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Clinical Investigation

Is There a Role for Hypofractionated Thoracic Radiation Therapy in Limited-Stage Small Cell Lung Cancer? A Propensity Score Matched Analysis

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Purpose: Various radiation schedules are used in concurrent chemoradiation therapy for limited-stage small cell lung cancer (LS-SCLC). Since there is currently no randomized evidence comparing hypofractionated radiation therapy (HFRT) and conventionally fractionated radiation therapy (CFRT), the aim of this study was to compare overall survival (OS), progression-free survival (PFS), and toxicity of HFRT and CFRT in LS-SCLC.

Methods and Materials: Patients with LS-SCLC treated between 2000 and 2013 with HFRT (40 Gy/15 fractions, 45 Gy/15 fractions, 45 Gy/20 fractions) or CFRT (60 Gy/30 or 66 Gy/33 fractions) were included. Propensity scores were generated using a multivariable logistic regression model. Patients were matched on a 1:1 ratio with a caliper distance of 0.20. OS and PFS were estimated by the Kaplan-Meier method and compared using log-rank tests. As a sensitivity analysis, univariable and multivariable Cox regression was performed including all patients without matching. Logistic regression was performed to identify predictors of pulmonary and esophageal adverse events.

Results: In the overall group of 117 patients, there were significant baseline differences between the HFRT and CFRT cohorts. Patients who received CFRT were older, more often smoked concurrently with treatment, had higher Eastern Cooperative Oncology Group performance status, different T and N stage patterns, and more commonly received concurrent chemoradiation therapy and prophylactic cranial irradiation. After propensity score matching for these differences, 72 patients were included, 36 in the HFRT and CFRT cohorts, respectively. There was no difference in OS ($P = .724$), PFS ($P = .862$), or any pulmonary ($P = .350$) or esophageal ($P = .097$) adverse events between cohorts. Skin adverse events were significantly higher for CFRT (41.7%) compared with HFRT (16.7%, $P = .020$). Multivariable Cox regression also revealed no differences in OS ($P = .886$) or PFS ($P = .717$) between all HFRT and CFRT patients, without matching. No grade 5 adverse events were observed.

Note—An online CME test for this article can be taken at https://academy.astro.org.

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Sondos Zayed and Hanbo Chen made equal contributions to this study.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: In LS-SCLC patients, HFRT was associated with comparable survival and toxicity outcomes and may be considered as an alternative to CFRT, should its efficacy be confirmed in prospective studies.

Introduction

Thoracic radiation therapy plays an important role in the management of limited-stage small cell lung cancer (LS-SCLC).[1,2] Compared with chemotherapy alone, concurrent chemoradiotherapy (CRT) results in improved overall survival (OS).[1,3-7] A variety of radiation therapy dose fractionation regimens are commonly used in CRT for LS-SCLC.[4,5,8-15] Phase 3 clinical trial data support the use of both hyperfractionated radiation therapy (45 Gy in 30 twice-daily fractions) and high-dose conventionally fractionated radiation therapy (CFRT, 66 Gy in 33 daily fractions); these regimens appear to achieve comparable survival outcomes with similar toxicity profiles.[5,16] Alternatively, hypofractionated radiation therapy (HFRT) using $\geq$2.1 Gy per fraction is also practiced in certain parts of the world, with a common regimen being 40 Gy in 15 fractions.[15] A phase 2 trial comparing HFRT to hyperfractionated radiation therapy demonstrated similar progression-free survival (PFS) and OS outcomes, although this study had a limited sample size, restricting its power.[17] There is currently no completed randomized clinical trial comparing HFRT to CFRT, yet HFRT remains the preferred radiation therapy schedule in several countries.[15]

HFRT may be preferred over CFRT or hyperfractionation because of a shorter overall treatment time, decreased resource utilization, and patient convenience with single daily visits.[18] In the absence of randomized evidence, nonrandomized evidence can be used judiciously after controlling for confounding factors that contribute to selection bias. Propensity score methods can attain more stable estimates of comparative effectiveness in the setting of a low ratio of outcome events to potential confounders.[19] Therefore, the objective of this study was to compare the survival outcomes and toxicities of HFRT with CFRT using propensity score–matched retrospective data.

Methods and Materials

We retrospectively analyzed patients with LS-SCLC treated with either HFRT or CFRT between January 2000 and December 2013, identified from an institutional database at the London Health Sciences Centre. Patients who had extrathoracic metastases were excluded, with the exception of those with ipsilateral supraclavicular lymphadenopathy, ipsilateral malignant pleural effusion, or contralateral mediastinal lymphadenopathy, which could be encompassed within the same radiation field. HFRT was defined as $\geq$2.1 Gy per fraction with a total dose between 37 and 50 Gy. CFRT was defined as 2 Gy per fraction, with $\geq$29 fractions, and a total dose $\geq$58 Gy. The institutional ethics review board approved the study (project ID: 105398).

