in SEER; cancers were classified as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, or other histological type. NSCLCs were staged according to the seventh edition of the American Joint Committee on Cancer Staging Manual [16].

Patients were coded as having received chemotherapy if there were Medicare inpatient, outpatient, or physician claims for chemotherapy within 4 months of diagnosis [17]. Use of RT was determined by a combination of SEER and Medicare claims, a method that has been previously validated [18]. We grouped stage IIIB NSCLC patients into four treatment categories: RT alone, chemotherapy alone, chemoradiotherapy (CRT), and those who were untreated. Stage IV NSCLC patients were categorized as treated with chemotherapy or no chemotherapy.

The outcome of the study was treatment-related toxicity, defined as harm resulting in hospitalization. This criterion has been previously validated using SEER-Medicare data to ascertain chemotherapy toxicity [19]. We studied the time period between 2 and 6 months following the date of diagnosis, as it enabled a comparison of rates of hospitalizations across all groups. We evaluated the following serious adverse events: 1) infection; 2) neutropenia; 3) thrombocytopenia; 4) anemia or red blood cells transfusion; 5) nausea, emesis, or diarrhea; 6) dehydration or electrolyte abnormality; 7) fever; 8) renal failure; 9) esophagitis; and 10) pneumonitis. These were identified using a combination of International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes and Diagnostic Related Group codes contained in the Medicare Provider Analysis and Review File.

Statistical Analysis

We compared the baseline characteristics of patients with stage IIIB NSCLC who received no treatment, RT alone, chemotherapy alone, and CRT and of stage IV NSCLC who received no chemotherapy and those who received chemotherapy with the chi-square test.

The unadjusted rates of toxicities of each treatment modality were calculated for stage IIIB and IV patients. We estimated the odds of toxicity with 95% confidence intervals (CI) in each treatment group as compared with untreated stage IIIB or IV patients, as appropriate. The decision to withhold treatment may be determined, in part, by the risk of toxicity. Thus, we used propensity scores to reduce potential selection bias in treatment utilization. We

estimated each patient's propensity score for RT, chemotherapy, or CRT compared to no treatment using logistic regression [20]. The propensity score models included information about patients' characteristics such as sociodemographics, use of home services, comorbidities, tumor characteristics, and diagnostic work-up data. We used multiple regression analysis to evaluate whether these characteristics were balanced across study groups after adjusting for propensity scores. Then, we calculated odds ratios (OR) for severe toxicity for patients in each treatment group compared to no treatment controlling for propensity scores.

We identified predictors of toxicity for stage IIIB and IV patients using logistic regression. Variables in the logistic regression model included sociodemographic characteristics, tumor characteristics, comorbidity burden, and type of treatment received. Analyses were performed with SAS statistical software (SAS Institute, Cary, NC, USA) using two sided p-values. The study was considered exempt by the Mount Sinai Medical Center Institutional Review Board (#07-0091).

Results

Of the 2,596 unresected stage IIIB NSCLC patients, 24% received no treatment, 23% underwent RT alone, 18% received chemotherapy alone, and 36% were treated with CRT (Table Ia). Overall, 45% of the 14,803 stage IV NSCLC patients were treated with chemotherapy (Table Ib). For both stages, patients who did not receive treatment were more likely to be older, non-white, unmarried, with low neighborhood income, and with a higher burden of comorbidity ($p<0.05$ for all comparisons).

