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Short Communication

Optimal timing of thoracic radiotherapy in limited stage small cell lung cancer (SCLC) with daily fractionation: A brief report

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SUMMARY

Survival in limited stage small cell lung cancer (LS-SCLC) improves with faster initiation of hyperfractionated thoracic radiotherapy (TRT) following chemotherapy, however, it is unknown if this association exists for more commonly employed daily fractionated regimens. Our results suggest that this association is present even with daily fractionation.

De Ruysscher et al. published several meta analyses detailing limited stage small cell lung cancer (SCLC) trials, and determined that the sooner thoracic radiotherapy (TRT) is delivered with chemotherapy (CTX), the better the outcome. Specifically, 30 days has been the recommended timeframe for initiation, duration, and completion of TRT following CTX [1–3]. Notably, most trials included in such meta analyses comprised of hyperfractionated, twice daily radiation – a regimen associated with superior survival, although recent trials showed daily fractionation schemes to be equivalent [4]. The aforementioned timeframes cannot be reasonably achieved with conventional daily fractionation, which perhaps due to convenience or presumed reduction in toxicity, is employed in almost 90% of nonmetastatic SCLC cases in America [5]. Using the national cancer database (NCDB), herein we report on trends in timing of TRT in limited stage SCLC treated with daily fractionation, the significance of the 30 day window to initiate TRT in this patient population, as well as optimal duration and completion times of TRT.

Methods

Patient selection

We queried the national cancer database, which details approximately 70% of cancers diagnosed in the United States, to identify presumed limited stage SCLC patients treated definitively with double agent CTX and TRT with daily fractionation between the years 2004–2014 in this IRB-exempt study. Since limited/extensive stage is not coded, patients without metastatic/N3 disease were surrogates for limited stage cases. Starting from 238,641 patients, cases were excluded for unknown stage/metastasis/N3 disease ($n = 162{,}522$), if TRT ($n = 41{,}544$) or double agent CTX ($n = 5503$) were not administered, if patients were lost to follow-up ($n = 4734$), or if TRT was administered before CTX ($n = 6185$), less than 54 Gy ($n = 6268$), delivered twice daily ($n = 2450$), or completed over 180 days after CTX ($n = 415$). Otherwise, we included all patients who completed a definitive course of therapy and reported associated treatment parameters. Ultimately, 8990 patients were eligible for analysis.

Statistics

Because 30 days is frequently cited as the goal timeframe to initiate TRT after CTX, the primary comparison groups in this study were those who started TRT within and beyond 30 days of CTX. Since a 30-day interval is not realistic for duration of definitive TRT with daily fractionation, receiver operating characteristic (ROC) analyses determined a priori (optimal cutoff) values for initiation, duration, and completion times of TRT following CTX that were predictive of the greatest survival discrepancy. All timing parameters were then analyzed in separate propensity score-matched multivariable cox regression analyses for survival. Adjusted hazard ratios (HR) and 95% confidence interval (CI) are reported, with $\alpha = 0.05$ used to indicate statistical significance.

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TRT timing parameters of interest were not included in the same multivariable analysis because of covariability. Bivariate logistic regression models evaluated the association between independent variables of interest and particular timing group. Overall survival was calculated from the date of diagnosis to the date of last contact or death using Kaplan–Meier methodology to present the cumulative probability of survival, and log-rank statistics to assess statistical significance between groups.

Propensity score analysis was used to account for indication bias caused by lack of randomization [6]. Propensity scores were calculated by multivariable logistic regression to provide a score reflecting the conditional probability of receiving TRT within or beyond the particular time frame of interest. The propensity model included observable variables significantly associated with time-frame selection on multivariable logistic regression. Subsequently we constructed a Cox proportional hazards model adjusting for propensity score. To strengthen the assumption of balance between groups, the propensity-adjusted score was validated by stratification into propensity score-based quintiles, which demonstrated that standardized difference between the treatment groups was less than 0.10 [7]. Statistical analysis was performed via SPSS version 20.

Table 1
Baseline characteristics for patients with TRT within and after 30 days of CTX initiation.