Propensity score matching

Propensity scores were generated using multivariable logistic regression models predictive of treatment assignment (HFRT or CFRT). Matching was performed on age, smoking concurrent with treatment, Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2-3), T stage, N stage (*American Joint Committee on Cancer Staging Manual*, sixth edition), concurrent CRT, prophylactic cranial irradiation (PCI), central tumor location, and the presence of a pleural effusion. Central tumors were defined according to the International Classification of Diseases (ICD), Ninth and Tenth Revision, site code as those located at or near the main bronchus, carina, or hilus of the lung.[20,21] All possible interaction terms were examined, and no significant interactions were found.

Using the initial sample size (n = 117) and a ratio of 1:1, 3 matches were generated. Three scenarios for each match were examined using caliper widths of 0.10, 0.20, and 0.2 × (standard deviation) × logit(propensity score), respectively.[22-25] The caliper distance of 0.20 was selected because it generated the best final match with no standardized differences $\geq$0.3 in the covariates of interest. Standardized differences were used to assess balance between treatment groups across variables in the propensity score model. A standardized difference $<$0.10 was considered representative of "negligible imbalance" between treatment groups.[26-28] Only one standardized difference was between 0.2 and 0.3 (T3 stage), and 3 standardized differences were between 0.1 and 0.2 (T4 stage, PCI status, and central tumor location; Table EA). The final match was selected before analysis of treatment outcomes.

Statistical analysis

Descriptive statistics were generated for baseline patient characteristics, stratified by cohort (HFRT vs CFRT), for all patients and for the subset of matched patients. The χ^2 test, Fisher exact test, 2-sample *t* test, or Wilcoxon rank-sum test were used as appropriate to compare the cohorts (HFRT vs CFRT). Variables included in the propensity-score model were compared using the paired *t* test, Wilcoxon signed-rank test, or McNemar test as appropriate. Standardized

differences were calculated for variables included in the propensity score model.

Kaplan-Meier estimates were generated for OS and PFS for all patients and for the subset of matched patients, stratified by cohort (HFRT vs CFRT). Comparisons were made using the log-rank test for unmatched patients or the stratified log-rank test for matched patients.

The endpoints of this study included OS, PFS, any pulmonary adverse events (PAEs) of any grade, and any esophageal adverse events (EAEs) of any grade. OS was calculated as the time from date of diagnosis to date of last follow-up or death of any cause, whichever came first. PFS was calculated as time from the date of diagnosis to date of recurrence, date of last follow-up, or death from any cause, whichever came first.

Both propensity score matching and multivariable modeling can be used to control for confounders. However, because there is no clear consensus on a preferred method,[29] a sensitivity analysis was performed using univariable and multivariable Cox proportional hazards models for OS and PFS for all patients (n = 117). We wished to examine whether the reduced power associated with propensity score matching led to different results compared with traditional statistical techniques that may be prone to unstable estimates with a high number of potential confounders. Multivariable Cox regression models were generated by using treatment as the main exposure and adjusting for the potential confounders of age, smoking concurrent with treatment, ECOG performance status, T stage, N stage, concurrent CRT, PCI, central location, and pleural effusion. Violation of the proportional hazards assumption in Cox regression was evaluated using the Kolmogorov-Supremum test. If violations were detected, a time-dependent covariate was added to the Cox regression model and a P value was reported from a likelihood ratio test.

Logistic regression was performed to compare PAE and EAE between CFRT and HFRT cohorts in the matched and unmatched patient groups. For matched comparisons, only univariable models were performed, and these models were stratified by matched pair to account for the matched design. Multivariable logistic regression models in the unmatched cohort were generated for any PAE and any EAE, adjusting for the potential confounders of age, smoking concurrent with treatment, ECOG performance status, T stage, N stage, concurrent CRT, and central location.

All statistical analysis was performed in SAS version 9.4 (SAS Institute, Cary, NC), using 2-sided statistical testing at the .05 significance level.

Results

Baseline characteristics

A total of 117 patients were treated with HFRT or CFRT from 2000 to 2013 at our institution. Fifty-six received low-dose HFRT and 61 received high-dose CFRT. In the original group of 117 patients, there were significant standardized baseline differences between the CFRT and HFRT cohorts for age, smoking concurrent with treatment, ECOG performance status, T and N stage, concurrent CRT, and PCI. After matching for the variables included in the propensity-score model, the best final match generated a total of 72 matched patients: 36 in the HFRT and CFRT cohorts, respectively. Standardized differences between matched cohorts persisted only for T3 ($P = .257$, SD = 0.218), T4 ($P = .405$, SD = 0.190), and central tumor location ($P = .286$, SD = 0.112).