Among stage IIIB patients, rates of any severe toxicity were 10.1%, 23.8%, 30.4%, and 39.2% for patients who received no treatment, RT, chemotherapy alone, and CRT, respectively (Table II). Unadjusted analyses showed that patients who received RT alone (OR:2.8, 95% CI:2.0–3.8); chemotherapy alone (OR:3.9, 95% CI:2.8–5.4), and CRT (OR: 5.7, 95% CI:4.3–7.7) had increased odds of experiencing at least one toxicity (Table III). Among patients who were treated with RT alone, there were higher odds of experiencing hospitalization due to abnormal electrolytes or dehydration (OR:3.4, 95%: CI 2.1–5.4), infection (OR:3.3, 95% CI:1.6–6.9), and anemia or transfusion (OR:3.0, 95% CI:1.9–4.8). All other toxicities were not significantly increased. Compared to patients who did not receive any treatment, chemotherapy-treated patients had increased odds of all toxicities except renal failure and esophagitis. The toxicities associated with the highest odds were neutropenia (OR: 17.1, 95% CI: 4.0–72.6) and nausea/diarrhea (OR: 3.9, 95% CI: 1.4–10.8). Individuals treated with CRT had increased odds of all toxicities compared to untreated patients. In these patients, the toxicities associated with the highest odds were esophagitis (OR:48.5, 95% CI:6.7–350.5) and neutropenia (OR:22.7, 95% CI:5.5–92.9). Similar results were obtained in propensity score-adjusted (Table III).

Rates of any severe toxicity among elderly stage IV patients were 31.5% vs. 13.5% among those treated with vs. without chemotherapy, respectively (OR: 3.0, 95% CI:2.7–3.2; Table II). In unadjusted analyses, patients treated with chemotherapy had higher odds of experiencing all toxicities; the risks were highest for neutropenia (OR: 8.4, 95% CI:616–

11.5) and non-specific adverse events (OR:7.0, 95% CI; 3.9–12.6) (Table III). These findings were confirmed in adjusted analyses (Table III) in which the background rates of toxicities of patients who were not treated were the reference group to calculate the incremental toxicity rate.

Our analysis of predictors of toxicity showed that among stage IIIB NSCLC patients, those of 75–79 years of age (OR:1.0, 95% CI:0.8–1.3) and those >80 years (OR:1.1, 95% CI:0.9–1.4) were not more likely to have at least one severe toxicity compared to patients 70–74 years of age (Table IV). Black patients (OR:1.7, 95% CI:1.2–2.3) had increased risk of toxicity compared to Whites; no significant differences were observed among other ethnic/racial groups among stage IIIB patients. Treatment with RT (OR:2.8, 95% CI:2.0–3.9), chemotherapy (OR:4.0, 95% CI:2.9–5.6), and CRT (OR:6.0, 95% CI:4.4–8.1) were associated with increased risk of toxicity. All other factors were not significantly associated with risk of toxicity. In our analysis of predictors of severe toxicity among stage IV NSCLC patients, Black race was associated with an increased odds of toxicity (OR:1.4, 95% CI:1.2–1.7) as was Other race (OR:1.3, 95% CI:1.1–1.5; Table V). Patients with a comorbidity score 1–2 (OR:1.2, 95% CI:1.1–1.3) and score >2 (OR:1.2, 95% CI:1.1–1.4) was associated with increased odds of experiencing any severe toxicity compared to those with a comorbidity score <1. Compared to patients with adenocarcinomas, squamous cell histology (OR:1.1, 95% CI:0.9.–1.2) was associated with increased toxicity risk. Treatment with chemotherapy was associated with an increased odds of toxicity (OR:3.1, 95% CI:28–3.4). All other factors were not significantly associated with risk of toxicity.

Discussion

Despite frequent physicians concerns about possible adverse events of chemotherapy and RT, there is limited data regarding the incidence and predictors of treatment-related toxicity, particularly among community elders with advanced stage NSCLC. In this study, we described the rates of severe toxicity requiring hospitalization among a large population-based cohort of patients ≥70 years with advanced NSCLC. Among stage IIIB patients, we observed an almost 6 fold increase in the odds of toxicity in the group treated with CRT followed by those treated with chemotherapy (4 fold increase) or RT alone (almost 3 fold increase). Similarly, we found a 3 fold increase in the odds of severe toxicity among stage IV patients who received chemotherapy. This information, as well as rates of specific toxicities, should be helpful informing patients about the potential consequences of different lung cancer treatments and to guide discussions about the risk-benefit ratio of chemotherapy and RT in elderly patients with advanced NSCLC.

