Original Study

Survival Outcomes With Thoracic Radiotherapy in Extensive-Stage Small-Cell Lung Cancer: A Propensity Score-Matched Analysis of the National Cancer Database

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Abstract

The role of consolidative thoracic radiotherapy is unclear in extensive-stage small-cell lung carcinoma, for which chemotherapy is standard. We aimed to evaluate its effect on survival using a large national database using propensity-matching methods. On the basis of a cohort of >14,000 patients, we found its use in addition to chemotherapy was associated with a significant improvement in survival.

Background: The prognosis of patients with extensive-stage small-cell lung carcinoma (ES-SCLC) is poor. The benefit of consolidative thoracic radiation therapy (TRT) in ES-SCLC has been inconclusive, and its use inconsistent. The objective of this study was to evaluate overall survival (OS) of ES-SCLC patients treated with chemotherapy (CT) with or without TRT using an administrative database approach. **Patients and Methods:** The National Cancer Database was queried to identify patients with ES-SCLC diagnosed between 2010 and 2014. Those with brain metastases, those who received radiotherapy before CT, or radiotherapy outside the thorax, were excluded. Propensity score-matching (PSM) was used to compare OS of patients treated with CT and TRT with those who received CT alone. Patients who received >10 radiotherapy fractions were also compared with those who received 10 or fewer. **Results:** We included 14,367 patients in the primary analysis; 12,019 received CT alone, and 2348 received CT with TRT. In multivariate analysis, CT was associated with an increased risk of death relative to CT with TRT (hazard ratio [HR], 1.74 [95% confidence interval (CI), 1.64-1.84]; log-rank $P < .001$), which remained significant with PSM. Median OS was 12.1 versus 8.2 months (CT with TRT vs. CT); 12-month OS was 50.5% versus 28.5%, and 5-year OS 7.6% versus 2.0% (HR, 1.80 [95% CI, 1.67-1.95], HR $P < .001$). Of 3099 patients who received TRT, >10 radiotherapy fractions was associated with superior OS (HR, 1.70 [95% CI, 1.49-1.95], log-rank $P < .001$); this finding remained significant with PSM. **Conclusion:** Use of TRT after CT in ES-SCLC patients was associated with long-term survival; its use should be considered in addition to standard of care CT.

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Keywords: Chemoradiation, Chemotherapy, Consolidative radiotherapy, Small-cell lung carcinoma, Thoracic radiation therapy

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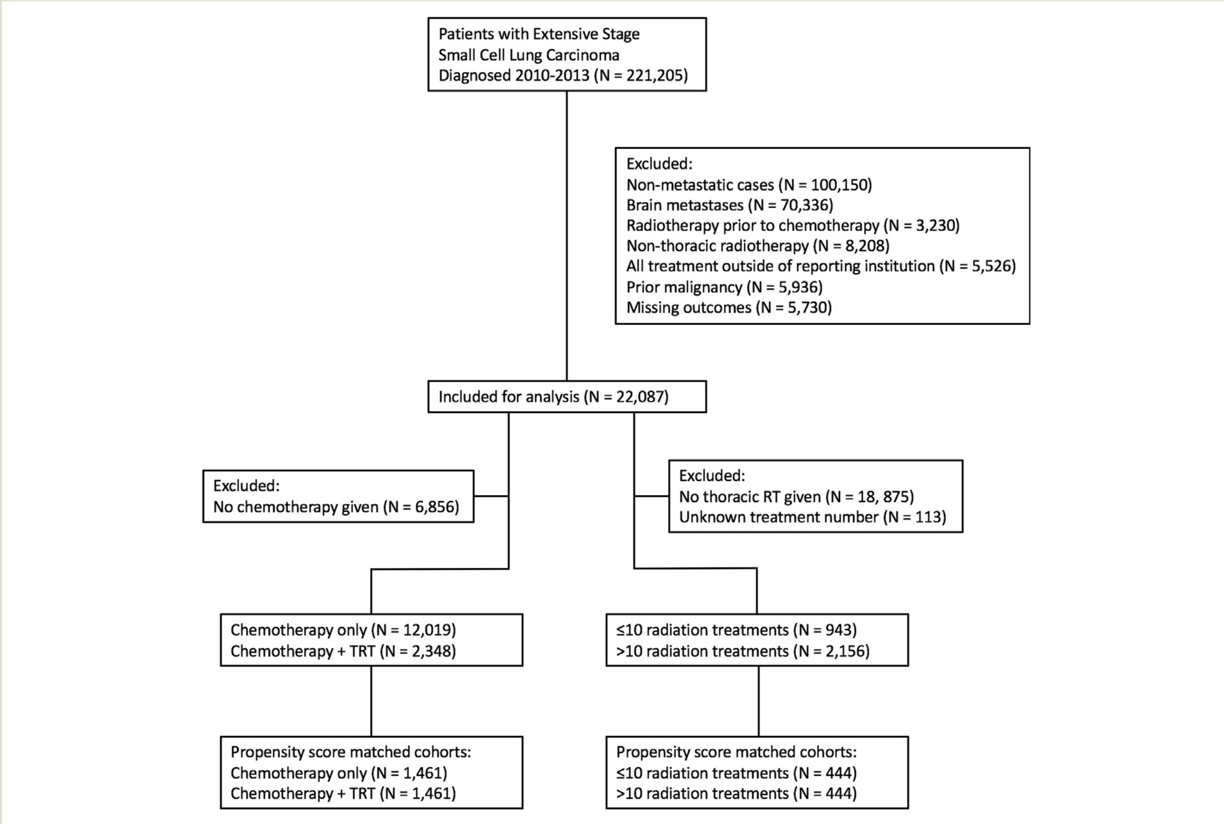
Figure 1 Selection Diagram With Inclusion and Exclusion Criteria Applied for the Chemotherapy and Thoracic Radiotherapy Therapy Cohorts



Abbreviations: RT = radiation therapy; TRT = thoracic radiation therapy.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States, which is estimated to account for approximately 228,150 new cases and 142,670 deaths in 2019. Small-cell lung carcinoma represents approximately 10% to 15% of lung cancer diagnoses; most patients present with extensive-stage disease.[1] The standard of care includes platinum-based chemotherapy (CT) and prophylactic cranial irradiation (PCI) for those who show at least a partial response (PR) to systemic therapy.[2-4]

Despite high initial response rates to CT, prognosis for extensive-stage small-cell lung cancer (ES-SCLC) is poor; median survival ranges from 7 to 12 months, and 2-year survival is 4% to 7%.[5] After upfront CT, approximately 75% have residual intrathoracic disease[6] and up to 90% develop intrathoracic progression with a year. The thorax is the most common site of progression.[7] Chest radiotherapy has been historically reserved for palliative-intent treatment.[8] The role of consolidative thoracic radiation therapy (TRT) was the subject of 2 large randomized trials.[9,10] The CREST (Chest Radiotherapy Extensive Stage Trial) study showed an improvement in 2-year overall survival (OS) with the additional use of thoracic radiation after CT, supporting the Yugoslavian study; the survival benefit was primarily confined to patients with residual thoracic disease after CT.[11] The additional use of TRT and ablative radiotherapy to additional metastatic sites was explored in a randomized phase II study, Radiation Therapy Oncology Group (RTOG) 0937, which showed no survival differences.[12]

For ES-SCLC patients, there is no consensus for offering consolidative chest radiation therapy after CT; its use clinically appears practitioner-dependent.[13-15] The aim of the current study was to evaluate the association between consolidative TRT and survival using population-based data for patients with ES-SCLC.