The most common HFRT dose and fractionation regimens for unmatched patients were 45 Gy in 20 fractions (46.4%), 40 Gy in 15 fractions (37.5%), and 45 Gy in 15 fractions (7.1%). A similar trend was found for matched HFRT patients. Other less common HFRT regimens in matched patients included 44 or 43 Gy in 20 fractions and 45 Gy in 21 fractions. The most common CFRT dose and fractionation regimen was 60 Gy in 30 fractions for unmatched (81.7%) and matched patients (85.7%). Other less common CFRT regimens in matched patients included 54 Gy in 32 fractions and 68 Gy in 34 fractions. Most patients received chemotherapy in both the matched (HFRT: 100%; CFRT: 97.2%) and unmatched (HFRT: 100%; CFRT: 98.4%) groups with no difference between CFRT or HFRT ($P > .99$ for both comparisons). For both HFRT and CFRT, 94.4% of matched patients received concurrent CRT, with no significant difference between cohorts ($P > .99$). In matched patients, the median number of chemotherapy cycles received in the CFRT cohort was 5 cycles (interquartile range, 4-6), compared with 6 cycles in the HFRT cohort (interquartile range, 6-6; $P < .001$). Baseline patient and treatment characteristics for both matched and unmatched patients, stratified by cohort (HFRT and CFRT), are shown in Table 1.

The median follow-up duration was significantly longer in the HFRT cohort (13.5 years) compared with the CFRT cohort (5.0 years) for all patients ($P = .020$) and for matched patients ($P = .001$). Baseline treatment outcomes, stratified by cohort, are shown in Table 2 for all patients and for matched patients.

Overall survival and progression-free survival for matched patients

Kaplan-Meier plots for OS and PFS are displayed in Figure 1B and 1D for matched patients (n = 72), stratified by treatment cohort (HFRT vs CFRT). Five-year OS was 31.5% for the matched patients who received HFRT compared with 26.1% for the matched patients who received CFRT (Table EB). Five-year PFS was 28.6% for the matched patients who received HFRT compared with 18.2% for the matched patients who received CFRT. No statistically significant difference was noted between cohorts for OS ($P = .724$) or PFS ($P = .862$).

Table 1 Baseline characteristics stratified by cohort (HFRT and CFRT) for all patients and for matched patients

	All patients (n = 117)					Matched patients (n = 72)				
Characteristic	N	HFRT (n = 56)	CFRT (n = 61)	*P* value	SD	N	HFRT (n = 36)	CFRT (n = 36)	*P* value	SD
Baseline patient characteristics										
Age (y),* mean ± SD	117	63.3 ± 9.2	68.2 ± 7.2	.002	0.597	72	66.6 ± 7.8	66.4 ± 7.6	.910	0.026
Year of diagnosis, median (IQR)	116	2002 (2001-2003)	2010 (2009-2012)	<.001	-	72	2002.5 (2001-2004.5)	2010 (2009-2012.5)	<.001	-
Male, n (%)	117	31 (55.4)	31 (50.8)	.623	-	72	20 (55.6)	16 (44.4)	.346	-
Smoking pack-years, mean ± SD	111	49.7 ± 28.3	47.9 ± 17.6	.551	-	70	52.3 ± 30.4	49.1 ± 16.7	.827	-
Smoking concurrent with treatment,* n (%)	117	14 (25.0)	21 (34.4)	.266	0.207	72	9 (25.0)	8 (22.2)	.796	0.065
Predicted FEV_1 (%), mean ± SD	74	72.2 ± 19.2	70.9 ± 19.2	.777	-	54	71.9 ± 19.0	69.6 ± 19.6	.666	-
DLCO (%), mean ± SD	65	64.4 ± 16.3	63.3 ± 21.9	.818	-	48	62.8 ± 17.2	61.7 ± 25.0	.866	-
ECOG performance status,* n (%)										
0-1	115	37 (68.5)	37 (60.7)	.380	0.165	72	23 (63.9)	23 (63.9)	>.99	0.000
2-3		17 (31.5)	24 (39.3)				13 (36.1)	13 (36.1)		
Baseline tumor characteristics										
T stage,* n (%)				.135					.694	
T0-T1	117	10 (17.9)	9 (14.8)	.649	0.084	72	7 (19.4)	8 (22.2)	.763	0.068
T2		14 (25.0)	13 (21.3)	.636	0.088		9 (25.0)	9 (25.0)	>.99	0.000
T3		7 (12.5)	20 (32.8)	.009	0.500		5 (13.9)	8 (22.2)	.257	0.218
T4		19 (33.9)	15 (24.6)	.266	0.206		11 (30.6)	8 (22.2)	.405	0.190
TX		6 (10.7)	4 (6.6)	.517	0.148		4 (11.1)	3 (8.3)	.706	0.094
N stage,* n (%)				.079					.996	
N0	117	15 (26.8)	11 (18.0)	.255	0.211	72	10 (27.8)	11 (30.6)	.808	0.061
N + (N1-N3)		36 (64.3)	49 (80.3)	.052	0.364		25 (69.4)	24 (66.7)	.819	0.060
NX		5 (8.9)	1 (1.6)	.103	0.330		1 (2.8)	1 (2.8)	>.99	0.000
M stage, n (%)										
M0	117	40 (71.4)	39 (63.9)	.291	-	72	27 (75.0)	25 (69.4)	.599	-
M1		13 (23.2)	21 (34.4)				9 (25.0)	11 (30.6)		
MX		3 (5.4)	1 (1.6)				0 (0)	0 (0)		
Stage (sixth edition), n (%)										
IA	117	2 (3.6)	1 (1.6)	.235	-	72	1 (2.8)	1 (2.8)	.584	-
IB		3 (5.4)	1 (1.6)				3 (8.3)	1 (2.8)		
IIA		0 (0)	3 (4.9)				0 (0)	3 (8.3)		
IIB		3 (5.4)	2 (3.3)				2 (5.6)	2 (5.6)		
IIIA		11 (19.6)	17 (27.9)				8 (22.2)	10 (27.8)		
IIIB		18 (32.1)	13 (21.3)				11 (30.6)	6 (16.7)		
IV		13 (23.2)	21 (34.4)				9 (25.0)	11 (30.6)		
Missing ("x")		6 (10.7)	3 (4.9)				2 (5.6)	2 (5.6)		
Central location,* n (%)	117	22 (39.3)	26 (42.6)	.714	0.068	72	15 (41.7)	17 (47.2)	.286	0.112
Pleural effusion,* n (%)	117	9 (16.1)	12 (19.7)	.612	0.094	72	5 (13.9)	4 (11.1)	.739	0.084
Baseline treatment characteristics										

