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Scientific Article

Consecutive Daily Versus Every Other Day Stereotactic Body Radiation Therapy Scheduling for Stage I Non-small Cell Lung Cancer

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Purpose: The optimal delivery schedule for stereotactic body radiation therapy (SBRT) in treating stage I non-small cell lung cancer (NSCLC) is unknown. This study used the National Cancer Database to examine daily versus every other day (QOD) SBRT scheduling, including trends over time and association with survival.

Methods and Materials: The National Cancer Database was used to retrospectively identify patients with stage I NSCLC treated with 3-, 4-, or 5-fraction of SBRT between 2004 and 2016. Survival analysis was performed using the Kaplan-Meier method and Cox regression modeling.

Results: Of 15,269 patients, 3927 (25.7%) received SBRT daily, and 11,342 (74.3%) received treatment QOD. The use of QOD treatment increased from 63.2% in 2007 to 78.3% in 2016, and 5-fraction SBRT increased from 3.7% in 2004 to 51.4% in 2016 (both $P < .0001$). QOD 5-fraction became the most prevalent scheduling from 2012 to 2016 (28.5% in 2012 to 41.6% in 2016). Factors significantly associated with daily SBRT scheduling included number of fractions, race, lower income, lower comorbidities, and treatment at academic/research programs (all $P \leq .01$).

Median survival for daily SBRT was 37.9 months versus 38.4 months for QOD ($P = .4$). On multivariable analysis, no difference was found in overall survival between daily versus QOD scheduling (adjusted hazard ratio [aHR], 0.99; 95% confidence interval [CI], 0.94-1.04; $P = .55$). Five-fraction SBRT was associated with worse survival versus 3 fractions (aHR, 1.09; 95% CI, 1.03-1.15; $P = .002$). With 3-fraction SBRT, QOD treatment was associated with improved survival versus daily treatment (aHR, 0.91; 95% CI, 0.84-0.98; $P = .02$). With 5-fraction SBRT, QOD treatment was associated with worse survival versus daily treatment (aHR, 1.11; 95% CI, 1.02-1.22; $P = .02$).

Conclusions: QOD SBRT schedules were more frequently used to treat stage I NSCLC than daily regimens by a factor of 3:1, and QOD 5-fraction SBRT became the most common dose schedule after 2012. Three-fraction QOD SBRT was associated with improved survival versus daily, whereas 5-fraction QOD SBRT was associated with worse survival versus daily.

Introduction

Despite the decline of smoking in the past decade,[1] lung cancer remains the leading cause of cancer death in the United States, accounting for almost one-quarter of all cancer deaths.[2] Non-small cell lung cancer (NSCLC) is

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the most common type of lung cancer, representing >80% of all lung cancer diagnoses.[3] The standard-of-care treatment for patients with stage I NSCLC continues to be surgical resection,[4] but in the subset of patients who cannot undergo or decline surgery, stereotactic body radiation therapy (SBRT) represents an efficacious alternative.[5-7] SBRT is a highly conformal, precise external beam radiation technique that delivers a high dose of radiation (commonly defined as ≥6 Gy/fraction) over a limited number of fractions (typically ≤5).[8] It has been shown to provide an excellent local tumor control rate (>90%) with limited toxicity in early-stage NSCLC.[9-11] In addition, SBRT is cost effective and offers increased convenience with fewer treatment visits.[12]

Although SBRT has emerged as a promising therapy for stage I NSCLC, no single standardized regimen has been established, with various dose and fraction combinations used across clinical practices.[13,14] Past Radiation Therapy Oncology Group (RTOG) trials also employed different treatment schedules.[15-18] As a result, scant data exist on whether daily versus every other day (QOD) SBRT treatments impact overall survival (OS). Therefore, this study uses a large national database to analyze trends in SBRT utilization over time and investigate the impact of daily versus QOD SBRT scheduling on survival.