Patients and Methods

The National Cancer Database (NCDB) is a joint project of the American College of Surgeons and the American Cancer Society, which captures information from approximately 70% of new diagnoses representing more than 1500 Commission on Cancer-accredited program registries.[16] The data and statistical methodology are not verified by the Commission on Cancer or the participating hospitals. Access to deidentified patient data and the corresponding data files was provided to the authors as part of the NCDB Participant Use File program. The current study was exempt from requiring institutional review board approval.

Small-cell lung carcinoma was defined according to the *International Classification of Disease for Oncology*, third edition topography codes C340, C341, C342, C343, C348, and C349 in combination

Table 1 Descriptive Baseline Characteristics for the CT-Only and CT With TRT Cohorts

Characteristic	CT Only (n = 12,019)	CT With TRT (n = 2348)	Parametric *P*
Median Age at Diagnosis (SD)	66 (9.83)	63 (9.55)	**<.001**
Sex			**<.001**
Male	6296 (52.4)	1141 (48.6)	
Female	5723 (47.6)	1207 (51.4)	
Year of Diagnosis			**.013**
2010	2978 (24.8)	581 (24.7)	
2011	2878 (23.9)	620 (26.4)	
2012	3071 (25.6)	607 (25.9)	
2013	3092 (25.7)	540 (23)	
Clinical T Classification			**<.001**
T0-1	1161 (12.2)	189 (9.1)	
T2	2384 (25)	463 (22.4)	
T3	1896 (19.9)	421 (20.4)	
T4	4096 (42.9)	995 (48.1)	
Clinical N Classification			**<.001**
N0	1026 (9.4)	189 (8.5)	
N1	752 (6.9)	125 (5.6)	
N2	6292 (57.7)	1203 (54.2)	
N3	2840 (26)	701 (31.6)	
CT			**<.001**
None	—	—	
Type unknown	399 (3.3)	48 (2)	
Single-agent	470 (3.9)	48 (2)	
Multiagent	11,150 (92.8)	2252 (95.9)	
CT, Median Days From Dx	13	14	.699
Radiation, Median Days From Dx	NA	77	
Median Radiation Dose	NA	45 Gy	
Median Number of Treatments	NA	25	
Charlson-Deyo Score			
0	6273 (52.2)	1343 (57.2)	**<.001**
1	3834 (31.9)	702 (29.9)	
2	1912 (16)	303 (12.9)	
Race			.715
White	10,744 (89.4)	2095 (89.2)	
Black	974 (8.1)	199 (8.5)	
Other/unknown	301 (2.5)	54 (2.3)	
Median Income Quartiles			.235
Unknown	167 (1.4)	25 (1.1)	
<$38,000	2621 (21.8)	536 (22.8)	
$38,000-$47,999	3255 (27.1)	652 (27.8)	
$48,000-$62,999	3122 (26)	619 (26.4)	
≥$63,000	2854 (23.7)	516 (22)	
Primary Payor			**<.001**
Not insured/unknown	788 (6.6)	158 (6.7)	
Private	3190 (26.5)	775 (33)	
Medicaid	1115 (9.3)	250 (10.6)	
Medicare/other government	6926 (57.6)	1165 (49.6)	
Facility Type			.223
Community cancer program	1563 (13)	337 (14.2)	

Table 1 Continued

Characteristic	CT Only (n = 12,019)	CT With TRT (n = 2348)	Parametric *P*
Comprehensive community cancer program	5910 (49.3)	1157 (48.9)	
Academic/research program	3376 (28.1)	663 (28)	
Integrated network cancer program	1147 (9.6)	208 (8.8)	
Facility Location			**.031**
Northeast	2318 (19.3)	417 (17.8)	
South	4915 (41)	976 (41.7)	
Midwest	3418 (28.5)	715 (30.6)	
West	1345 (11.2)	230 (9.8)	

Data are presented as n (%) except where otherwise noted.
Bold values indicate significance ($P < .05$).
Abbreviations: CT = chemotherapy; Dx = diagnosis; TRT = thoracic radiation therapy.

with morphology codes 8041-8045. We identified 221,205 patients with small-cell lung cancer. Exclusion criteria were applied to remove patients with nonmetastatic disease, those with brain metastases, those who received nonthoracic and pre-CT radiation therapy, including PCI (Figure 1). Additionally, those who received all of their treatment outside of the reporting institution, had a previous malignancy, or missing outcome data were excluded. We determined 22,087 patients who were eligible for analysis, which was further refined to include 14,367 patients who received CT, and 3099 patient who received TRT.

Demographic factors including sex, age, year of diagnosis, race, median income, insurance status, census region, and treatment facility type were examined. Clinicopathologic characteristics including American Joint Committee on Cancer (AJCC) group staging, clinical and pathologic T, N, and M classification, Charlson-Deyo comorbidity score, and interventions received during the initial course of treatment were evaluated. Information regarding radiation therapy included treatment site, treatment modality, total dose, number of treatments, length of radiation course, and time from diagnosis. Details of systemic therapy (ie, single-agent, multiagent, or no CT) were included.

The length of median follow-up was calculated using the reverse Kaplan−Meier method.[17] OS was defined as time from diagnosis to death or last follow-up, for which those alive at last follow-up were censored at the time of their last follow-up. Five-year and median OS was estimated using the Kaplan−Meier method and compared via the log rank test. Univariate and multivariate Cox proportional hazards models were used to analyze the association between TRT, as well as radiation dose, and the risk of death. To minimize bias from baseline characteristics, propensity score-matching was performed using 1:1 matching without replacement using the nearest neighbor method. The inverse probability of treatment weighting method was used as an adjunct for balance check.[18] A caliper width of 0.05 times the standard deviation of the logit of the propensity score was estimated to eliminate >99% of bias due to confounding variables.[19] For the primary CT versus CT with TRT comparison, cohorts were matched on: age, sex, race, Charlson-Deyo comorbidity score, year of diagnosis, median income quartiles, primary payor, location of primary site, grade, clinical T and clinical N classification, group stage, CT agent/status, presence of ipsilateral tumor nodules, lymph node positivity, tumor size, and days elapsed from diagnosis to the start of treatment. The thoracic radiation cohort, for a comparison of number of radiation treatments, was matched on the previously mentioned variables with exception of race, year of diagnosis, location of primary site, and grade; additional variables used for matching were: days elapsed from diagnosis to radiation therapy, and readmission within 30 days of surgical discharge. The balance between the matched groups was checked using mean standardized differences. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC); the significance level was .05.