(*continued on next page*)

Table 1 (*continued*)

Characteristic	All patients (n = 117) N	HFRT (n = 56)	CFRT (n = 61)	*P* value	SD	Matched patients (n = 72) N	HFRT (n = 36)	CFRT (n = 36)	*P* value	SD
4D planning technology, n (%)	117	8 (14.3)	55 (90.2)	<.001	-	72	6 (16.7)	32 (88.9)	<.001	-
Treatment technology, n (%)										
3D-CRT	117	36 (64.3)	7 (11.5)	<.001	-	72	27 (75.0)	4 (11.1)	<.001	-
Conventional 2D-RT		16 (28.6)	0 (0)				6 (16.7)	0 (0)		
IMRT		3 (5.4)	50 (82.0)				2 (5.6)	29 (80.6)		
VMAT		1 (1.8)	4 (6.6)				1 (2.8)	3 (8.3)		
Staging PET scan, n (%)	117	0 (0)	20 (32.8)	<.001	-	72	0 (0)	13 (36.1)	<.001	-
Chemotherapy, n (%)	117	56 (100)	60 (98.4)	>.99	-	72	36 (100)	35 (97.2)	>.99	-
Concurrent CRT,* n (%)	117	45 (80.4)	59 (96.7)	.005	0.532	72	34 (94.4)	34 (94.4)	>.99	0.000
Chemotherapy, no. of cycles received, median (IQR)	110	6 (5, 6)	5 (4, 6)	.011	-	68	6 (6, 6)	5 (4, 6)	<.001	-
Dose and fractionation, n (%)	116			<.001	-	71			<.001	
40 Gy/15 fractions		21 (37.5)	-				10 (27.8)	-		
45 Gy/15 fractions		4 (7.1)	-				3 (8.3)	-		
45 Gy/20 fractions		26 (46.4)	-				18 (50.0)	-		
Other (HFRT)		5 (8.9)	-				5 (13.9)	-		
60 Gy/30 fractions		-	49 (81.7)				-	30 (85.7)		
66 Gy/33 fractions		-	2 (3.3)				-	-		
Other (CFRT)		-	9 (15.0)				-	5 (14.3)		
PCI,* n (%)	117	30 (53.6)	42 (68.9)	.090	0.318	72	21 (58.3)	24 (66.7)	.439	0.173

Abbreviations: 3D-CRT = 3D conformal radiation therapy; 4D = 4-dimensional; CFRT = conventionally fractionated radiation therapy; CI = confidence interval; CRT = chemoradiotherapy; DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in 1 second; HFRT = hypofractionated radiation therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PCI = prophylactic cranial irradiation; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiation therapy; SD = standardized difference; VMAT = volumetric modulated arc therapy.

* Included in propensity-score model.

Similarly, univariable Cox proportional hazards regression models did not reveal any significant differences in OS (hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.57-2.27; $P = .724$) or PFS (HR, 1.06; 95% CI, 0.54-2.10; $P = .862$) between HFRT and CFRT cohorts for matched patients.

The most common locations for progression in matched HFRT patients were brain (30.6%) and ipsilateral lung (19.4%). For matched CFRT patients, the most common locations for progression were ipsilateral lung (30.6%), lymph nodes (22.2%), brain (19.4%), contralateral lung (16.7%), and bone (13.9%). A significantly higher proportion of matched CFRT patients progressed in the lymph nodes compared with HFRT patients (HFRT: 2.8%; CFRT: 22.2%; $P = .028$). No other statistically significant differences in patterns of progression were noted between matched cohorts.