Methods and Materials

Data source and study population

The institutional review board exempted this retrospective study. Data were queried from the National Cancer Database (NCDB), a clinical oncology database sponsored by the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. It is sourced from >1500 CoC-accredited programs, accounting for >70% of all lung cancer cases in the United States.[19] Patients with American Joint Committee on Cancer clinical stage I NSCLC from 2004 to 2016 (as defined by the American Joint Committee on Cancer sixth edition from 2004-2009 and the seventh edition from 2010-2016) were identified for analysis. Patients with treatments other than SBRT, treatment fractions other than 3, 4, or 5 fractions, and prior history of cancer and/or treatment were excluded from the analysis. Full exclusion criteria are detailed in Table 1.

Common prescriptions of SBRT for treating stage I NSCLC in the United States include 3, 4, or 5 fractions.[5] Days of treatment were counted as each day from the initiation to the conclusion of treatment. Based on treatment duration determined from the NCDB, daily SBRT scheduling was defined as completing SBRT in 3, 4, or 5 days, respectively. QOD scheduling for 3, 4, and 5 fractions was defined as SBRT completion in 5 to 9, 8 to 12, and 10 to 14 days, respectively. Weekends and holidays were included in the days of treatment count.

Statistical analysis

Patient variables included age at diagnosis (years), gender, race, insurance status, median household income (based on patient Zone Improvement Plan code), Charlson-Deyo comorbidity score, and treatment facility type. Tumor variables included clinical T classification and histologic characteristics. Tumor histologic characteristics included adenocarcinoma, squamous cell carcinomas, and others. Other histologic characteristics include the following: large cell carcinoma, NSCLC not otherwise specified, keratinizing squamous cell carcinoma, bronchioloalveolar adenocarcinoma, adenocarcinoma combined with mixed subtypes, and adenosquamous carcinoma. Differences in patient and tumor characteristics by treatment scheduling were analyzed using χ^2 tests.

The primary outcome of interest was OS, determined using vital status (dead or alive) and the number of months from the date of diagnosis to last contact or death. The follow-up period was defined from cancer diagnosis to the date of death or last follow-up. Median OS and 3-year and 5-year actuarial OS rates were estimated using the Kaplan-Meier method, and log-rank tests were used to determine statistical significance. Crude hazard ratios (HRs) and adjusted HRs (aHRs) with 95% confidence intervals (CIs) were calculated using Cox regression modeling, adjusting for patient and tumor variables. All tests were 2-sided, and P values of <.05 were considered statistically significant. Statistical computations were performed on the SAS 9.3 system (SAS Institute).

Results

Patient characteristics

Between 2004 and 2016, 15,269 patients meeting the study criteria were identified (Table 1). The median age at diagnosis was 75 years (range, 43-90 years), with 13,570 (88.9%) patients identified as White and 8408 (55.1%) as female. Half (N = 7706; 50.5%) of the patients were aged ≥75 years. A total of 11,903 (78.0%) patients had T1 disease, and 7310 (47.9%) had a Charlson-Deyo score of 1 or higher. Adenocarcinoma was the most common histology (N = 6752; 44.2%), followed by squamous cell carcinoma (N = 5298; 34.7%). Most patients were treated at an academic/research program (N = 6201; 40.6%) or a comprehensive community program (N = 6201; 39.5%). Detailed patient and tumor characteristics are shown in Table 2.