Characteristics	≤30 days *N* = 6220	>30 days *N* = 2770	OR	95% CI	*P* value
			–	–	–
Gender					
Male	2723 (43.8)	1174 (42.4)	1	Reference	
Female	3497 (56.2)	1596 (57.6)	1.06	0.97–1.16	0.22
Age					
<65	3088 (49.6)	1287 (46.5)	1	Reference	
≥65	3132 (50.4)	1483 (53.5)	1.14	1.04 – 1.24	**0.005**
Race					
White	5638 (92.5)	2494 (91.7)	1	Reference	
Black	456 (7.5)	226 (8.3)	1.12	0.95–1.32	0.18
Insurance					
Uninsured	223 (3.6)	105 (3.8)	1	Reference	
Government	3829 (61.5)	1736 (63.4)	0.96	0.76–1.22	0.76
Private	2108 (33.9)	898 (32.8)	0.91	0.71–1.16	0.42
Income					
<48,000	3114 (69.2)	1387 (30.8)	1	Reference	
≥48,000	3011 (69.8)	1305 (30.2)	0.97	0.89–1.07	0.56
Facility					
Community	837 (13.5)	351 (12.7)	1	Reference	
Comprehensive Community	3191 (51.3)	1461 (52.8)	1.09	0.95–1.26	0.22
Academic	1384 (22.3)	602 (21.7)	1.04	0.87–1.21	0.65
Integrated network cancer program	808 (13.0)	356 (12.9)	1.06	0.88–1.26	0.56
Population					
Metro	4585 (76.2)	2066 (76.5)	1	Reference	
Urban	1265 (21.0)	546 (20.2)	0.96	0.86–1.08	0.53
Rural	171 (2.8)	87 (3.2)	1.18	0.89–1.56	0.24
Distance to facility					
<8miles	2763 (45.1)	1181 (43.1)	1	Reference	
≥8 miles	3359 (54.9)	1556 (56.9)	1.08	0.99–1.19	0.08
Comorbid (Charlson-Deyo)					
0	3768 (60.6)	1650 (59.0)	1	Reference	
1	1750 (28.1)	824 (29.5)	1.04	0.94–1.15	0.45
2 or higher	702 (11.3)	323 (11.5)	1.05	0.91–1.21	0.50
Years					
2004–2007	1723 (27.7)	981 (35.4)	1	Reference	
2008–2010	1664 (26.7)	719 (26.0)	0.76	0.68–0.85	**<0.001**
2011–2014	2833 (45.5)	1070 (38.6)	0.66	0.60–0.74	**<0.001**
Radiation Dose					
<60 Gy	3426 (55.1)	1680 (60.6)	1	Reference	
>60 Gy	2794 (44.9)	1090 (39.4)	0.83	0.76–0.91	**<0.001**
Clinical T Stage					
T1	1654 (26.6)	611 (22.1)	1	Reference	
T2	2162 (34.7)	961 (34.7)	1.20	1.07–1.36	**0.002**
T3	960 (15.4)	400 (14.4)	1.13	0.97–1.31	0.11
T4	1444 (23.2)	798 (28.8)	1.50	1.32–1.70	**<0.001**
Clinical N Stage					
N0/1	2200 (35.4)	864 (31.2)	1	Reference	
N2	4020 (64.6)	1906 (68.8)	1.20	1.10–1.33	**<0.001**

TRT, thoracic radiotherapy; CTX, chemotherapy; OR, odds ratio; CI, confidence interval.
Bold indicates statistical significance.

Results

Patient characteristics

A summary of characteristics for patients receiving TRT within and beyond 30 days of CTX is depicted on Table 1. Briefly, the median age was 65 years (range 28–79), majority of patients (75%) had stage III disease, and median TRT dose was 60 Gy (interquartile range 59.4–63 Gy) at 1.8 Gy per fraction (interquartile range 1.8–2 Gy). TRT was started on the first day of CTX in 24.5% of patients, between the first day and second cycle in 25%, during the second cycle in 25.7%, and after the second cycle in 24.8%. The median time from CTX to starting and completing TRT was 21 (interquartile range 0–41) and 70 (interquartile range 54–92) days, respectively. The median duration of TRT was 50 days (interquartile range 45–54). Patients were more likely to have initiated TRT within 30 days of CTX if they were under 65 years old, treated after 2007, received over 60 Gy, or had a lower T or N stage (Table 1). These indication biases remained for other tested timing parameters, except a lower TRT dose was associated with a shorter TRT duration and time to completion from CTX.

Survival

The median survival for the entire cohort was 20.7 months. Three and 5-year actuarial survival for those starting TRT within 30 days of CTX was 32.7% and 22.9% compared to 28% and 18.4% beyond 30 days ($P < 0.001$). ROC analysis revealed that the a priori values for initiation, completion, and duration of TRT following CTX were 29, 75, and 54 days, respectively. The difference in 3-year actuarial survival was 5.4% for completing TRT beyond 75 days of CTX, and 6.3% for TRT duration longer than 54 days ($P < 0.001$).

Table 2
Multivariable cox proportional hazards models for survival.

