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Original research article

Long-term outcome comparison for standard fractionation (≥59 Gy) versus hyperfractionated (≥45 Gy) radiotherapy plus concurrent chemotherapy for limited-stage small-cell lung cancer

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ABSTRACT

Background: Concurrent chemoradiotherapy (CCRT) is commonly employed in limited-stage small-cell lung cancer (LS-SCLC); however, the optimal radiotherapy regimen is still unknown. This 3-institution analysis compares long-term disease control and survival outcomes for once- (QD) versus twice-daily (BID) radiotherapy at contemporary doses.
Methods and Materials: Data were collected for LS-SCLC patients treated with platinum-based CCRT and planned RT doses of ≥5940 cGy at ≥180 cGy QD or ≥4500 cGy at 150 cGy BID. Comparative outcome analyses were performed for treatment groups.
Results: From 2005 through 2014, 132 patients met inclusion criteria for analysis (80 QD, 52 BID). Treatment groups were well-balanced, excepting higher rate of advanced mediastinal staging, longer interval from biopsy to treatment initiation, and lower rate of prophylactic cranial irradiation for the QD group, as well as institutional practice variation. At median survivor follow-up of 33.5 months (range, 4.6–105.8), 80 patients experienced disease failure (44 QD, 36 BID), and 106 died (62 QD, 44 BID). No differences in disease control or survival were demonstrated between treatment groups.
Conclusion: The present analysis did not detect a difference in disease control or survival outcomes for contemporary dose QD versus BID CCRT in LS-SCLC.

1. Introduction

Concurrent chemoradiotherapy is the standard-of-care management for limited-stage small-cell lung cancer (SCLC).[1] While platinum doublet chemotherapy is established as the most effective systemic therapy,[1–3] there remains uncertainty regarding the optimal radiotherapy regimen. Nearly twenty years ago, the 5-year results of the Intergroup 0139 were published, demonstrating superior survival for 4500 cGy in twice-daily hyperfractionation versus the 4500 cGy in standard once-daily fractionation.[4] However, as radiotherapy techniques have evolved, the safety and efficacy of higher doses of once-daily thoracic radiotherapy have been established,[5,6] and this has contributed to continued variability in practice patterns.[7–9] The present investigation compares mature disease control and survival outcomes for contemporary dose once-daily (QD) radiotherapy (to ≥5940 cGy) versus twice-daily (BID) radiotherapy (to ≥4500 cGy) with concurrent platinum-based chemotherapy in limited-stage SCLC patients treated across three institutions.

2. Methods and materials

Following Institutional Review Board approval at each study institution, study-specific demographic, staging, treatment, and outcome data were collected for analysis. Eligible cases were identified by local Cancer Registry or departmental quality assur-

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Table 1
Patient, tumor, and treatment characteristics.

Variable	Once-daily (n = 80)		Twice-daily (n = 52)		p-value
	n	%	n	%	
Institution					<0.01
1	7	9	43	83	
2	12	15	6	12	
3	61	76	3	6	
Age					
Median	65 yrs		63 yrs		0.21
(Range)	(39–83)		(43–81)		
≥70 years	29	36	10	19	0.04
Gender					0.77
Male (%)	41	51	28	54	
Race					0.06
White	78	97	46	88	
Pre-Existing COPD	33	41	16	31	0.22
Prior Lung Cancer?	3	4	2	4	1.00
Primary Laterality					0.10
Right	39	49	25	48	
Left	26	32	24	46	
Mediastinal	10	12	3	6	
Indeterminate	5	6	0	0	
Primary Tumor Size					0.68
Median	3.7 cm		3.6 cm		
(Range)	(0.5–13.9)		(0.6–11.3)		
Pleural Effusion at Diagnosis	14	18	8	15	0.75
Mediastinoscopy or EBUS	61	76	26	50	<0.01
PET Staging	65	81	36	69	0.11
Supraclavicular LN Involved	5	6	7	13	0.22
CNS Staging	76	95	52	100	0.15
Interval Biopsy to Treatment					<0.01
Start	13 days		21 days		
Median	(1–81)		(0–64)		
(Range)					
Chemotherapy					
RT start with cycle 1–2	70	88	47	90	0.61
Completion of ≥4 cycles	68	93	45	92	1.00
Radiotherapy					
Median Dose Planned	6120 cGy		4500 cGy		
(Range)	(5940–7000)		(4500–6000)		n/a
Median Dose Completed	6120 cGy		4500 cGy		
(Range)	(900–6660)		(4350–6000)		
Completed ≥95% RT dose	74	92	51	98	0.24
PCI	32	40	43	83	<0.01
Follow-Up Interval					0.18
Median	16.7 months		21.2 months		
(Range)	(0.4–102.6)		(2.6–117.1)		