Table 1 Exclusion criteria

	Exclusions	Patients remaining
Total NSCLC cases between 2004 and 2016	-	1,547,889
All cases except AJCC stage I	1,143,292	404,597
Missing or misclassification of clinical TNM stage	23,306	381,291
History of cancer	123,077	258,214
Vital status/missing follow-up information	25	258,189
Histology codes except for adenocarcinoma, squamous cell carcinoma, and others*	39,774	218,415
Palliative treatment	1596	216,819
Missing treatment information (n = 9506), treatment not given (n = 6755), treatment other than surgery, radiation, or chemotherapy (n = 3314)	19,575	197,244
Chemotherapy only (N = 2890), chemoradiation (n = 7658), surgery with adjuvant treatment (n = 19,117), surgery alone (n = 127,045)	156,710	40,534
Missing time from diagnosis to radiation start	430	40,104
Radiation 6 months after diagnosis	1273	38,831
Treatment fractions other than 3, 4, and 5	15,039	23,792
Regional dose is missing (n = 516), < 40 Gy (n = 1139) or > 70 Gy (n = 134)	1789	22,003
Regional treatment modalities except for external beam (photons or protons)	112	21,891
Dose fractionation outside of predetermined constraints	275	21,616
Radiation elapsed time outside of predetermined constraints†	6347	15,269
Final study population	-	***15,269***

Abbreviations: AJCC = American Joint Committee on Cancer; Gy = gray; n = number of cases; NSCLC= non-small cell lung cancer; TNM = tumor (T), nodes (N), and metastases (M).
*Other histology groups include large cell carcinoma, non-small cell lung cancer not otherwise specified (NOS), keratinizing squamous cell carcinoma, bronchioloalveolar adenocarcinoma, mixed subtypes, and adenosquamous carcinoma.
†3, 5 to 9 days for 3 fractions, 4, 8 to 12 days for 4 fractions, and 5, 10 to 14 days for 5 fractions.

SBRT scheduling patterns

Of 15,269 patients who met the study criteria, 3927 (25.7%) patients received treatment daily, and 11,342 (74.3%) patients received QOD treatment. A total of 4993 (32.7%), 4278 (28.0%), and 5998 (39.3%) patients received 3, 4, and 5 fractions, respectively. The most common treatment regimen was 5 fractions QOD (N = 4726; 31.0%). The most common dose fractionations were 10 Gy × 5 (26.7%), 12 Gy × 4 (18.4%), and 18 Gy × 3 (17.3%). Factors significantly associated with daily SBRT scheduling included number of fractions ($P < .0001$), race ($P = .01$), lower income ($P < .0001$), lower comorbidities ($P = .002$), and treatment at academic/research programs ($P < .0001$, Table 2). Patients with higher comorbidities ($P = .004$) and higher T stage ($P < .0001$) were more likely to receive 5-fraction SBRT (Table E1).

The use of daily SBRT scheduling decreased from a peak of 36.8% in 2007 to 21.7% in 2016, whereas QOD treatment increased from a low of 63.2% in 2007 to 78.3% in 2016 (both $P < .0001$; Fig. 1A). The use of 3-fraction SBRT decreased over time from 81.5% in 2004 to 23.4% in 2016, whereas 5-fraction SBRT increased from 3.7% in 2004 to 51.4% in 2016 (both $P < .0001$); there was no significant change in use of 4-fraction regimens ($P = .60$; Fig. 1B). The most common treatment schedule was 3 fractions QOD from 2004 to 2011 (25.5%-70.4%), whereas more recently, 5 fractions QOD was most prevalent from 2012 to 2016, rising from 28.5% in 2012 to 41.6% in 2016.

Survival analysis

The median follow-up for patients who received SBRT for stage I NSCLC was 28.9 months (35.5 months for surviving patients), and the median survival for all patients