Overall survival and progression free survival for all patients

Kaplan-Meier plots for OS and PFS are displayed in Figure 1A and 1C for all patients (n = 117), stratified by treatment cohort (HFRT vs CFRT). Five-year OS was 26.2% for all patients who received HFRT compared

Table 2 Baseline treatment outcomes stratified by cohort (HFRT and CFRT) for all patients and for matched patients

Characteristic	All patients (n = 117)				Matched patients (n = 72)			
	N	HFRT (n = 56)	CFRT (n = 61)	*P* value	N	HFRT (n = 36)	CFRT (n = 36)	*P* value
Median follow-up (y),* median (95% CI)	117	13.5 (5.2-15.3)	5.0 (3.9-6.8)	.020	72	13.5 (5.2-15.3)	5.0 (3.9-6.8)	.001
RECIST response, n (%)				.551				.901
Complete response	109	15 (30.0)	12 (20.3)	.244	68	10 (30.3)	8 (22.9)	.487
Partial response		24 (48.0)	36 (61.0)	.173		18 (54.6)	20 (57.1)	.829
Stable disease		4 (8.0)	4 (6.8)	>.99		2 (6.1)	4 (11.4)	.674
Progressive disease		7 (14.0)	7 (11.9)	.740		3 (9.1)	3 (8.6)	>.99
Last known status, n (%)								
Alive with disease	117	2 (3.6)	5 (8.2)	.364	72	0 (0)	4 (11.1)	.144
Alive without disease		9 (16.1)	9 (14.8)			7 (19.4)	6 (16.7)	
Dead from disease		28 (50.0)	37 (60.7)			17 (47.2)	20 (55.6)	
Dead from other/unknown cause		17 (30.4)	10 (16.4)			12 (33.3)	6 (16.7)	
Any progression, n (%)	117	27 (48.2)	37 (60.7)	.177	72	17 (47.2)	22 (61.1)	.237
Progression location, n (%)†								
Brain	117	16 (28.6)	11 (18.0)	.177	72	11 (30.6)	7 (19.4)	.276
Bone		6 (10.7)	8 (13.1)	.689		3 (8.3)	5 (13.9)	.710
Ipsilateral lung		12 (21.4)	21 (34.4)	.119		7 (19.4)	11 (30.6)	.276
Contralateral lung		2 (3.6)	8 (13.1)	.098		1 (2.8)	6 (16.7)	.107
Lymph node		4 (7.1)	16 (26.2)	.006		1 (2.8)	8 (22.2)	.028
Adrenal		3 (5.4)	5 (8.2)	.719		1 (2.8)	3 (8.3)	.614
Liver		2 (3.6)	13 (21.3)	.004		1 (2.8)	6 (16.7)	.107
Esophageal adverse events, n (%)								
Grade 1-3	117	49 (87.5)	47 (77.1)	.394	72	31 (86.1)	26 (72.2)	.282
Grade 4		2 (3.6)	4 (6.6)			2 (5.6)	2 (5.6)	
Pulmonary adverse events, n (%)								
Grade 1-3	117	21 (37.5)	30 (49.2)	.263	72	13 (36.1)	18 (50.0)	.332
Grade 4		1 (1.8)	0 (0)			1 (2.8)	0 (0)	
Neutrophil adverse events, n (%)								
Grade 1-3	117	19 (33.9)	22 (36.1)	.964	72	13 (36.1)	13 (36.1)	.842
Grade 4		8 (14.3)	8 (13.1)			5 (13.9)	3 (8.3)	
Skin adverse events, n (%)	117	11 (19.6)	21 (34.4)	.073	72	6 (16.7)	15 (41.7)	.020
Grade 1-3								

Abbreviations: CFRT = conventionally fractionated radiation therapy; CI = confidence interval; CRT = chemoradiotherapy; DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in 1 second; HFRT = hypofractionated radiation therapy; IQR = interquartile range; PCI = prophylactic cranial irradiation; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standardized difference.

* Calculated using reverse Kaplan-Meier method.

† Categories not mutually exclusive.

with 24.0% for all patients who received CFRT (Table EB). Five-year PFS was 22.2% for all patients who received HFRT compared with 19.4% for all patients who received CFRT. No statistically significant difference was found between cohorts for OS (P = .804) or PFS (P = .561).

No significant violations of the proportional hazards assumption in Cox regression were detected for the