Although most RCTs were initially focused on younger adults, there is growing evidence supporting the use of chemotherapy and RT in elderly patients with advanced NSCLC [9, 21–31]. The first RCT specifically focused on older patients (n=191), conducted by the Elderly Lung Cancer Vinorelbine Italian Study Group (ELVIS), found that single-agent chemotherapy, compared to supportive care, offered a survival benefit [26]. Since then, several RCTs involving primarily elderly patients with stage IIIB and IV NSCLC have examined the effectiveness of single and double agent regimens [26–31]. These trials have provided solid evidence that treatment with doublet chemotherapy is associated with the best

outcomes in elderly patients with advanced disease. Additionally, a recent phase III RCT comparing CRT to RT alone found that combined therapy led to longer survival in elderly patients [32]. Overall, these data shows that advanced age alone should not be a contraindication for treating patients with advanced NSCLC.

These RCTs also provide important information about the types and rates of treatment-related toxicity that may be expected in elderly patients. In the Multicenter Italian Lung Cancer in the Elderly Study, a phase III RCT involving 700 elderly patients comparing double to single agent chemotherapy in stage IIIB–IV NSCLC, approximately 20% of patients receiving double regimen experienced grade 3–4 neutropenia; rates of other toxicities was relatively low [30]. Overall, chemotherapy was also well tolerated among patients enrolled in other RCTs specific to elderly lung cancer patients [26–31]. Although physicians may attempt to extrapolate these findings to their patients in the community, most elderly-specific RCTs had strict inclusion and exclusion criteria which limit participation to patients with good performance status, and limited comorbidities. Moreover, these trials were mostly conducted in specialized tertiary centers under strict clinical protocols, factors that may also affect the rates of toxicity. Thus, the generalizability of the toxicity data from these RCTs to elderly lung cancer patients encountered in routine clinical practice is somewhat limited.

A population-based assessment of treatment-related toxicities has been previously performed using SEER-Medicare data [33]. This study included patients with Stage I to IV NSCLC diagnosed between 1991 and 2002 and thus, may not represent the types of toxicity observed among advanced stage patients treated with more modern regimens. The study sample included a large number of patients 65–69 years, a subgroup of patients that is at lower risk for toxicity and that is more likely to be included in RCTs not focused on the elderly. Presence of toxicities was ascertained using outpatient claims rather than being limited to severe toxicity associated to hospitalization. However, this method of ascertainment is not well validated and prior studies suggest that outpatient claims may capture ‘rule-out’ diagnosis rather than only true treatment-related toxicity events[13]. Finally, investigators did not apply advanced methods to reduce potential selection bias in the use of the different cancer treatments evaluated. The findings in our study are a substantial contribution as they provide important information about risk of treatment-related toxicity in elderly patients ≥70 years with advanced disease. Overall, we found that the rates of toxicities in this population-based cohort were higher to those reported in most RCTs [31]. These findings highlight the importance of evaluating toxicity risk among less selected, community elders.

In our examination of predictors of toxicity, we found that increasing age was not a significant risk factor in this cohort of patients ≥70 years of age. While these findings suggest that octogenarians may be as likely as patients age 70–79 years to tolerate chemotherapy and RT, it is also possible that the oldest patients in the cohort were treated with modified regimens or lower doses to reduce the risk of toxicity. Additionally, chemotherapy and RT may have only been administered to the most fit patients in the oldest age group. Thus, the tolerability of these treatments in patients >80 years of age should be further explored.