Table 2 Patient, tumor, and treatment characteristics

Characteristics	All patients (N = 15,269)	Daily (N = 3927)	Every other day (N = 11,342)	*P*
	n (column percent)			
Age (y)				.18
18 to <65	2272 (14.9)	603 (15.4)	1669 (14.7)	
65 to <75	5291 (34.7)	1392 (35.5)	3899 (34.4)	
75+	7706 (50.5)	1932 (49.2)	5744 (50.9)	
Gender				.64
Male	6861 (44.9)	1777 (45.3)	5084 (44.8)	
Female	8408 (55.1)	2150 (54.7)	6258 (55.2)	
Race				.01
White	13,570 (88.9)	3546 (90.3)	10,024 (88.4)	
Black	1306 (8.6)	298 (7.6)	1008 (8.9)	
Other	259 (1.7)	57 (1.5)	202 (1.8)	
Missing	134 (0.88)	26 (0.66)	108 (0.95)	
Insurance status				.07
Private	1966 (12.9)	490 (12.5)	1476 (13.0)	
Government	546 (3.6)	132 (3.4)	414 (3.7)	
Medicare	11,891 (77.9)	3074 (78.3)	8817 (77.7)	
Medicaid/uninsured	660 (4.3)	142 (3.6)	518 (4.6)	
Missing	206 (1.4)	89 (2.3)	117 (1.0)	
Median income				<.0001
<$30,000	1864 (12.2)	533 (13.6)	1331 (11.7)	
$30,000-$34,999	2578 (16.9)	752 (19.2)	1826 (16.1)	
$35,000-$45,999	4065 (26.6)	1014 (25.8)	3051 (26.9)	
$46,000 +	5098 (33.4)	1268 (32.3)	3830 (33.8)	
Missing	1664 (10.9)	360 (9.2)	1304 (11.5)	
Charlson-Deyo score				.002
0	7959 (52.1)	2028 (51.6)	5931 (52.3)	
1	4176 (27.4)	1149 (29.3)	3027 (26.7)	
2 or more	3134 (20.5)	750 (19.1)	2384 (21.0)	
Clinical T classification				.54
T1	11,903 (78.0)	3075 (78.3)	8828 (77.8)	
T2	3366 (22.0)	852 (21.7)	2514 (22.2)	
Histology				.55
Adenocarcinoma	6752 (44.2)	1733 (44.1)	5019 (44.3)	
Squamous cell carcinoma	5298 (34.7)	1386 (35.3)	3912 (34.5)	
Other	3219 (21.1)	808 (20.6)	2411 (21.3)	
Facility type				<.0001
Community program (CP)	514 (3.4)	85 (2.2)	429 (3.8)	
Comprehensive CP	6024 (39.5)	1457 (37.1)	4567 (40.3)	
Academic/research program	6201 (40.6)	1786 (45.5)	4415 (38.9)	

(*continued on next page*)

Table 2 (*Continued*)

Characteristics	All patients (N = 15,269)	Daily (N = 3927)	Every other day (N = 11,342)	*P*
Integrated Network Cancer Program	2530 (16.6)	599 (15.3)	1931 (17.0)	
Fractions				<.0001
3	4993 (32.7)	1284 (32.7)	3709 (32.7)	
4	4278 (28.0)	1371 (34.9)	2907 (25.6)	
5	5998 (39.3)	1272 (32.4)	4726 (41.7)	

Abbreviations: N = total number of patients; n = number of patients; SBRT = stereotactic body radiation therapy.
For race, insurance status, and median income, patients with missing data were excluded from the analysis.

was 38.3 months (Table 3). The overall 3-year and 5-year survival rates were 52.5% and 30.9%, respectively. Median survival for patients who received daily SBRT was 37.9 months versus 38.4 months for QOD (P = .41; Fig. 2A). Median survival for patients who received 3-fraction SBRT was 40.7 months; for 4-fractions, 38.6 months; and for 5-fractions, 35.4 months (P < .0001; Fig. 2B; Table 3).

On multivariable analysis adjusting for age, gender, race, insurance status, median income, Charlson-Deyo score, clinical T classification, histology, and facility type, no difference was found in OS between daily versus QOD SBRT scheduling (aHR, 0.99; 95% CI, 0.94-1.04; P = .55; Table 4). On subgroup analyses, 5-fraction SBRT was associated with worsened survival versus 3-fraction (aHR, 1.09; 95% CI, 1.03-1.115; P = .002). For patients who received 3-fraction SBRT, QOD treatment was associated with improved survival versus daily treatment on both univariate (HR, 0.90; 95% CI, 0.83-097; P = .008) and multivariate analyses (aHR, 0.91; 95% CI, 0.84-0.98; P = .02). With 5-fraction SBRT, QOD treatment was associated with worse survival versus daily treatment (HR, 1.14; 95% CI, 1.04-1.24; P = .004: aHR, 1.11; 95% CI, 1.02-1.22; P = .02). No difference was observed with daily versus QOD scheduling for 4-fraction SBRT (HR, 0.96; 95% CI, 0.88-1.05; P = .37: aHR, 0.97; 95% CI, 0.88-1.05; P = .43). Results remained largely the same when analyzing the more recent data from 2012 to 2016 (Table E2).