Characteristics	Without Propensity Score		Propensity Score-Adjusted	
	Hazard of Death (95% CI)	*P* Value	Hazard of Death (95% CI)	*P* Value
CTX to TRT initiation				
≤30 days	Reference		Reference	
>30 days	1.065 (1.01–1.12)	**0.019**	1.067 (1.03–1.13)	**0.015**
Gender				
Male	Reference		Reference	
Female	0.81 (0.77–0.85)	**<0.001**	0.80 (0.76–0.84)	**<0.001**
Comorbid (Charlson-Deyo)				
0	Reference		Reference	
1	1.10 (1.04–1.16)	**0.001**	1.10 (1.04–1.16)	**0.001**
2 or higher	1.29 (1.19–1.39)	**<0.001**	1.29 (1.20–1.40)	**<0.001**
Income (dollars)				
<48,000	Reference		Reference	
≥48,000	0.94 (0.89–0.99)	**0.015**	0.93 (0.88–0.98)	**0.006**
Population				
Metro	Reference		Reference	
Urban	0.86 (0.73–0.99)	0.05	0.92 (0.86–0.99)	**0.017**
Rural	0.83 (0.71–0.97)	**0.02**	1.08 (0.93–1.26)	0.33
Age				
<65	Reference			
≥65	1.21 (1.14–1.25)	**<0.001**	–	
Clinical T stage				
T1	Reference			
T2	1.18 (1.10–1.25)	**<0.001**		
T3	1.21 (1.12–1.31)	**<0.001**	–	
T4	1.25 (1.21–1.34)	**<0.001**		
Clinical N stage				
0/1	Reference		–	
2	1.28 (1.21–1.35)	**<0.001**		

CTX, chemotherapy; TRT, thoracic radiotherapy; bold indicates statistical significance.

Table 3
Summary of TRT timing parameters.

Timing parameter	Median days (range)	ROC value	HR for death beyond ROC value*	Difference in 3-year survival^	HR for death (continuous variable)
CTX to TRT start	21 (0–140)	29	1.067 (**P = 0.015**)	4.8%	1.001 (**P = 0.002**)
CTX to TRT completion	70 (30–179)	75	1.09 (**P = 0.001**)	5.4%	1.002 (**P < 0.001**)
TRT duration	50 (30–90)	54	1.18 (**P < 0.001**)	6.3%	1.007 (**P < 0.001**)

CTX, chemotherapy; TRT, thoracic radiotherapy; ROC, receiver operating characteristic; HR, hazard ratio.
Bold indicates statistical significance.
* With propensity matching.
^ Based on Kaplan–Meier analysis.

With multivariable analysis, initiation of TRT beyond 30 days of CTX was associated with reduced survival (HR = 1.07, $P = 0.02$) with and without propensity matching. Other predictors of reduced survival included male gender, lower income, higher comorbidity score, treatment prior to 2007, and higher T/N stage. There was no correlation with total dose (Table 2). Three additional propensity score-matched multivariable analyses were conducted utilizing ROC values as main comparison groups with results summarized in Table 3. TRT duration proved to be the most significant timing variable on survival, with a HR of 1.007 as a continuous variable and 1.18 when duration exceeded 54 days ($P < 0.001$).

Discussion

To our knowledge this is the first study utilizing a national database to investigate the timing of TRT in limited stage SCLC treated with daily, conventional fractionation. Our findings corroborate that of hyperfractionated-based meta analyses – the quicker TRT is delivered following CTX, the better the outcome [8]. While previous studies indicate that time from CTX to TRT completion was the greatest predictor of survival [1], here the strongest predictor was TRT duration, suggesting that every 2 days elapsed during treatment resulted in a 1.4% reduction in survival.

The majority of patients initiated TRT within 30 days of CTX and 44% started TRT by the second cycle. Predictably, older patients, greater disease burden, and cases prior to 2007 (when De Ruysscher studies were published) took longer to initiate and complete TRT. Of note, total dose, comorbidity score, location, income, type of facility, and distance from facility did not influence TRT timing parameters (TRT duration correlated with lower dose).

Although well powered, this study is limited by the selection bias inherent to all NCDB studies, such as the higher proportion of greater disease burden (reflected by T and N stage) in the cohorts with longer treatment time. While propensity score matching and multivariable analysis were employed to mitigate such bias, these statistical techniques can only control for observable variables and cannot account for the unobservable ones. Nevertheless, timing of TRT following CTX proved to be an independent predictor of survival in this carefully selected, relatively homogenous patient population. Continued investigation of TRT timing in prospective trials featuring daily fractionation, such as CONVERT and CALGB 30610/RTOG 0538, is warranted [4,9].

Disclosure

The authors have nothing to disclose and no conflicts of interest.

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