There are strengths and limitations to our study that should be noted. We conducted a large, population-based study of treatment-related toxicities in a mixed group of community-dwelling elders including many with comorbidities, a factor which increases the external validity of our findings. Moreover, we restricted our analysis to patients ≥70 years of age, a group typically underrepresented in RCTs not focused on the elderly. We were limited however, by the lack of information in SEER-Medicare regarding patients' performance status, as measured by the Karnofsky score, an important determinant of treatment receipt and toxicity risk. We did however attempt to gauge each patient's performance status by using their comorbidities score as well as claims specific to homebound patients. We were also unable to code toxicities according to the World Health Organization grading system with the data available in SEER-Medicare. Thus, we were limited in our ability to directly compare our results to the toxicity rates observed in RCTs. We did however only measure toxicities that caused hospitalization, thus our analyses represent clinically meaningful, severe adverse events. Finally, we did not examine specific chemotherapy regimens, and thus are unable to evaluate which drugs or combination of drugs was more toxic.

In summary, in this study, we quantified the rates of severe toxicity experienced by a large, nationally representative sample of elderly patients with stage IIIB and IV NSCLC. Our study fills an important gap in the evidence base informing the treatment of elderly patients with advanced NSCLC. This information will be an important component of future discussions among patients and their providers as they consider the risks and benefits of treatment.

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Table Ia

Baseline Characteristics According to Treatment of Stage IIIB Non-small Cell Lung Cancer Patients

Characteristic	Untreated (N=624)	RT Alone (N=584)	Chemotherapy Alone (N=461)	Chemotherapy and RT (N=927)	P-value
Age (median, IQR)	77 (8)	78 (8)	75 (6)	75 (6)	<0.0001
Female, N (%)	238 (38.1)	262 (44.9)	207 (44.9)	400 (43.2)	0.06
Married, N (%)	296 (47.4)	301 (51.5)	240 (52.1)	525 (56.6)	0.005
Race/Ethnicity, N (%)					
White	497 (79.7)	489 (83.7)	380 (82.4)	805 (86.8)	0.02
Black	65 (10.4)	53 (9.1)	38 (8.2)	61 (6.6)	
Hispanic	21 (3.4)	22 (3.8)	17 (3.7)	23 (2.5)	
Other	41 (6.6)	20 (3.4)	26 (5.6)	38 (4.1)	
Median Annual Neighborhood Income, N (%)					
First Quartile *	191 (30.6)	157 (26.9)	104 (22.6)	187 (22.5)	0.03
Second Quartile	158 (25.3)	151 (25.9)	117 (25.4)	237 (25.6)	
Third Quartile	144 (23.1)	139 (23.8)	116 (25.2)	236 (25.5)	
Fourth Quartile	131 (21.0)	137 (23.5)	124 (26.9)	245 (26.5)	
Comorbidity Score, N (%)					
<1	257 (41.2)	217 (37.2)	189 (41.0)	409 (44.1)	0.0005
1–2	152 (24.4)	171 (29.3)	132 (28.6)	286 (30.9)	
>2	215 (34.5)	196 (33.6)	140 (30.4)	232 (25.0)	
Histology, N (%)					
Adenocarcinoma	251 (40.2)	176 (30.1)	208 (45.1)	334 (36.0)	<0.0001
Squamous Cell	267 (42.8)	306 (52.4)	170 (36.9)	465 (50.2)	
Large Cell	37 (5.9)	48 (8.2)	32 (6.9)	68 (7.3)	
Other	69 (11.1)	54 (9.3)	51 (11.1)	60 (6.5)	
Tumor Site, N (%)					
Upper	300 (48.1)	325 (55.7)	227 (49.2)	515 (55.6)	0.002
Middle	30 (4.8)	16 (2.7)	23 (5.0)	37 (4.0)	
Lower	137 (22.0)	126 (21.6)	128 (27.8)	199 (21.5)	

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Characteristic	Untreated (N=624)	RT Alone (N=584)	Chemotherapy Alone (N=461)	Chemotherapy and RT (N=927)	P-value
Unknown	157 (25.2)	117 (20.0)	83 (18.0)	176 (19.0)	

RT denotes radiation therapy, IQR denotes interquartile range

* Indicates lowest income quartile

Table Ib

Baseline Characteristics of Stage IV Non-small Cell Lung Cancer Patients According to Treatment Received