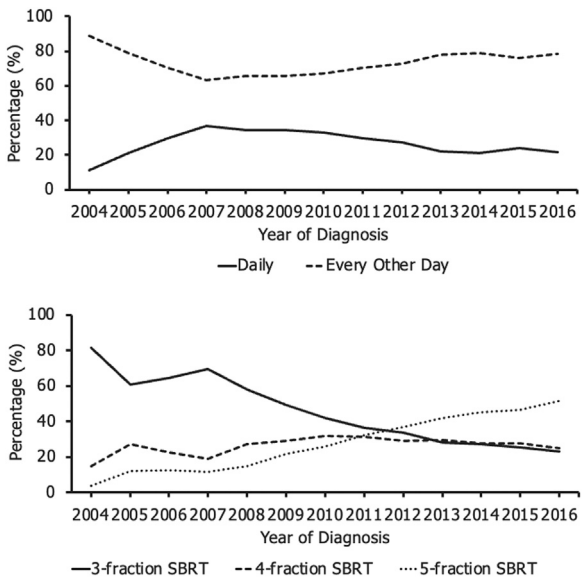

Figure 1 (A) Trends in daily versus every other day stereotactic body radiation therapy (SBRT) from 2004 to 2016, (B) Trends in use of 3-, 4-, or 5-fraction SBRT from 2004 to 2016.

Discussion

In this NCDB analysis of 15,269 patients with stage I NSCLC treated with SBRT, QOD treatment schedules were more frequently used than daily treatment by almost 3-fold. QOD 5-fraction treatment became more popular over time and was the most common dose schedule after 2012. Daily versus QOD scheduling was not associated with significant differences in OS. However, 5-fraction SBRT was associated with worsened survival versus 3-fractions. In subgroup analyses, 3-fraction QOD SBRT was associated with improved survival compared with 3-fraction daily SBRT, while 5-fraction QOD SBRT was associated with worse survival compared with 5-fraction daily treatment.

Our study found that myriad SBRT dose and fractionation combinations were used across the United States. The most common schedule from 2004 to 2011 was 3 fractions QOD, with 18 Gy × 3 being one of the most common SBRT treatment schedules. This finding mirrored the prescription dose used in the RTOG 0236 and 0618 trials.[9,15,16] The more recent RTOG 0813 used a nonconsecutive 5-fraction SBRT schedule with 10 to 12 Gy/fraction.[17] Our study found that 5-fraction QOD treatment became the most prevalent SBRT schedule from 2012 to 2016, with 10 Gy × 5 being the most common prescription. Similarly, Corso et al[5] found that from 2004 to 2011, there was a decrease in the use of 18

Table 3 Survival analysis by treatment

Treatment Regimen	N	Events	Median Survival (mo)	Survival rate 3-y	Survival rate 5-y	*P*
Overall	15,269	9122	38.3	52.5	30.9	
Treatment time						
Daily	3927	2451	37.9	51.9	30.0	.41
Every other day	11,342	6671	38.4	52.7	31.2	
Fractions						
3	4993	3130	40.7	55.6	32.2	<.0001
4	4278	2582	38.6	53.0	31.9	
5	5998	3410	35.4	49.3	28.9	

Abbreviations: N = total number of patients.
Note: 9122 deaths were reported during the follow-up period (median follow-up = 28.9 months) with an overall 5-year survival rate of 30.9% (median survival = 38.3 months). Surviving patients had a median follow-up of 35.5 months.