Results

A total of 14,367 patients with ES-SCLC who were diagnosed between 2010 and 2014 and received CT were included in the primary analysis; 12,019 (83.7%) patients were treated with CT alone, and 2348 (16.3%) patients received TRT after CT (see Supplemental Table 1 in the online version). Most were AJCC stage IV (n = 14,229, 99.3%). 93.3% (n = 13,402) were treated with multiagent CT, and a small proportion received single-agent CT (n = 518, 3.6%). The median time to start of systemic treatment was 14 days from diagnosis, whereas the median time to radiation therapy was 77 days. Other characteristics including clinical staging, comorbidity, treatment, and demographic data are summarized in Supplemental Table 1 in the online version. Notable baseline differences between CT and CT with TRT cohorts include age, comorbidity status, and sex (Table 1). The median age at diagnosis was 66 versus 63 years ($P < .001$; CT alone vs. CT with TRT). The CT-only group had a higher proportion of male patients—52.3% versus 48.6% ($P < .001$). Fewer patients who received CT had a Charlson-Deyo comorbidity score of 0 to 52.2% (n = 6273) versus 57.2% (n = 1343, $P < .001$).

A univariate analysis of OS in the CT (with or without TRT) cohort revealed age, male sex, race, year of diagnosis, median income, primary payor, advanced clinical T and N classification, single-agent CT, and medical comorbidity were associated with increased risk of death (see Supplemental Table 2 in the online version). These characteristics remained significant in the multivariate setting (Table 2). TRT used in addition to CT was associated with a decreased risk of death. Univariate and multivariate

Table 2 Multivariate Association With Overall Survival in the Chemotherapy (With or Without Thoracic Radiotherapy) Cohort

Characteristic	Hazard Ratio (95% CI)	HR *P*	Log-rank *P*
Age at Diagnosis, y	1.01 (1.01-1.02)	**<.001**	**<.001**
Sex			
Male	1.20 (1.15-1.24)	**<.001**	**<.001**
Female	—	—	
Year of Diagnosis			
2010-2011	1.08 (1.03-1.14)	**.003**	**<.001**
2012	0.99 (0.93-1.05)	.688	
2013	—	—	
Clinical T Classification			
T0-1	0.84 (0.78-0.90)	**<.001**	**<.001**
T2	0.93 (0.88-0.98)	**.006**	
T3	0.92 (0.87-0.98)	**.008**	
T4	—	—	
Clinical N Classification			
N0	0.81 (0.75-0.88)	**<.001**	**<.001**
N1	0.91 (0.83-1.00)	**.045**	
N2	0.95 (0.91-1.00)	.054	
N3	—	—	
Treatment Group			
Chemotherapy	1.74 (1.64-1.84)	**<.001**	**<.001**
Chemotherapy with RT	—	—	
Chemotherapy			
Multiagent	1.05 (0.92-1.20)	.489	**<.001**
Single agent	1.53 (1.28-1.82)	**<.001**	
Type unknown	—	—	
Charlson-Deyo Score			
0	0.87 (0.84-0.91)	**<.001**	**<.001**
≥1	—	—	
Race			
Other/unknown	0.84 (0.73-0.96)	**.013**	**<.001**
Black	0.83 (0.77-0.90)	**<.001**	
White	—	—	
Median Income Quartiles			
Unknown	1.37 (1.15-1.63)	**<.001**	**<.001**
<$38,000	1.11 (1.04-1.18)	**.001**	
$38,000-$47,999	1.06 (1.00-1.12)	.061	
$48,000-$62,999	1.06 (1.00-1.13)	**.039**	
≥$63,000	—	—	
Primary Payor			
Not insured/unknown	1.02 (0.93-1.11)	.747	**.030**
Private	0.96 (0.91-1.01)	.136	
Medicaid	1.07 (0.99-1.16)	.081	
Medicare/other government	—	—	

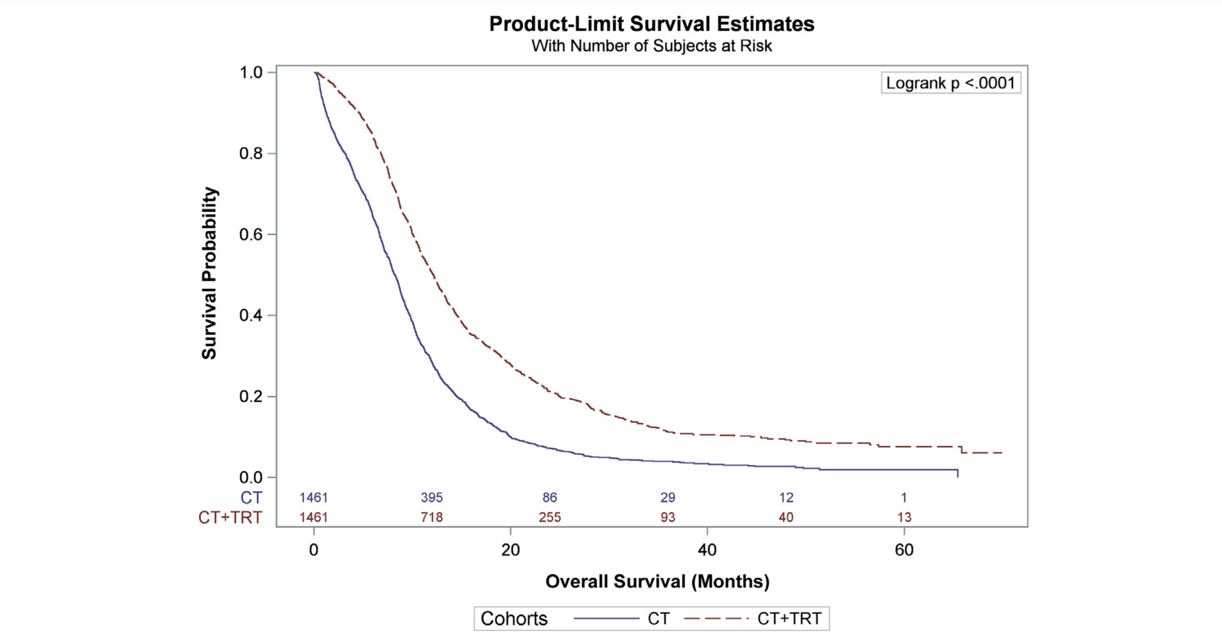
Bold values indicate significance ($P < .05$).
Abbreviations: HR = hazard ratio; RT = radiation therapy.