COPD = chronic obstructive pulmonary disease; EBUS = endobronchial ultrasound; PET = positron emission tomography; LN = lymph node; CNS = central nervous system; PCI = prophylactic cranial irradiation.

ance database software. Criteria for inclusion were: diagnosis of SCLC between 2005 and 2014, limited-stage at diagnosis (ipsilateral supraclavicular lymph node involvement permitted; cytologically negative or small unsampled pleural effusion was permitted), unresected primary tumor, initiation of radiotherapy during platinum-based chemotherapy (concurrent), and planned radiotherapy dose of ≥5940 cGy (if once-daily fractionation) or ≥4500 cGy (twice-daily).

Treatment planning involved CT-based simulation with patients lying supine with arms abducted above the head. In all cases, the primary tumor site and any clinically or radiographically involved lymph nodes were included in the radiotherapy treatment volumes; in some cases, uninvolved at-risk hilar and/or mediastinal nodal regions were included in the treatment volumes as well. All patients were treated using megavoltage linear accelerators with ≥6 MV photons, using 3-dimensional conformal or intensity-modulated radiotherapy treatment techniques. Prescriptions were made to treatment volumes, which included the primary tumor (and lymph node(s), when involved), with expansions for peri-tumoral extension and set-up variability. In general, inhomogeneity calculations for varying tissue density were performed.

Specific to the radiotherapy fractionation groups, radiotherapy fractionation regimens varied at the discretion of the treating radiation oncologist. The QD group included patients prescribed at 180–200 cGy per daily fraction, 5 days per week, to total doses of ≥5940 cGy, while the BID group included patients planned to ≥4500 cGy at 150 cGy per twice-daily fraction, five days per week, with minimum six hours between fractions. Variations in radiotherapy prescriptions were attributable to the practice paradigms of different treating radiation oncologists over time.

Specific to chemotherapy, the most common chemotherapy regimens involved etoposide (80–120 mg/m^2/day on days 1–3) and cisplatin (60–80 mg/m^2 on day 1 or 20 mg/m^2 on days 1–3) or carboplatin (AUC = 5–6 on day 1), administered every 3–4 weeks for 4–6 cycles at the discretion of the treating medical oncologist. Radiotherapy initiated with cycle 1 or 2 of chemotherapy in most cases; however, these data were specifically recorded for comparison, as evidence suggests superior outcomes for earlier radiotherapy initiation.[9–11] Four to eight weeks after completion of concurrent chemoradiotherapy, prophylactic cranial irradiation was offered to patients with favorable clinical and radiographic responses.

Overall survival (OS) was measured from date of radiotherapy initiation to last follow-up or death. Freedom from failure (FFF) was measured from the date of radiotherapy initiation to the date of recurrence (earliest sign of radiographic recurrence, or pathologic confirmation thereof), or to last follow-up or death if no recurrence had manifest. For patients lost to follow-up (no follow-up within 3 months prior to death) without prior evidence of recurrence, FFF was calculated utilizing the last reported date the patient was without evidence of disease. Deaths determined to be directly related to treatment were counted as an event for FFF. Chi-squared tests, Fisher's exact tests, and Wilcoxon rank sum tests were used to investigate differences between the QD and BID treatment groups. Groups were compared based upon demographic (e.g., age at diagnosis), staging work-up (e.g., PET/CT), tumor characteristics (e.g., tumor size), treatment characteristics (e.g., chemotherapy cycle at radiotherapy initiation), and follow-up interval.