Gy × 3, whereas the use of 10 Gy × 5 increased significantly; our study used newer NCDB data from 2004 to 2016. In addition, we observed a steady decline in the use of daily SBRT scheduling, whereas QOD treatment increased from 2007 to 2016. The shift from 3 to 5 fractions in recent years could be associated with emerging data demonstrating increased toxicity with 3-fraction treatment.[20] The overall utilization trend of SBRT in treating stage I NSCLC most likely reflects that physicians are shifting their practice to balance maximizing efficacy while minimizing toxicity and side effects.

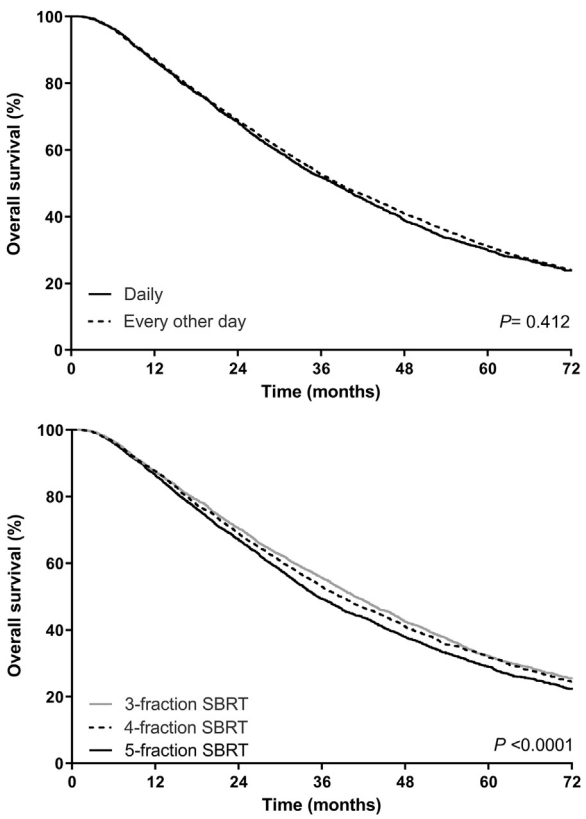

Figure 2 (A) Kaplan-Meier analysis for overall survival in patients with clinical stage I non-small cell lung cancer (NSCLC) receiving daily versus every other day stereotactic body radiation therapy (SBRT), (B) Kaplan-Meier analysis for overall survival in patients with clinical stage I NSCLC receiving 3-, 4-, or 5-fraction SBRT.

In addition to fraction number, SBRT treatment schedules for stage I NSCLC remain variable. Phase 2 clinical trials investigating SBRT for early-stage NSCLC have used different treatment schedules. For example, RTOG 0236 and 0618 specified prescription doses of 3 fractions total, separating each fraction by at least 40 hours.[15,16] Similarly, RTOG 0813 used fractionation scheduling of 5 nonconsecutive fractions delivered every second to third day.[17] In contrast, RTOG 0915 compared 1-fraction scheduling to 4-fraction treatments administrated over 4 consecutive days.[18] Lastly, the ongoing Veteran Affairs Lung Cancer Surgery or Stereotactic Radiotherapy trial employs daily or QOD 3-, 4-, and 5-fraction treatment.[21] The hypothesis has been raised that hypofractionation can result in tumor hypoxia and suboptimal tumor radiosensitization.[22] One study found that oxygenation in tumor cells decreases after SBRT and recovers after 24 to 48 hours[23]; thus, it has been postulated that nonconsecutive treatment could potentially improve the efficacy of SBRT. Theories regarding the role of reoxygenation and radiosensitivity are largely induced from in vitro cell and animal models, and the clinical relevance of this phenomenon, especially in NSCLC, is not well explored.[23,24]