Table 3 Multivariate Association With Overall Survival in the Thoracic Radiation Therapy (With or Without Chemotherapy) Cohort

Characteristic	HR (95% CI)	HR *P*	Log Rank *P*
Age at Diagnosis, y	1.01 (1.01-1.02)	**<.001**	<.001
Sex			
Male	1.21 (1.09-1.33)	**<.001**	<.001
Female	—	—	
Clinical T Classification			
T0-1	0.95 (0.79-1.13)	.558	.139
T2	0.98 (0.86-1.12)	.754	
T3	0.86 (0.76-0.98)	**.022**	
T4	—	—	
Clinical N Classification			
N0	0.73 (0.61-0.88)	**<.001**	.006
N1	0.96 (0.78-1.20)	.745	
N2	0.98 (0.87-1.09)	.689	
N3	—	—	
Treatment Group			
≤10 Radiation treatments	1.42 (1.24-1.63)	**<.001**	<.001
>10 Radiation treatments	—	—	
Chemotherapy			
Unknown	0.06 (0.02-0.20)	**<.001**	<.001
Multiagent	0.29 (0.24-0.34)	**<.001**	
Single agent	0.40 (0.28-0.59)	**<.001**	
Type unknown	0.29 (0.20-0.43)	**<.001**	
No	—	—	
Comorbidity			
0	0.83 (0.75-0.92)	**<.001**	<.001
≥1	—	—	
Median Income Quartiles			
Unknown	1.83 (1.18-2.82)	**.007**	.042
<$38,000	1.10 (0.95-1.27)	.209	
$38,000-$47,999	0.99 (0.86-1.14)	.931	
$48,000-$62,999	1.08 (0.94-1.24)	.281	
≥$63,000	—	—	
Primary Payor			
Not insured/unknown	1.03 (0.84-1.27)	.771	.002
Private	0.85 (0.74-0.97)	**.016**	
Medicaid	1.17 (0.96-1.42)	.115	
Medicare/other government	—	—	

Bold values indicate significance ($P < .05$).
Abbreviation: HR = hazard ratio.

Figure 2 Propensity Score-Matched Overall Survival Outcomes With and Without Thoracic Radiotherapy in the Chemotherapy Cohort



Abbreviations: CT = chemotherapy; TRT = thoracic radiation therapy.

analyses of OS for patients who received TRT are summarized in Table 3 and Supplemental Table 3 in the online version. Notably, treatment at an academic or research program was associated with a decreased risk of death in univariate analyses of the CT and TRT groups (hazard ratio [HR], 0.90 [HR $P = .002$]; and HR, 0.81 [HR $P = .006$]); location of the other 3 facility types were not significant (see Supplemental Tables 2 and 3 in the online version).

The additional of TRT after CT was associated with improved OS (HR, 1.74; 95% confidence interval [CI], 1.64-1.84; log rank $P < .001$). Median survival was 7.5 months (95% CI, 7.4-7.7) versus 11.5 months (95% CI, 11.1-12). Actuarial survival at 12 months was 25.0% versus 47.7%, and at 5-years was 2.0% versus 7.1% (CT vs. CT with TRT). Unadjusted Kaplan−Meier survival curves are shown in Supplemental Figure 1 in the online version. Propensity score-matching was performed to minimize bias from baseline imbalances between treatment groups; 1461 patients from each arm constituted this cohort. The survival advantage to TRT used in addition to CT remained significant in this population (HR, 1.80; 95% CI, 1.67-1.95; HR $P < .001$). Median survival was 8.2 versus 12.1 months; 12-month OS was 28.5% versus 50.5%, and 5-year OS was 2.0% versus 7.6% (Figure 2).

Three thousand ninety-nine patients who received TRT were queried to analyze the effect of the number of radiation treatments, approximating total dose, on survival. Baseline characteristics were similar between patients who had received ≤10 versus >10 treatments; notable exception were seen in age, sex, year of diagnosis, Charlson-Deyo score, primary payor, median income, clinical T classification, and CT status (Table 4). The median thoracic dose received was 21 Gy versus 45 Gy. Receiving >10 radiation treatments was associated with improved survival (HR, 1.42; 95% CI, 1.24-1.63; log rank $P < .001$). Univariate and multivariate associations for OS for this cohort are summarized in Supplemental Table 3 in the online version and Table 3, respectively. Unadjusted survival end points favored >10 radiation treatments: median OS was 6.3 versus 10.9 months; 12-month OS was 20.4% versus 51.0%; 5-year OS was 3.6% versus 7.6% (see Supplemental Figure 2 in the online version). The propensity score-matched analysis, comprised of 444 patients in each group confirmed a survival advantage to receiving >10 treatments (HR, 1.70; 95% CI, 1.49-1.95; HR $P < .001$). Median OS was 6.3 versus 10.9 months; actuarial rates of 12-month OS were 26.2% versus 46.9%; and 5-year OS 3.8% versus 5.3% (Figure 3).

Discussion

In this study we assessed survival outcomes with consolidative TRT using a large national database, and found the use of TRT after systemic therapy was associated with an OS advantage with notable differences in OS at 12 months and 5 years. An analysis limited to patients who received chest radiotherapy showed a significant association between the number of radiation treatment and OS. Both findings using unadjusted cohorts and multivariate models remained statistically significant with their respective propensity-matched populations. Additionally, this is the only study to our knowledge to report long-term survival outcomes at 5 years in the era of modern radiotherapy. The findings of this retrospective analysis support 2 clinical investigations in the randomized setting.[9,10]

A single-institutional Yugoslavian trial randomized 109 patients with ES-SCLC who achieved a complete response (CR) at all distant sites and either a CR or PR in the chest to receive either accelerated

Table 4 Descriptive Baseline Characteristics for Patients in the Thoracic Radiation Therapy Cohort Who Received ≤10 versus >10 Treatments

Characteristic	≤10 Treatments (n = 943)	>10 Treatments (n = 2156)	Parametric *P*
Median Age at Diagnosis (SD)	66	63	**<.001**
Sex			**.028**
Male	484 (51.3)	1014 (47)	
Female	459 (48.7)	1142 (53)	
Year of Diagnosis			**.014**
2010	224 (23.8)	563 (26.1)	
2011	243 (25.8)	567 (26.3)	
2012	218 (23.1)	549 (25.5)	
2013	258 (27.4)	477 (22.1)	
Clinical T Classification			**<.001**
T0-1	45 (5.4)	182 (9.5)	
T2	166 (20)	418 (21.9)	
T3	175 (21)	396 (20.8)	
T4	446 (53.6)	910 (47.7)	
Clinical N Classification			**.797**
N0	82 (9.3)	183 (9)	
N1	49 (5.6)	122 (6)	
N2	469 (53.2)	1114 (54.7)	
N3	281 (31.9)	617 (30.3)	
Chemotherapy			**<.001**
None	292 (31)	138 (6.4)	
Type unknown	21 (2.2)	67 (3.1)	
Single-agent	22 (2.3)	44 (2)	
Multiagent	599 (63.5)	1903 (88.3)	
Unknown	9 (1)	4 (0.2)	
Chemotherapy, Median Days From Dx	12	14	**.002**
Radiation, Median Days From Dx	23	62	<.001
Median Radiation Dose	21 Gy	45 Gy	<.001
Median Number of Treatments	8	30	<.001
Charlson-Deyo Score			**<.001**
0	469 (49.7)	1245 (57.7)	
1	307 (32.6)	645 (30)	
2	167 (17.7)	266 (12.3)	
Race			.050
White	819 (86.9)	1936 (89.8)	
Black	96 (10.2)	175 (8.1)	
Other/unknown	28 (2.9)	45 (2.1)	
Median Income Quartiles			**.036**
Unknown	13 (1.4)	16 (0.7)	
<$38,000	221 (23.4)	491 (22.8)	
$38,000-$47,999	287 (30.4)	587 (27.2)	
$48,000-$62,999	245 (26)	571 (26.5)	
≥$63,000	177 (18.8)	491 (22.8)	
Primary Payor			**<.001**
Not insured/unknown	71 (7.5)	149 (6.9)	
Private	218 (23.1)	726 (33.7)	
Medicaid	106 (11.2)	228 (10.6)	
Medicare/other government	548 (58.1)	1053 (48.8)	