The Kaplan-Meier method was used to calculate 3- and 5-year estimates of FFF and OS for the QD and BID treatment groups. Estimates, along with 95% pointwise confidence intervals, were reported. Differences between survival curves were compared using the log-rank test. All statistical testing was two-sided and assessed for significance at the 5% level using SAS software (Cary, NC, U.S.A.).

3. Results

Between 2005 and 2014, 132 patients met criteria for inclusion in the present analysis (80 QD, 52 BID). Treatment groups were generally well-balanced, though institutional differences in regimen were observed, as anticipated. Overall, the QD group had more patients aged ≥70 years at diagnosis (without significant difference in age for overall populations), higher rates of advanced mediastinal staging (employing endobronchial ultrasound or mediastinoscopy), longer interval from biopsy to treatment initiation, and lower rate of prophylactic cranial irradiation. Follow-up interval was similar between treatment groups. Comprehensive comparison of factors is demonstrated in Table 1. Additionally, one patient in the BID group was initially prescribed 4500 cGy in 30 BID fractions, but changed to once-daily fractionation midway through treatment, while another was prescribed 120 cGy BID to 6000 cGy total (completing 5400 cGy).

At a median follow-up of 18.5 months (range, 0.4–117.1; with median 33.5 months for surviving patients), 80 patients experienced disease failure (44 QD / 36 BID) and 106 died (62/44), including 74 from known SCLC recurrence or treatment (45/33). Patterns of failure and causes of death are outlined in Table 2. No differences in FFF ($p = 0.64$) or OS ($p = 0.68$) were demonstrated between treatment groups (Figs. 1 and 2; Table 3).

Table 2
Patterns of failure.

	QD	(n = 80)[a]	BID	(n = 52)[b]
	n	%	n	%
Initial Failure Site(s)				
No Failure	33	43	16	31
Locoregional In-Field	8	10	7	14
Locoregional In + Out-of-Field	0	0	5[c]	10
Locoregional Out-of-Field	1[d]	1	4[e]	8
Distant Only	24	31	11	22
Any Locoregional + Distant	8	10	8	16
Overall Survival Events				
Alive, NED	17	21	4	8
Alive with Disease	1	1	4	8
Died of/with Disease	43	54	32	62
Died from Treatment Effects	2	2	1	2
Died Other Cause	7	9	9	17
Died Unknown Cause	10	12	2	4

QD = once-daily group; BID = twice-daily group; NED = no evidence of disease.

[a] Patterns of failure analysis excludes five patients with treatment-related toxicity (one died with chemotherapy-associated pancytopenia while on treatment, two with severe decline midway through chemoradiotherapy, and one with rapid clinical decline after prophylactic cranial irradiation) and one patient without known pattern of failure, who was lost to post-treatment follow-up prior to death.

[b] Patterns of failure analysis excludes one patient who died of heart failure less than 2 months post-radiotherapy, without overt recurrence.

[c] Includes failures at primary site plus supraclavicular node (2), primary site plus ipsilateral out-of-volume lung (2),and primary site plus ipsilateral lung plus supraclavicular node (1); of note, 3 of these patients had treatment breaks of 5, 10, and 25 days, respectively.

[d] Patient with ipsilateral hilum and out-of-volume lung failure (had been PET/CT staged).

[e] Includes one patient each with superior mediastinal plus retrotracheal nodal failure (1), superior mediastinal plus ipsilateral supraclavicular nodal failure (1), contralateral hilar failure (1), and ipsilateral supraclavicular nodal failure (1); 3 of these patients had been PET/CT staged at diagnosis.