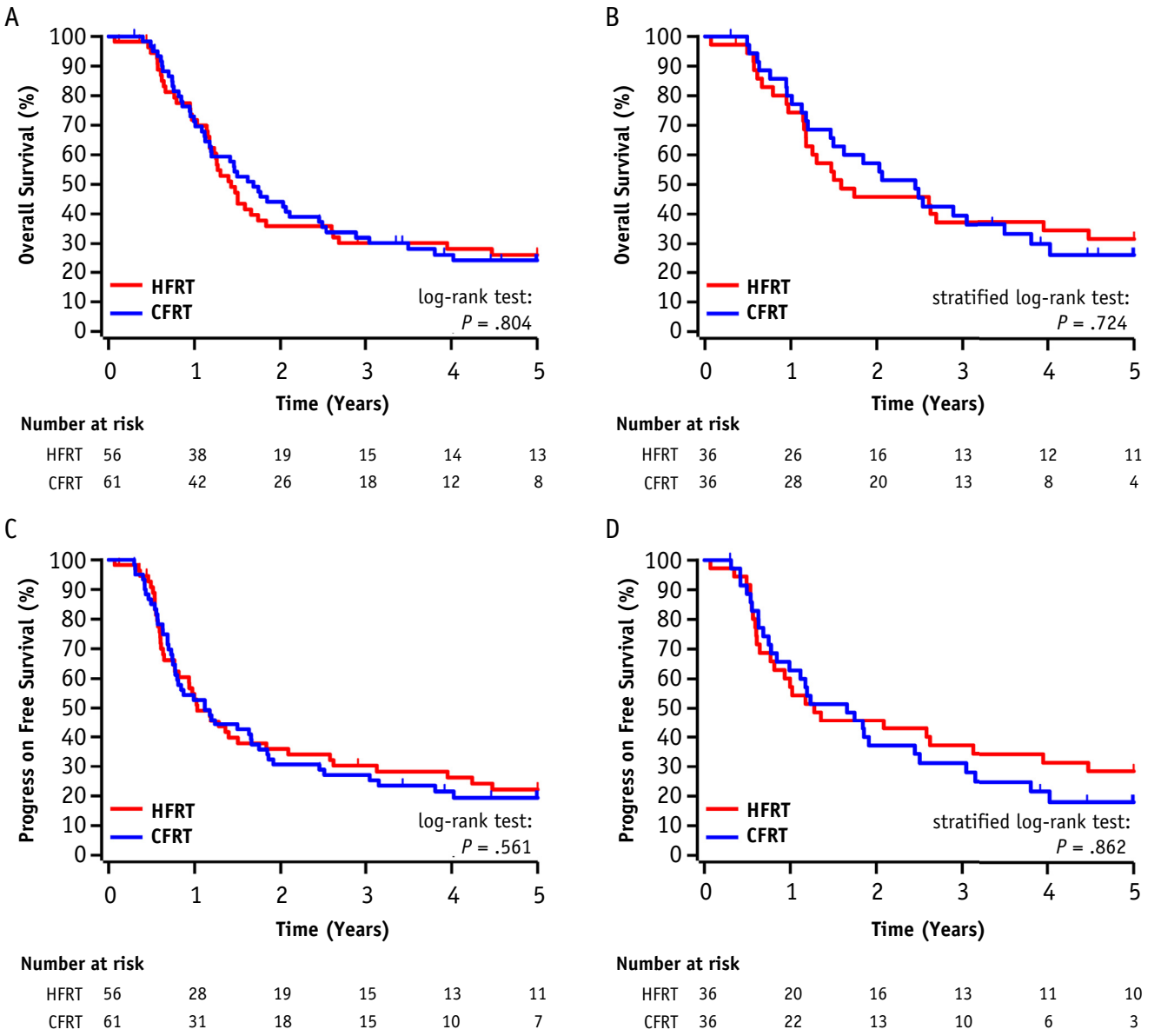

Fig. 1. Kaplan-Meier plots for overall survival for (A) all patients (n = 117) and (B) matched patients (n = 72) and progression-free survival for (C) all patients (n = 117) and (D) matched patients, stratified by treatment cohort. *Abbreviations*: CFRT = conventionally fractionated radiation therapy; HFRT = hypofractionated radiation therapy.

univariable and multivariable regression analyses. Univariable Cox proportional hazards regression models did not reveal any significant difference in OS (HR, 0.95; 95% CI, 0.62-1.45; $P = .806$) or PFS (HR, 0.88; 95% CI, 0.58-1.34; $P = .562$) between HFRT and CFRT cohorts for all patients. Similarly, no significant OS (HR, 0.96; 95% CI, 0.59-1.58; $P = .886$) or PFS (HR, 0.92; 95% CI, 0.57-1.48; $P = .717$) benefit was found between cohorts on multivariable Cox proportional hazards regression models for all patients.

PCI was associated with an increase in OS (HR, 0.51; 95% CI, 0.34-0.78; $P = .002$) and in PFS (HR, 0.53; 95% CI, 0.35-0.81; $P = .003$) on univariable analysis. A similar trend was also found on multivariable analysis (Table 3). On univariable analysis only, concurrent CRT was associated with an improvement in PFS (HR, 0.51; 95% CI, 0.27-0.97; $P = .039$), without a statistically significant OS benefit (HR, 0.53; 95% CI, 0.27-1.02; $P = .056$). Smoking during radiation therapy treatment was associated with a reduction in OS (HR, 1.85; 95% CI, 1.10-3.13; $P = .021$) on multivariable analysis only.

Toxicity

For all patients and for matched patients, no significant differences between cohorts were noted for PAE, EAE, or neutrophil adverse events (Table 2). No significant difference in skin adverse events was noted between cohorts for

Table 3 Overall survival and progression-free survival univariable and multivariable Cox proportional hazards regression models for all patients (n = 117) and for matched patients (n = 72)