Table 4 Continued

Characteristic	≤10 Treatments (n = 943)	>10 Treatments (n = 2156)	Parametric *P*
Facility Type			.139
Community cancer program	134 (14.3)	325 (15.1)	
Comprehensive community cancer program	443 (47.1)	1081 (50.4)	
Academic/research program	279 (29.7)	553 (25.8)	
Integrated network cancer program	84 (8.9)	187 (8.7)	
Facility Location			**.012**
Northeast	159 (16.9)	406 (18.9)	
South	406 (43.2)	849 (39.6)	
Midwest	255 (27.1)	671 (31.3)	
West	120 (12.8)	220 (10.3)	

Data are presented as n (%) except where otherwise noted.
Bold values indicate significance ($P < .05$).
Abbreviation: Dx = diagnosis.

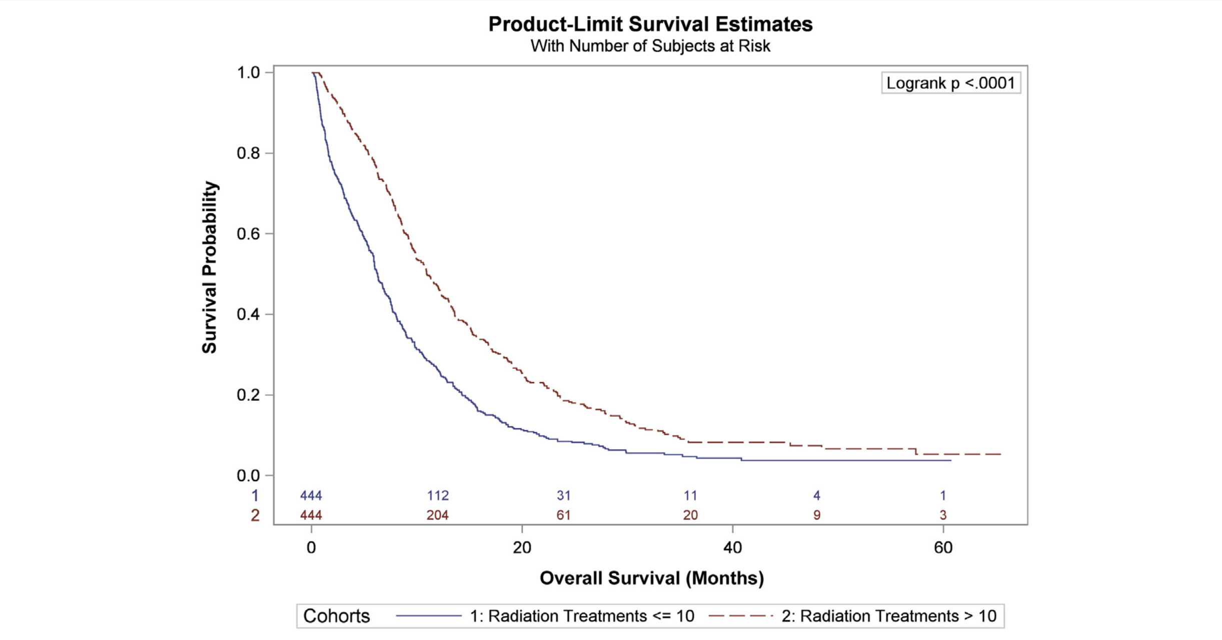
hyperfractionated chest radiotherapy or additional CT and PCI.[9] The intrathoracic gross disease, with extensive coverage of the regional lymph nodes, including the ipsilateral hilum, mediastinum, and bilateral supraclavicular fossae, was prescribed 54 Gy given in twice-daily treatments with concurrent low-dose CT. The additional use of TRT resulted in an improvement in median OS from 11 to 17 months, 2-year OS of 28% versus 38%, and 5-year OS of 3.7% versus 9.1% ($P = .04$). Twenty-seven percent of patients who received chest radiation experienced Grade ≥3 acute esophagitis. The CREST study, led by the Dutch Lung Cancer Study group, randomized a contemporary population of approximately 500 ES-SCLC patients with any response after standard platinum-based CT to PCI with or without thoracic radiation of 30 Gy to the post-CT volume and any involved pretreatment adenopathy.[10] Although it failed to meet a prespecified primary end point of 1-year OS (28% vs. 33%; $P = .07$), a significant benefit of TRT was seen at 18 months and maintained at 2 years (3% vs. 13%; $P = .004$); median OS from randomization was 8 months in both groups. A corresponding meta-analysis of the 2 studies showed TRT improved survival in its multivariate model (HR, 0.66; $P = .032$).[20]

The survival outcomes of our database study support the results of Jeremic et al,[9] with comparable absolute 5-year OS benefit (5.6% vs. 5.4%) and median OS benefit (3.9 vs. 6 months). The Yugoslavian study enrolled a highly selected population at a single institution. Patient and treatment factors, including duration between diagnosis and radiation therapy, treatment package time, use of concurrent therapy, and radiation dose have been postulated to reconcile the 2 studies.[21] Despite differences in study design, they highlight the value of aggressive local treatment for a systemic diagnosis. Intrathoracic progression was seen in 90% of patients within a year of diagnosis in the ES-SCLC PCI study by Slotman et al.[6] Similar rates were seen in CREST without TRT (81.3%), and intrathoracic failures were observed in 43.7% of cases despite consolidative therapy. Progressive local disease is often fatal, because of respiratory and vascular compromise. Thus, improved control at the primary site might confer a survival benefit for at least a subset of patients. As a corollary, patient selection is key. The authors of the CREST study proposed in its original publication that offering TRT to patients with any response in the thorax is a pragmatic approach to patient selection.[10] Subsequent subgroups analyses revealed that an OS benefit (HR, 0.81; $P = .03$) with TRT was limited to patients who had residual thoracic disease; and TRT conferred a progression-free survival advantage for patients with ≤2 metastatic sites, and in those without liver and/or bone metastases.[22,23]

Our analysis of patients who received TRT showed an association between number of radiation treatments and OS. Patients treated with >10 fractions had absolute improvements in OS of 20.7% and 1.6% at 1 and 5 years, respectively. TRT dose and fractionation are not well established: in a phase II single-arm study, and in a retrospective series, patients were treated with TRT of 40 Gy in 15 fractions.[24,25] The median total dose in the current study was 45 Gy and approximately 70% of patients received >10 treatments, which approximates this intermediate approach. A randomized cooperative group phase II trial, RTOG 0937, investigated the use of radiotherapy to the chest and limited extracranial metastatic sites in addition to the use of PCI. In this study, TRT of 45 Gy in 15 fractions was recommended, but the study allowed doses of 30 to 40 Gy as necessary to meet radiation planning objectives.[26] The study showed a 1-year OS for the consolidative radiation arm nearly identical to our findings (50.5% vs. 50.8%). The study was closed for futility after 97 patients were randomized.[12] Possible reasons for lack of an OS benefit in this study included unbalanced prognostic factors, including younger age in the control arm.