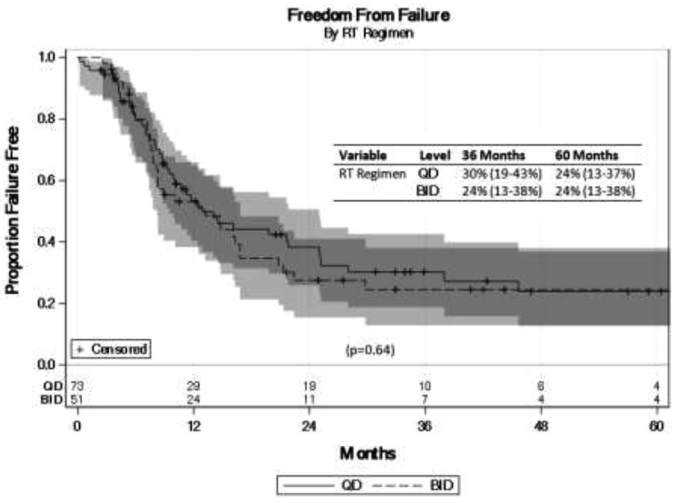

Fig. 1. Freedom from failure by once- versus twice-daily radiotherapy group.

4. Discussion

While the Intergroup 0139 trial demonstrated a 10% absolute improvement in 5-year survival for BID over QD radiotherapy almost twenty years ago,[4] traditional standard fractionation (QD) has remained the most common approach over the past decade.[9] Aside from patient and clinical scheduling convenience, the strongest argument for continuing with QD has been the relatively low total radiotherapy dose in the QD arm (4500 cGy in 25 fractions) of the Intergroup trial, for which higher dose thresholds have been achieved in combination with platinum doublet chemotherapy.[5,6] Unfortunately, there has been little long-term comparative outcome data to support this approach, likely attributable to relatively consistent practice patterns within institutions. By including both academic and community-based practices, with varying intra- and inter-departmental patterns of treatment, the present study suggests that contemporary-dose QD regimens have similar efficacy to BID regimens, applicable across multiple treatment centers. These data are supported by findings from the phase III CONVERT trial, which compared 6600 cGy in 33 once-daily fractions against 4500 cGy in 30 twice-daily fractions, initiated at day 22 of cisplatin/etoposide doublet chemotherapy (for total 4–6 cycles).[12] No difference in survival was noted between trial arms, with 2-year survival of 51% versus 56%, and median survivals of 25 versus 30 months, respectively ($p = 0.14$). While these figures appear superior to the present investigation, the CONVERT trial selected for favorable performance status patients and mandated prophylactic cranial irradiation for patients with non-progressive disease. A

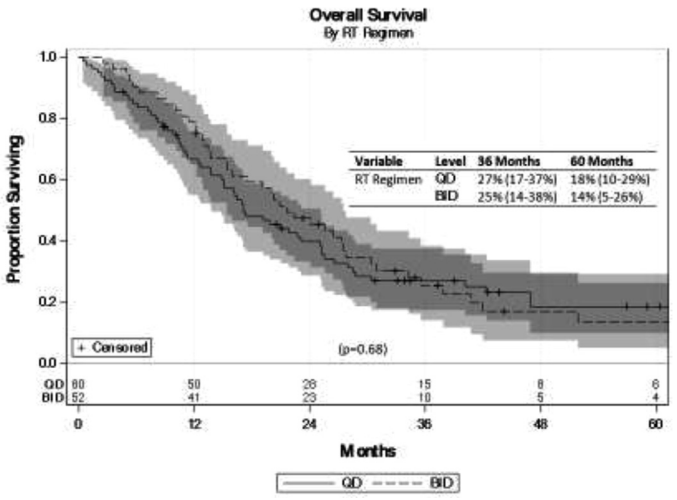

Fig. 2. Overall survival by once- versus twice-daily radiotherapy group.

Table 3
Disease control and survival outcomes.

Outcome measure	Once-daily	Twice-daily	p[a]
Overall Survival			0.68
Median	16.7 months	21.2 months	
(Range)	(0.4–102.6)	(2.6–117.1)	
Median (survivors)	33.9 months	32.9 months	
(Range)	(4.6–91.9)	(12.4–105.8)	
3-year	27%	25%	
(95% CI)	(17%-37%)	(14%-38%)	
5-year	18%	14%	
(95% CI)	(10%-29%)	(5%-26%)	
Freedom From			0.64
Failure	12.9 months	13.2 months	
Median	30%	24%	
3-year	(19%-43%)	(13%-38%)	
(95% CI)	24%	24%	
5-year	(13%-37%)	(13%-38%)	
(95% CI)			