Our study's median OS of 38.3 months and 5-year survival rate of 30.9% were within the range of previous clinical trials. The RTOG 0236 trial[25] reported a 5-year OS of 40.0% (95% CI, 27.1%-52.5%) and a median OS of 48 months (95% CI, 30-63 months), whereas RTOG 0618[16] reported a median OS of 55.2 months (95% CI, 37.7 months to not reached). Although our survival rates were

Table 4 Univariable and multivariable analysis of overall survival

			Hazard ratio (95% confidence interval) *P*			
	N	Events	Univariable		Multivariable	
Treatment time						
Daily	3463	2229	Reference	.82	Reference*	.55
Every other day	935	6050	0.99 (0.95-1.04)		0.99 (0.94-1.04)	
Fractions						
3	4392	2876	Reference		Reference†	
4	3714	2344	1.05 (0.99-1.11)	.10	1.05 (0.99-1.11)	.11
5	5192	3059	1.13 (1.08-1.19)	<.0001	1.09 (1.03-1.15)	.002
3 Fractions						
Daily	1151	830	Reference	.008	Reference‡	.02
Every other day	3241	2046	0.90 (0.83-0.97)		0.91 (0.84-0.98)	
4 Fractions						
Daily	1190	761	Reference	.37	Reference‡	.43
Every other day	2524	1583	0.96 (0.88-1.05)		0.97 (0.88-1.05)	
5 Fractions						
Daily	1122	638	Reference	.004	Reference‡	.02
Every other day	4070	2421	1.14 (1.04-1.24)		1.11 (1.02-1.22)	

Abbreviations: N = total number of patients.
*Multivariable model includes age, gender, race, insurance status, median income, Charlson-Deyo score, clinical T classification, histology, facility type, and fractions.
†Multivariable model includes age, gender, race, insurance status, median income, Charlson-Deyo score, clinical T classification, histology, facility type, and treatment time.
‡Multivariable model includes age, gender, race, insurance status, median income, Charlson-Deyo score, clinical T classification, histology, and facility type.

on the lower end of the 95% CIs reported in these trials, the differences might be attributed to variations in patient selection, treatment protocols, and sample size comparing national cohort versus clinical trial populations. These prospective clinical trials focused on specific treatment regimens without comparing daily versus QOD scheduling, highlighting the need for further studies to evaluate the impact of scheduling on survival outcomes. In our study, we did not find a statistically significant survival difference comparing the daily versus QOD SBRT treatment schedule, consistent with prior smaller studies. A multi-institutional study with 245 patients with stage I NSCLC showed no difference in survival between daily versus QOD scheduling (median 38.0 months vs 38.0 months, log-rank $P = .7$).[24] Similarly, in another multicenter retrospective study with 747 patients, Stahl et al[26] found that a daily or nonconsecutive treatment schedule was not significantly associated with OS on univariable analysis (HR, 0.89; 95% CI, 0.64-1.25; $P = .50$). A retrospective single institutional analysis of 107 patients found that daily SBRT treatment was associated with lower 3-year local control compared with QOD treatment (63.6% vs 93.3%; $P = .001$).[27] However, there was no statistically significant difference in survival between daily and QOD treatment groups (3-year OS: 61.7% vs 46.5%, $P = .19$).

On multivariable analyses, we found that 5-fraction SBRT might be associated with worse OS compared with 3 fractions. Of note, patients with higher comorbidities and T stage were more likely to receive 5-fraction treatment in our study, in line with RTOG 0813 demonstrating that 5-fraction SBRT may be used to treat frail populations and minimize risk of toxicity for centrally located tumors where increased fractionation would be more protective for critical organs at risk.[17] Interestingly, our results demonstrated that 3-fraction QOD treatment was associated with improved survival versus 3-fraction daily treatment, whereas 5-fraction QOD SBRT was associated with worse survival versus 5-fraction daily treatment. It is possible that daily 3-fraction SBRT leads to increased toxicity,[28] whereas QOD 3-fraction SBRT provides more time for interfractional normal tissue repair after high radiation doses.[29] Because QOD treatment may be linked to reduced toxicity, prioritizing QOD scheduling over daily scheduling in 3-fraction treatments might allow a more favorable balance between tumoricidal dose and protection of critical adjacent organs. In contrast, 5-