Current society guidelines support the use of consolidative thoracic radiation, although they vary in the strength of endorsements. The American Society of Clinical Oncology's endorsement of the American College of Chest Physicians guidelines suggests the use of consolidative TRT for extensive disease is a weak recommendation, citing low-quality evidence.[4,5] It adds the caveat that further evaluation is required before a treatment recommendation can be made. The National Comprehensive Cancer Network's practice guidelines support TRT for selected patients with ES-SCLC who have responded to systemic therapy.[27] The American College of Radiology's appropriateness criteria states that the role of TRT is unclear on the basis of preliminary evidence from the

Figure 3 Propensity Score-Matched Overall Survival Outcomes Stratified According to Number of Radiation Therapy Treatments



Yugoslavian study and should not be considered standard of care.[3] As a result, practice patterns are heterogeneous. Clinical oncologists from 52 radiotherapy centers in the United Kingdom were surveyed in 2007, finding consolidative radiotherapy was routinely delivered in 35.9% of surveyed centers.[13] Of 473 radiation oncologists surveyed in 2015, only 4% of respondents did not recommend TRT in any scenario, although only 45% of respondents estimated that more than 80% of patients in their practice received TRT.[14] There was considerable variability in patient selection and offered radiation dose—assuming a CR at metastatic sites, 52% recommended TRT for CR in the thorax versus 78% if PR in the thorax. For the latter clinical scenario, 31% recommended 30 Gy, 35% recommended 60 Gy, and the remainder elected either 45 Gy or 50 to 54 Gy. A smaller survey limited to 43 academic radiation oncologists showed similar variability in practice patterns.[15] Overall, only 4.7% of respondents reported the use of TRT in >75% of their patients. Interestingly, 54% would offer TRT regardless of brain metastases, and 23% regardless of the number of involved extrathoracic sites after CT.

Patients with brain metastases at presentation represent a clinically distinct population, and have been excluded from all major studies on consolidative thoracic radiation, including RTOG 0937. PCI has traditionally been offered for patients with any response after induction CT, on the basis of randomized data showing a survival benefit; however its routine use has been recently challenged.[6] The European Organisation for Research and Treatment of Cancer 08933, which evaluated approximately 300 patients with extensive disease who received PCI or no additional therapy, showed a 13.8% 1-year absolute survival advantage and more than 60% reduction of symptomatic brain metastases. Recent results from a Japanese study that mandated a negative magnetic resonance imaging of the brain before enrollment failed to find a similar survival benefit; the median OS was 11.6 versus 13.7 months, favoring observation.[28] Because of the controversial, and potentially confounding effects of brain metastasis, and prophylactic cranial radiation therapy, both were excluded from the current study.

The current study's retrospective design is an inherent limitation. Because of the considerable variability in offering TRT, its use is often at the discretion of their treating radiation oncologist. Accordingly, patient characteristics such as performance status and medical comorbidities are concerning for potential sources of bias. We aimed to minimize such bias with propensity score-matching, accounting for Charlson-Deyo comorbidity status, age, sex, and 15 other variables. This does not eliminate hypothetical bias from unmeasured variables such as post-treatment tumor size, burden of extrathoracic disease, and clinical response at primary and distant sites, which might affect providers' inclination to recommend TRT. Our analysis is limited by variables captured by the National Cancer Database—cause of death, patterns of failure after radiotherapy, radiation-associated toxicity, and CT details are not routinely encoded. Regardless, our analysis reflects patient data encompassing most diagnoses that were delivered in academic and community settings. Last, the currently study predates the approval and use of immunotherapy. The additional use of atezolizumab with standard platinum CT led to a significant improvement in OS (HR, 0.70; $P = .007$) for ES-SCLC patients in the phase III IMpower133 study.[29] Atezolizumab was subsequently approved in 2019 by the Food and Drug Administration for use in combination with CT in the first-line setting. As breakthroughs in systemic treatment improve OS, primarily driven by reducing distant progression, the role of local therapies become more relevant.

Conclusion

Using a large national database approach, we found that consolidative TRT was associated with superior long-term survival in patients with ES-SCLC, and, to our knowledge, are the first to provide evidence suggesting a survival advantage with higher radiotherapy doses. The findings herein warrant further study of TRT, with a focus on its integration with now standard-of-care immunotherapy.

Clinical Practice Points

- Extensive-stage small-cell lung carcinoma is an uncommon, but highly aggressive malignancy.
- Standard-of-care therapy is platinum-based CT. Improvements in survival with the additional use of consolidative TRT has been seen in the randomized setting; however, its utilization has been varied.
- This study, using a large cohort of patients from the National Cancer Database, we found a significant difference in survival with the additional use of TRT with CT.
- Propensity score-matching methods were used to minimize the effect of confounders and biases.
- Additionally, a survival difference was seen with greater number of radiation treatments.
- Our results support the use of TRT; and warrant the investigation of its additional use with systemic treatment, especially in light of recent improvements in OS driven by immunotherapy.

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Disclosure

Kristin A. Higgins: consultant to Astra Zeneca and Varian Medical Systems; advisory boards for Astra Zeneca and Genetech; and industry-funded research from RefleXion Medical. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.06.014.