[a] p-value for log-rank test.

recently-published registry-based study evaluating the impact of radiotherapy fractionation and timing within a large population demonstrated findings similar to our own, with 5-year overall survivals of approximately 20% when radiotherapy was initiated 0–20 days after chemotherapy ("early" radiotherapy).[9] Interestingly, the survival advantage of early radiotherapy was noted only for the BID group (5-year survival 28% versus 21% for early versus late, respectively; p = 0.004) but not for the QD group (20% versus 18%, p = 0.29), with multivariable analysis demonstrating independence of BID radiotherapy (HR 0.90; p = 0.001), but not early radiotherapy (HR 0.98; p = 0.53). However, these data must be interpreted with caution, as selection of fractionation and timing are frequently influenced by disease burden and patient performance status, and no data regarding the extent of staging work-up or prophylactic cranial irradiation was captured in the database.

Another explanation for the higher rate of QD utilization in general practice is the facilitation of planning and correlative predictability of toxicity. General and thoracic specialist radiation oncologists typically see a much higher caseload of locoregionally advanced non-small-cell lung cancer (NSCLC), in which standard fractionation remains the standard-of-care, as hyperfractionation did not demonstrate superiority.[13] Further, whereas comprehensive mediastinal nodal irradiation was required in the Intergroup 0139 trial, contemporary SCLC treatment volumes more closely reflect those of NSCLC,[14] with PET/CT-based involved-field radiotherapy resulting in low rates of out-of-field regional failure.[15–17] Thus, radiation oncologists more familiar with the planning process and organ tolerances of NSCLC-style treatment have more commonly applied the QD dose-fractionation in clinical practice, albeit with limited outcome data to support the approach.[9,18–21] Within the present study population, we had initially hoped to make comparison of toxicities between the treatment groups, nearly all of whom were treated to involved-field (CT- or PET/CT-defined) sites only; however, owing to variations in documentation methods and record access, we were unable to ensure accuracy for such a comparison across the institutions. While investigators from one of the participating institutions have previously reported on similar tolerance at these dose levels,[18] and others have reported similar findings (with possible higher grade >2 skin and lung toxicity for QD),[19,20] the most convincing data will be those yielded from the standardized, prospectively-collected data from the randomized trials. The recently-reported CONVERT trial demonstrates equivalent rates of grade 3–4 esophagitis (19%), pneumonitis (~2%), and febrile neutropenia (~21%), though the BID arm did demonstrate a significantly higher rate of grade 4 neutropenia (49% versus 38%; p = 0.05). Preliminary results of the 3-arm Cancer and Leukemia Group B (CALGB) 30610 / Radiation Therapy Oncology Group (RTOG) 0538, comparing 7000 cGy (35 once-daily fractions) versus 6120 cGy (16 once-daily fractions followed by 9 twice-daily fractions) versus 4500 cGy (30 twice-daily fractions), have yet to be reported.

To our knowledge, the present study is one of the largest reported retrospective experiences for limited-stage SCLC chemoradiotherapy comparing outcomes between QD and BID radiotherapy regimens at contemporary doses.[20] As the majority of recurrences take place within the first two years of treatment,4 the median survivor follow-up of nearly three years suggests that data are sufficiently robust to consider either QD or BID treatment as an acceptable option. With regard to recurrence sites, the most common pattern of initial disease failure involved distant foci (~50% for total population, representing approximately two-thirds of all failures), consistent with previously-reported findings.[4,15,17] We did not appreciate a difference in crude rates of isolated in-field failure, though given the retrospective nature of the study and non-uniform re-staging protocol over time and across institutions, we did not perform specific statistical analysis, as this aspect of the results should be interpreted with appropriate caution. However, the similar long-term disease control and survival findings for each treatment group suggest that either radiotherapy regimen should result in a similar outcome.

In conclusion, the present study did not detect a difference in disease control or survival outcomes for limited-stage SCLC patients treated with contemporary-dose QD versus BID radiotherapy and concurrent chemotherapy. Patterns of failure appear similar, dominated by recurrence at distant sites. Thus, clinicians may elect either QD or BID regimen based upon clinical experience and patient preference.

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