Characteristic	Untreated (N=8,169)	Chemotherapy (N=6,634)	P-value
Age (median, IQR)	78 (8)	75 (7)	<0.0001
Female, N (%)	3,689 (45.2)	2,895 (43.6)	0.06
Married, N (%)	3,928 (48.1)	3,967 (59.8)	<0.0001
Race/Ethnicity, N (%)			
White	6,464 (79.1)	5,647 (85.1)	<0.0001
Black	822 (10.1)	437 (6.6)	
Hispanic	341 (4.2)	217 (3.3)	
Other	542 (6.6)	333 (5.0)	
Median Annual Neighborhood Income, N(%)			
First Quartile *	2,281 (27.9)	1,491 (22.5)	<0.0001
Second Quartile	2,022 (24.8)	1,594 (24.1)	
Third Quartile	1,946 (23.8)	1,641 (24.8)	
Fourth Quartile	1,917 (23.5)	1,903 (28.7)	
Comorbidity Score, N (%)			
<1	3,021 (37.0)	3,036 (45.8)	<0.0001
1–2	1,964 (24.0)	1,745 (26.3)	
>2	3,184 (39.0)	1,853 (27.9)	
Histology, N (%)			
Adenocarcinoma	4,459 (54.6)	4,008 (60.4)	<0.0001
Squamous Cell	2,198 (5.7)	1,593 (24.0)	
Large Cell	464 (5.7)	406 (6.1)	
Other	1,048 (12.8)	627 (9.5)	
Tumor Site, N (%)			
Upper	3,358 (41.1)	2,946 (44.4)	<0.0001
Middle	310 (3.8)	257 (3.9)	
Lower	2,050 (25.1)	1,695 (25.6)	
Unknown	2,451 (30.0)	1,736 (26.2)	

* Indicate lowest income quartile

Table II

Unadjusted Rates of Severe Treatment Toxicity in Elderly Patients with Stage IIIB and IV NSCLC

	Stage IIIB					Stage IV		
Type of Toxicity	**Untreated**	**RT Alone**	**Chemotherapy Alone**	**CRT**	**P-value**	**No Chemotherapy**	**Chemotherapy Alone**	**P-value**
Any toxicity, N(%)	63(10.1)	139(23.8)	140(30.4)	363(39.2)	<0.0001	1100(13.5)	2087(31.5)	<0.0001
Infection, N(%)	≤11(≤1.8)*	30(5.1)	31(6.7)	114(12.3)	<0.0001	260(3.2)	523(7.9)	<0.0001
Neutropenia, N(%)	≤11(≤1.8)	≤11(≤1.9)	24(5.2)	63(6.8)	<0.0001	45(0.6)	295(4.5)	<0.0001
Fever, N(%)	≤11(≤1.8)	≤11(≤1.9)	≤11(≤2.4)	21(2.3)	<0.0001	21(0.3)	71(1.2)	<0.0001
Abnormal Electrolytes/Dehydration, N(%)	26(4.2)	75(12.8)	70(15.2)	212(22.9)	<0.0001	626(7.7)	1104(16.6)	<0.0001
Nausea, Emesis or Diarrhea, N(%)	≤11(≤1.8)	≤11(≤1.9)	14(3.0)	26(2.8)	0.01	65(0.8)	202(3.0)	<0.0001
Anemia or Transfusion, N(%)	26(4.2)	67(11.5)	66(14.3)	196(21.1)	<0.0001	409(5.0)	1013(15.3)	<0.0001
Thrombocytopenia, N(%)	≤11(≤1.8)	≤11(≤1.9)	≤11(≤2.4)	30(3.2)	0.0006	45(0.6)	217(3.3)	<0.0001
Renal failure, N(%)	≤11(≤1.8)	≤11(≤1.9)	≤11(≤2.4)	25(2.7)	0.005	128(1.6)	158(2.4)	0.0003
Non-specific adverse events, N(%)	≤11(≤1.8)	≤11(≤1.9)	≤11(≤2.4)	13(≤1.4)	0.0001	13(0.2)	73(1.1)	<0.0001
Radiation Pneumonitis, N(%)	≤11(≤1.8)	13(2.2)	≤11(≤2.4)	37(4.0)	< 0.0001	–	–	–
Esophagitis, N(%)	≤11(≤1.8)	≤11(≤1.9)	≤11(≤2.4)	62(7.2)	<0.0001	–	–	–

RT: radiation therapy; CRT: chemoradiation therapy; CI: confidence interval

*Cells with ≤11 patients not reported to maintain patient confidentiality.