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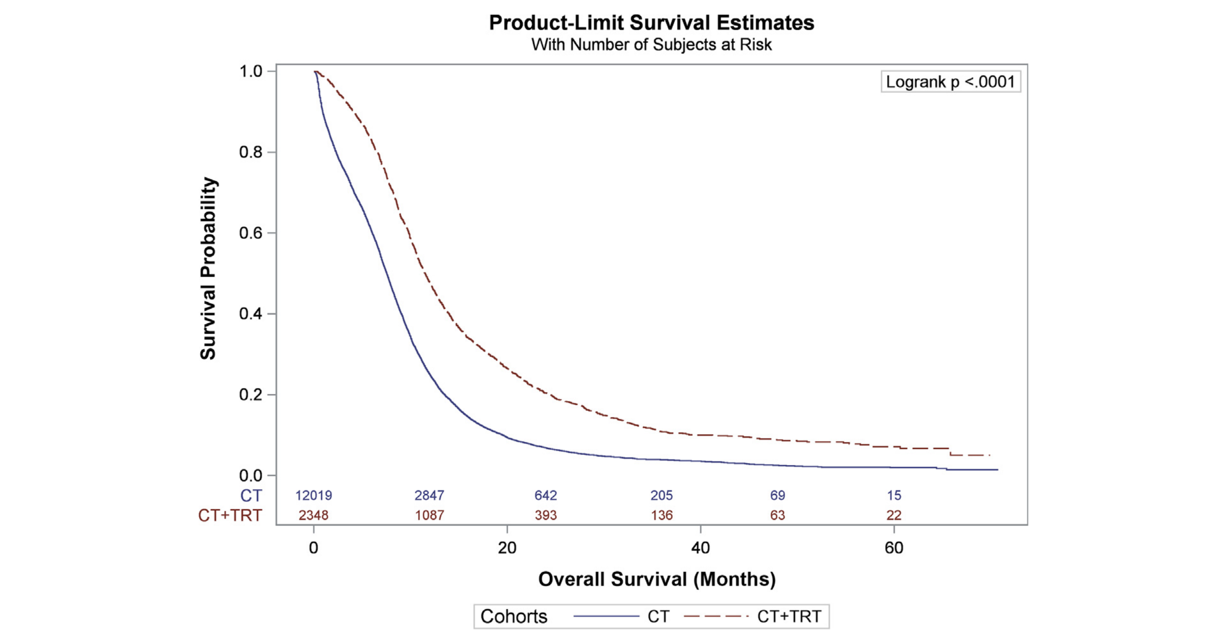
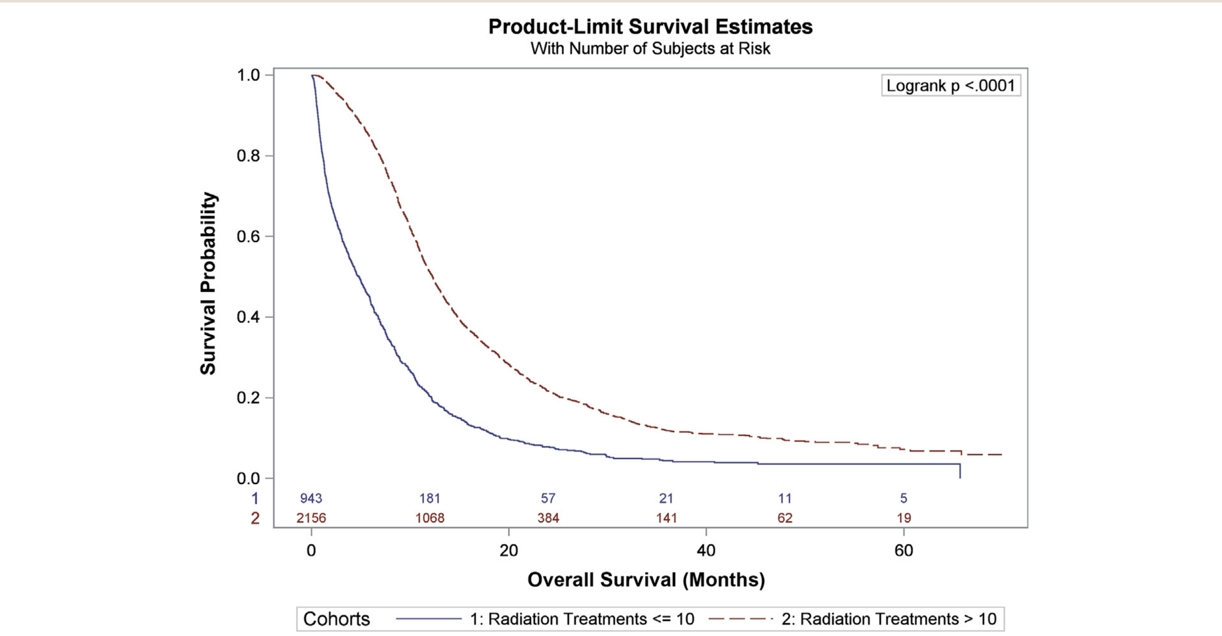
Supplemental Data

Supplemental Figure 1 Overall Survival Outcomes With and Without Thoracic Radiotherapy (TRT) in the Chemotherapy (CT) Cohort Without Propensity Score-Matching



Supplemental Figure 2 Overall Survival Outcomes Stratified According to Number of Radiation Therapy Treatments; Without Propensity Score-Matching



Supplemental Table 1 Descriptive Baseline Characteristics for the Chemotherapy (With or Without Thoracic Radiation Therapy) and Thoracic Radiation (With or Without Chemotherapy) Cohorts

Characteristic	Chemotherapy Group (n = 14,367)	Thoracic Radiation Group (n = 3099)
Median Age at Diagnosis (SD)	66 (9.84)	64 (10.1)
Sex		
Male	7437 (51.8)	1498 (48.3)
Female	6930 (48.2)	1601 (51.7)
Year of Diagnosis		
2010	3559 (24.8)	787 (25.4)
2011	3498 (24.3)	810 (26.1)
2012	3678 (25.6)	767 (24.7)
2013	3632 (25.3)	735 (23.7)
Clinical T Classification		
T0-1	1350 (11.6)	227 (8.3)
T2	2847 (24.5)	584 (21.3)
T3	2317 (20.0)	571 (20.9)
T4	5091 (43.9)	1356 (49.5)
Clinical N Classification		
N0	1215 (9.3)	265 (9.1)
N1	877 (6.7)	171 (5.9)
N2	7495 (57.1)	1583 (54.3)
N3	3541 (27.0)	898 (30.8)
Treatment Group		
Chemotherapy	12,019 (83.7)	—
Chemotherapy with radiation	2348 (16.3)	—
≤10 Radiation Treatments	—	943 (30.4)
>10 Radiation Treatments	—	2156 (69.6)
Chemotherapy		
None	—	430 (13.9)
Type unknown	447 (3.1)	88 (2.8)
Single-agent	518 (3.6)	66 (2.1)
Multiagent	13,402 (93.3)	2502 (80.7)
Unknown	—	13 (0.4)
Chemotherapy, Days From Dx	14	14
Radiation, Days From Dx	77	51
Radiation Dose	45	45
Median Number of Treatments	25	20
Charlson-Deyo Score		
0	7616 (53.0)	1714 (55.3)
1	4536 (31.6)	952 (30.7)
2	2215 (15.4)	433 (14.0)
Race		
White	12,839 (89.4)	2755 (88.9)
Black	1173 (8.2)	271 (8.7)
Other/unknown	355 (2.5)	73 (2.4)
Median Income Quartiles		
Unknown	192 (1.3)	29 (0.9)
<$38,000	3157 (22.0)	712 (23.0)
$38,000-$47,999	3907 (27.2)	874 (28.2)
$48,000-$62,999	3741 (26.0)	816 (26.3)
≥$63,000	3370 (23.5)	668 (21.6)
Primary Payor		
Not insured/unknown	946 (6.6)	220 (7.1)
Private	3965 (27.6)	944 (30.5)
Medicaid	1365 (9.5)	334 (10.8)
Medicare/other government	8091 (56.3)	1601 (51.7)
Facility Type		
Community cancer program	1900 (13.3)	459 (14.9)
Comprehensive community cancer program	7067 (49.3)	1524 (49.4)
Academic/research program	4012 (28.0)	832 (27.0)
Integrated network cancer program	1355 (9.5)	271 (8.8)
Facility Location		
Northeast	2735 (19.1)	565 (18.3)
South	5891 (41.1)	1255 (40.7)
Midwest	4133 (28.8)	926 (30.0)
West	1575 (11.0)	340 (11.0)

Data are presented as n (%) except where otherwise noted.
Abbreviation: Dx = diagnosis.