Dependent variable	Overall survival		Progression-free survival		Overall survival		Progression-free survival	
	Univariable analysis				Multivariable analysis			
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HFRTvs CFRT (all)	0.95 (0.62-1.45)	.806	0.88 (0.58-1.34)	.562	0.96 (0.59-1.58)	.886	0.92 (0.57-1.48)	.717
HFRT vs CFRT* (matched)	1.13 (0.57-2.27)	.724	1.06 (0.54-2.10)	.862	-†	-†	-†	-†
Age (per 5 y)	1.09 (0.97-1.24)	.151	1.08 (0.95-1.22)	.238	1.16 (0.99-1.35)	.064	1.16 (1.00-1.36)	.057
Smoking concurrent with treatment (yes vs no)	1.35 (0.86-2.12)	.195	1.29 (0.83-2.01)	.264	1.85 (1.10-3.13)	.021	1.66 (1.00-2.77)	.0504
ECOG performance status 2-3 (vs 0-1)	1.01 (0.65-1.57)	.954	1.03 (0.67-1.59)	.902	1.26 (0.77-2.07)	.352	1.19 (0.73-1.93)	.496
T stage		.712		.496		.575		.430
T2 vs T0-T1	1.12 (0.57-2.19)	.740	1.16 (0.60-2.25)	.656	1.36 (0.66-2.81)	.406	1.29 (0.63-2.64)	.481
T3 vs T0-T1	1.26 (0.65-2.44)	.494	1.17 (0.62-2.22)	.632	1.46 (0.69-3.09)	.327	1.27 (0.62-2.61)	.513
T4 vs T0-T1	1.54 (0.82-2.91)	.184	1.68 (0.90-3.14)	.104	1.70 (0.84-3.45)	.144	1.92 (0.95-3.88)	.071
TX vs T0-T1	1.30 (0.53-3.20)	.570	1.45 (0.59-3.54)	.416	0.96 (0.33-2.78)	.933	1.42 (0.50-4.07)	.513
N stage								
N +vs N0	1.09 (0.67-1.79)	.722	1.07 (0.66-1.75)	.787	1.40 (0.79-2.47)	.250	1.48 (0.82-2.66)	.194
Concurrent CRT (yes vs no)	0.53 (0.27-1.02)	.056	0.51 (0.27-0.97)	.039	0.57 (0.26-1.26)	.168	0.57 (0.26-1.21)	.144
PCI (yes vs no)	0.51 (0.34-0.78)	.002	0.53 (0.35-0.81)	.003	0.39 (0.24-0.64)	<.001	0.44 (0.27-0.72)	.001
Central location (ICD-9/ICD-10 site code) (yes vs no)	1.19 (0.79-1.81)	.406	1.28 (0.84-1.93)	.249	1.36 (0.86-2.15)	.192	1.41 (0.90-2.21)	.134
Pleural effusion (yes vs no)	1.62 (0.97-2.69)	.064	1.64 (0.99-2.72)	.056	1.31 (0.74-2.32)	.352	1.25 (0.71-2.21)	.436

Abbreviations: CI = confidence interval; HR = hazard ratio; NR = not reported.
* Stratified by matched pair groups.
† Multivariable analysis was only performed for unmatched (all) patients.

all patients (P = .073). However, for matched patients, skin adverse events were significantly higher in the CFRT cohort (41.7%) compared with the HFRT cohort (16.7%, P = .020). No grade 5 adverse events were observed for all patients.

Univariable logistic regression did not reveal a significant difference in any PAE between the HFRT and CFRT cohorts for all patients (odds ratio [OR], 0.67; 95% CI, 0.32-1.39; P = .283) or for matched patients (OR, 0.64; 95% CI, 0.25-1.64; P = .350; Table 4). No significant difference in any EAE was found between HFRT and CFRT cohorts for all patients (OR, 2.00; 95% CI, 0.64-6.26; P = .234) or for matched patients (OR, 6.00; 95% CI, 0.72-49.84; P = .097). Similarly, no significant difference in any PAE (OR, 0.61; 95% CI, 0.25-1.46; P = .266) or EAE (OR, 3.80; 95% CI, 0.77-18.81; P = .102) was noted between HFRT and CFRT cohorts on multivariable logistic regression for all patients. Age, smoking concurrent with treatment, T stage, N stage, concurrent CRT, and central tumor location did not appear to be significantly associated with any PAE or any EAE on univariable or multivariable logistic regression analysis for all patients.

Discussion

Concurrent CRT is the cornerstone of LS-SCLC treatment, with various radical radiation therapy fractionation regimens used worldwide.[5] Although twice-daily or standard fractionation is considered standard of care,[5,30] hypofractionation offers a viable, more convenient alternative that may partly alleviate barriers to access by reducing the total number of fractions and therefore overall treatment time.[31]

To our knowledge, this is the first study to use propensity score–matched analysis of retrospective data to compare OS, PFS, and toxicity profiles of HFRT and CFRT in LS-SCLC. We found no statistically significant difference in OS or PFS between HFRT and CFRT in unmatched

Table 4 Pulmonary and esophageal adverse event univariable and multivariable logistic regression models for all patients (n = 117) and for matched patients (n = 72).