fraction QOD SBRT commonly employs lower daily doses, resulting in decreased biologically effective doses and longer overall treatment duration. As a result, this approach may result in decreased tumoricidal effects compared with daily SBRT. Although other retrospective studies did not show a significant difference in survival between daily versus QOD scheduling for 5-fraction SBRT,[24,27] these analyses may have been limited by the small sample size. Because 5-fraction QOD treatment has become increasingly prevalent, future studies are needed to test these hypotheses and characterize factors affecting survival, including the balance between tumor local control and toxicity due to irradiation of organs at risk. We did not observe a significant difference between daily and QOD 4-fraction treatments, perhaps because of a balance between toxicity and local control/tumoricidal effects with 4 fractions.

Other studies have found that shortening overall treatment time with consecutive daily treatment schedules might be associated with increased acute toxicity.[28,30] In a study with 92 patients from 12 institutions, Verma et al[28] reported that patients treated with QOD SBRT experienced significantly fewer Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher toxicities compared with daily SBRT treatment (7% vs 43%, $P < .001$). Similarly, in a randomized prospective study, Jain et al[30] showed that grade 2 or higher acute toxicity was more common in the daily SBRT group, approaching statistical significance (55.6% vs 33.3%, $P = .09$). In contrast, Alite et al[27] found no significant difference in CTCAE Grade 2 or higher on-treatment or posttreatment toxicity between daily and QOD 5-fraction SBRT, with grade 2 or higher pulmonary toxicity rate in the daily group 13.9% versus 10.8% in the QOD group ($P = .78$). Our study could not analyze toxicity because the NCDB does not capture CTCAE or other measures of treatment adverse events. The effect of SBRT scheduling on treatment toxicity requires further investigation in larger independent and prospective cohorts.

Our study has several limitations. First, it is retrospective, which can lead to inherent reporting bias. The study population was limited to CoC-accredited institutions and patients with SBRT dose, fractionation, and scheduling data, which might have introduced selection bias. The NCDB does not capture all critical patient, tumor, and treatment characteristics or cancer-specific outcomes (including local relapse, distant metastasis, or cancer-specific survival), limiting our analysis. Variables that could impact clinician treatment selection and OS, such as performance status, medical operability, tumor location (including proximity to critical organs at risk), and treatment toxicity, are not available in the database. This absence of data may introduce potential confounding factors. Although we adjusted for known confounders in our multivariable analysis, residual confounding may still be present, including those caused by clinician biases. Although retrospective analyses of treatment variables always bear the risk of confounding by indication, our analysis revealed the novel finding that daily versus QOD scheduling fractionation was not significantly associated with survival, and furthermore that increasing the number of fractions did not mitigate the poorer prognosis of centrally located tumors that were more likely treated with 5 fractions. When examining the 5-fraction subgroup, every other day treatment was associated with worse survival, but for the 3-fraction subgroup, every other day fractionation was associated with improved survival. As such, our study demonstrated signals that were not solely accountable by any assumed clinician biases.

Conclusions

Between 2004 and 2016, QOD and 5-fraction SBRT schedules for stage I NSCLC became increasingly common. There was no statistically significant difference in survival comparing daily versus QOD treatment schedules, but 5-fraction SBRT was associated with worse survival versus 3 fractions. With 3-fraction SBRT, QOD treatment was associated with improved survival compared with daily treatment. With 5-fraction SBRT, QOD treatment was associated with worse survival versus daily treatment. Because the implementation and utilization of SBRT continues to expand, future prospective studies are necessary to determine optimal SBRT scheduling for stage I NSCLC.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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