Supplemental Table 2 Univariate Association With Overall Survival in the Chemotherapy Cohort

Characteristic	n	HR (95% CI)	HR *P*	Log Rank *P*
Age at Diagnosis	14,367	1.02 (1.01-1.02)	<.001	
Sex				
Male	7437	1.18 (1.14-1.22)	<.001	<.001
Female	6930	—	—	
Year of Diagnosis				
2010-2011	7057	1.07 (1.02-1.11)	.004	<.001
2012	3678	0.95 (0.90-1.00)	.042	
2013	3632	—	—	
Clinical T Classification				
T0-1	1350	0.85 (0.80-0.91)	<.001	<.001
T2	2847	0.96 (0.92-1.01)	.103	
T3	2317	0.95 (0.91-1.00)	.075	
T4	5091	—	—	
Clinical N Classification				
N0	1215	0.85 (0.79-0.91)	<.001	<.001
N1	877	0.93 (0.86-1.00)	.054	
N2	7495	1.02 (0.98-1.06)	.355	
N3	3541	—	—	
Treatment Group				
Chemotherapy	12,019	1.80 (1.71-1.89)	<.001	<.001
Chemotherapy with radiation	2348	—	—	
Chemotherapy				
Multiagent	13,402	0.99 (0.89-1.09)	.811	<.001
Single-agent	518	1.45 (1.26-1.65)	<.001	
Unknown	447	—	—	
Charlson-Deyo Score				
0	7616	0.73 (0.69-0.76)	<.001	<.001
1	4536	0.86 (0.81-0.90)	<.001	
2	2215	—	—	
Race				
Other/unknown	355	0.87 (0.77-0.97)	.016	<.001
Black	1173	0.87 (0.82-0.93)	<.001	
White	12,839	—	—	
Median Income Quartiles				
Unknown	472	1.13 (1.02-1.24)	.018	<.001
<$38,000	2309	1.00 (0.95-1.06)	.978	
$38,000-$47,999	2939	1.02 (0.97-1.07)	.407	
$48,000-$62,999	4239	1.06 (1.01-1.11)	.010	
≥$63,000	4408	—	—	
Primary Payor				<.001
Not insured/unknown	946	0.87 (0.81-0.93)	<.001	
Private	3965	0.79 (0.76-0.83)	<.001	
Medicaid	1365	0.86 (0.81-0.92)	<.001	
Medicare/other government	8091	—	—	
Facility Type				
Community cancer program	1900	0.98 (0.91-1.05)	.514	<.001
Comprehensive community cancer program	7067	0.97 (0.92-1.04)	.404	
Academic/research program	4012	0.90 (0.85-0.96)	.002	

Supplemental Table 2 Continued

Characteristic	n	HR (95% CI)	HR *P*	Log Rank *P*
Integrated network cancer program	1355	—	—	
Facility Location				
Northeast	2735	0.93 (0.87-0.99)	.021	.004
South	5891	0.98 (0.92-1.04)	.456	
Midwest	4133	1.01 (0.96-1.08)	.634	
West	1575	—	—	

Abbreviation: HR = hazard ratio.

Supplemental Table 3 Univariate Association With Overall Survival in the Thoracic Radiation Therapy Cohort

Characteristic	n	HR (95% CI)	HR *P*	Log Rank *P*
Age at Diagnosis	3099	1.02 (1.01-1.02)	<.001	
Sex				
Male	1498	1.14 (1.06-1.23)	<.001	<.001
Female	1601	—	—	
Year of Diagnosis				
2010-2011	1597	1.06 (0.96-1.16)	.273	<.443
2012	767	1.01 (0.90-1.13)	.859	
2013	735	—	—	
Clinical T Classification				
T0-1	227	0.75 (0.64-0.88)	<.001	<.001
T2	584	0.85 (0.77-0.95)	.003	
T3	571	0.92 (0.82-1.02)	.105	
T4	1356	—	—	
Clinical N Classification				
N0	265	0.73 (0.63-0.85)	<.001	<.001
N1	171	0.85 (0.72-1.02)	.080	
N2	1583	0.93 (0.85-1.02)	.111	
N3	898	—	—	
Treatment Group				
≤10 Radiation treatments	943	2.32 (2.14-2.52)	<.001	<.001
>10 Radiation treatments	2156	—	—	
Chemotherapy				
Unknown	13	0.20 (0.10-0.40)	<.001	<.001
Multiagent	2502	0.23 (0.20-0.25)	<.001	
Single-agent	66	0.27 (0.21-0.36)	<.001	
Type unknown	88	0.24 (0.19-0.31)	<.001	
No	430	—	—	
Charlson-Deyo Score				
0	1714	0.69 (0.62-0.77)	<.001	<.001
1	952	0.88 (0.78-0.99)	.038	
2	433	—	—	
Race				
Other/unknown	73	0.84 (0.65-1.09)	.193	.228
Black	271	0.92 (0.80-1.06)	.239	
White	2755	—	—	
Median Income Quartiles				
Unknown	29	1.40 (0.94-2.07)	.095	.133
<$38,000	712	1.13 (1.01-1.27)	.036	
$38,000-$47,999	874	1.06 (0.95-1.18)	.305	
$48,000-$62,999	816	1.11 (0.99-1.23)	.073	
≥$63,000	668	—	—	
Primary Payor				
Not insured/unknown	220	0.88 (0.75-1.02)	.100	<.001
Private	944	0.72 (0.66-0.79)	<.001	
Medicaid	334	0.93 (0.82-1.05)	.238	
Medicare/other government	1601	—	—	
Facility Type				
Community cancer program	459	0.94 (0.80-1.10)	.466	.009
Comprehensive community cancer program	1524	0.93 (0.81-1.06)	.268	

Supplemental Table 3 Continued

Characteristic	n	HR (95% CI)	HR *P*	Log Rank *P*
Academic/research program	832	0.81 (0.70-0.94)	.006	
Integrated network cancer program	271	—	—	
Facility Location				
Northeast	565	0.84 (0.73-0.97)	.020	.012
South	1255	0.99 (0.87-1.13)	.939	
Midwest	926	0.92 (0.80-1.05)	.213	
West	340	—	—	