Table III

Relative Odds of Toxicity among Elderly Stage IIIB and IV Non-small Cell Lung Cancer Patients Who Received Chemotherapy or Radiation Compared to Untreated Patients

	Stage IIIB									Stage IV		
	RT Alone			Chemotherapy Alone			CRT			Chemotherapy		
Type of Toxicity	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**	**P value**	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**	**P value**	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**	**P value**	**Unadjusted OR[1] (95% CI)**	**Adjusted OR[1] (95% CI)**	**P value**
Any toxicity	2.8(2.0–3.8)	2.6(1.9–3.7)	<0.0001	3.9(2.8–5.4)	3.9(2.7–5.4)	<0.0001	5.7(4.3–7.7)	5.9(4.3–8.1)	<0.0001	3.0(2.7–3.2)	2.9(2.7–3.2)	<0.001
Infection	3.3(1.6–6.9)	3.2(1.5–6.7)	0.002	4.4(2.1–9.1)	4.0(1.9–8.4)	0.0003	8.6(4.5–16.6)	8.8(4.5–17.4)	<0.0001	2.6(2.2–3.0)	2.6(2.2–3.0)	<0.0001
Neutropenia	2.1(0.4–11.8)	1.8(0.3–10.3)	0.51	17.1(4.0–72.6)	20.6(4.7–89.4)	<0.0001	22.7(5.5–92.9)	23.9(5.7–99.8)	<0.0001	8.4(6.1–11.5)	8.4(6.1–11.7)	<0.0001
Fever	*–[1]*	*–[2]*	–	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	–	4.2(2.6–6.8)	3.2(1.9–5.4)	<0.0001
Abnormal electrolytes or dehydration	3.4(2.1–5.4)	3.1(1.9–4.9)	<0.0001	4.1(2.6–6.6)	4.0(2.5–6.5)	<0.0001	6.8(4.5–10.4)	6.8(4.3–10.5)	<0.0001	2.4(2.2–2.7)	2.5(2.2–2.8)	<0.0001
Nausea, emesis or diarrhea	1.9(0.6–5.8)	1.4(0.4–4.3)	0.57	3.9(1.4–10.8)	3.5(1.2–10.2)	0.02	3.6(1.4–9.4)	2.9(1.1–8.1)	0.04	3.9(3.0–5.2)	3.9(2.9–5.2)	<0.0001
Anemia or transfusion	3.0(1.9–4.8)	3.0(1.9–4.9)	<0.0001	3.8(2.4–6.2)	4.0(2.5–6.6)	<0.0001	6.2(4.0–9.4)	5.9(3.8–9.2)	<0.0001	3.4(3.0–3.9)	3.4(3.0–3.9)	<0.0001
Thrombocytopenia	1.6(0.5–5.7)	2.1(0.6–7.8)	0.27	3.8(1.2–12.0)	3.4(1.0–11.2)	0.04	5.2(1.8–14.8)	5.5(1.8–16.4)	0.002	6.1(4.4–8.4)	5.4(3.9–7.6)	<0.0001
Renal failure	1.6(0.5–5.7)	1.9(0.5–7.2)	0.32	1.4(0.3–5.5)	1.4(0.3–5.8)	0.69	4.3(1.5–12.4)	4.9(1.6–15.0)	0.005	1.5(1.2–1.9)	1.6(1.3–2.1)	0.0002
Non-specific adverse events	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	–	7.0(3.9–12.6)	7.0(3.8–12.9)	<0.0001
Radiation pneumonitis	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	–	*–[2]*	*–[2]*	
Esophagitis	7.6(0.9–61.6)	8.3(1.0–69.7)	0.05	4.1(0.4–39.4)	5.3(0.5–55.2)	0.16	48.5(6.7–350.5)	48.9(6.7–358.0)	0.0001	*–[2]*	*–[2]*	

[1] OR (Odds ratio) compared to untreated stage IIIB or IV patients, as appropriate

RT: radiation therapy; CRT: chemoradiation therapy; CI: confidence interval

[2] Results not reported due to lack of model convergence

Table IV

Predictors of Toxicity among Elderly Stage IIIB Lung Cancer Patients

Predictors	OR(95% CI)	P-value
Age 70–74 75–59 ≥80	Ref 1.0(0.8–1.3) 1.1(0.9–1.4)	Ref 0.88 0.51
Female	0.9(0.7–1.1)	0.25
Married	1.0(0.8–1.2)	0.68
Race White Black Hispanic Other	Ref 1.7(1.2–2.3) 0.8(0.5–1.4) 1.0(0.7–1.6)	Ref 0.003 0.46 0.95
Income Quartile First Quartile Second Quartile Third Quartile Fourth Quartile	Ref 1.1(0.9–1.4) 1.0(0.7–1.3) 1.0(0.8–1.3)	Ref 0.44 0.75 0.92
Comorbidity Score <1 1–2 >2	Ref 1.1(0.9–1.4) 1.1(0.9–1.4)	Ref 0.46 0.30
Histology Adenocarcinoma Squamous Large cell Other	Ref 1.1(0.9–1.4) 1.1(0.8–1.6) 0.8(0.5–1.1)	Ref 0.30 0.49 0.18
Tumor Site Upper Middle Lower Other	Ref 1.3(0.9–2.1) 1.1(0.9–1.4) 0.8(0.7–1.1)	Ref 0.20 0.50 0.19
Treatment Untreated RT Alone Chemotherapy Alone CRT	Ref 2.8(2.0–3.9) 4.0(2.9–5.6) 6.0(4.4–8.1)	Ref <0.0001 <0.0001 <0.0001

OR: odds ratio; RT: radiation therapy; CRT: chemoradiation therapy; CI: confidence interval

Table V

Predictors of Toxicity among Elderly Stage IV Non-small Cell Lung Cancer Patients

Predictors	OR(95% CI)	P-value
Age 70–74 75–59 ≥80	Ref 1.0(0.9–1.1) 1.0(0.9–1.1)	Ref 0.50 0.98
Female	1.0(0.9–1.1)	0.72
Married	1.0(0.9–1.1)	0.47
Race White Black Hispanic Other	Ref 1.4(1.2–1.7) 1.2(0.9–1.4) 1.3(1.1–1.5)	Ref <0.0001 0.15 0.003
Income Quartile First Quartile Second Quartile Third Quartile Fourth Quartile	Ref 1.0(0.9–1.1) 1.1(1.0–1.2) 1.0(0.9–1.2)	Ref 0.81 0.17 0.65
Comorbidity Score <1 1–2 >2	Ref 1.2(1.1–1.3) 1.2(1.1–1.4)	Ref 1.3 1.4
Histology Adenocarcinoma Squamous Large cell Other	Ref 1.2(1.1–1.3) 1.1(0.9–1.2) 1.1(1.0–1.2)	Ref <0.0001 0.77 0.22
Tumor Site Upper Middle Lower Other	Ref 1.0(0.8–1.2) 1.0(0.9–1.1) 0.8(0.8–0.9)	Ref 0.79 0.55 0.0005
Treatment Untreated Chemotherapy Alone	Ref 3.1 (2.8–3.4)	Ref <0.0001

OR: odds ratio; RT: radiation therapy; CRT: chemoradiation therapy; CI: confidence interval