Dependent variable	Any pulmonary AE		Any esophageal AE		Any pulmonary AE		Any esophageal AE	
	Univariable analysis				Multivariable analysis			
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
HFRT vs CFRT (all)	0.67 (0.32-1.39)	.283	2.00 (0.64-6.26)	.234	0.61 (0.25-1.46)	.266	3.80 (0.77-18.81)	.102
HFRT vs CFRT* (matched)	0.64 (0.25-1.64)	.350	6.00 (0.72-49.84)	.097	-*	-*	-*	-*
Age (per 5 y)	1.05 (0.85-1.30)	.672	1.23 (0.90-1.67)	.190	1.03 (0.80-1.32)	.844	1.48 (0.96-2.28)	.073
Smoking concurrent with treatment (yes vs no)	1.27 (0.57-2.81)	.558	0.60 (0.20-1.82)	.365	1.49 (0.61-3.63)	.382	0.89 (0.22-3.50)	.861
ECOG performance status 2-3 (vs 0-1)	0.83 (0.39-1.80)	.643	0.23 (0.07-0.71)	.011	0.77 (0.34-1.78)	.548	0.18 (0.05-0.67)	.011
T stage		.691		.838		.702		.684
T2vs T0-T1	1.37 (0.41-4.56)	.744	2.34 (0.35-15.61)	.317	1.67 (0.46-6.11)	.637	5.11 (0.59-44.53)	.259
T3vs T0-T1	1.37 (0.41-4.56)	.744	1.50 (0.27-8.38)	.727	1.26 (0.34-4.64)	.814	2.60 (0.36-18.61)	.846
T4vs T0-T1	1.93 (0.61-6.09)	.176	1.09 (0.23-5.16)	.790	2.25 (0.63-7.97)	.183	2.11 (0.32-13.77)	.886
TXvs T0-T1	0.74 (0.14-3.80)	.381	0.75 (0.10-5.43)	.463	1.09 (0.18-6.64)	.703	2.25 (0.22-22.90)	.983
N stage								
N +vs N0	0.63 (0.26-1.52)	.941	0.51 (0.11-2.43)	.741	0.63 (0.24-1.62)	.964	0.55 (0.09-3.47)	.930
Concurrent CRT (yes vs no)	0.93 (0.29-2.94)	.895	1.27 (0.25-6.40)	.770	0.83 (0.22-3.04)	.774	2.87 (0.37-22.35)	.315
Central location (ICD-9/ICD-10 site code) (yes vs no)	0.95 (0.45-2.00)	.900	1.05 (0.35-3.17)	.931	0.88 (0.39-2.00)	.766	1.08 (0.30-3.91)	.902

Abbreviations: AE = adverse event; CI = confidence interval; HR = hazard ratio; NR = not reported; PCI = prophylactic cranial irradiation.
* Multivariable analysis was only performed for unmatched (all) patients.

analysis, propensity score-matched analysis, or univariable and multivariable regression analyses. The pulmonary and esophageal toxicity profile for both CFRT and HFRT was similar for all patients and for matched patients on univariable logistic regression model analysis and for unmatched patients on multivariable logistic regression model analysis. Neutrophil toxicity is most likely attributed to chemotherapy given that there was no significant difference in neutrophil adverse events between HFRT and CFRT for all and for matched patients, respectively. Both treatment approaches therefore have comparable tolerability and toxicity profiles, with the exception of a possible increased risk of skin toxicity with the high-dose CFRT regimen. Age, smoking concurrent with treatment, T stage, N stage, concurrent CRT, and central location do not appear to be predictors of either pulmonary or esophageal adverse events.

The recent American Society for Radiation Oncology SCLC clinical practice guideline indicates that mild hypofractionation is not routinely recommended for ES-SCLC because of the limited evidence for its equivalence.[30] However, reducing overall treatment time is important for patients who may struggle with prolonged treatment courses, a challenge further amplified by the current COVID-19 viral pandemic. Advantages of hypofractionation thus include patient convenience and reduction in health care resource utilization, without compromising clinical efficacy, according to the present study.[32] These findings will need to be verified with more thorough prospective studies, which should also focus on early and late toxicities. An increasingly appreciated late effect of thoracic radiation therapy is cardiotoxicity, which warrants further examination in the context of different fractionation regimens.

Several retrospective studies have explored the role of hypofractionated radiation therapy in LS-SCLC.[33-36] Zhang et al and Videtic et al concluded that HFRT and CFRT regimens yield similar OS, local control, treatment failure patterns, and toxicity outcomes, corroborating our findings.[33,34] Bettington et al suggested that 40 Gy in 15 fractions and 45 Gy in 30 fractions, given twice daily, provided equivalent relapse-free survival rates.[36] Turgeon et al only described local control and OS rates in 68 patients treated with 40 Gy in 16 fractions, with no comparison or control group.[35] Given the small sample size and retrospective nature of these studies, they are notably limited by selection bias, which can

be appropriately accounted for using propensity score matching, as in this study.

Currently, no other analysis compares the most common HFRT and CFRT dose and fractionation regimens in LS-SCLC. To compare the potency of these regimens, biological effective dose (BED) may be calculated using the formula $BED_{\alpha/\beta} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$, where α/β is the alpha/beta ratio of the tissue (assumed to be 10 Gy for tumor and 3 Gy for normal tissue), n is total number of fractions of radiation therapy, and d is the dose per fraction. BED_{10} is used to predict the tumor response, whereas BED_3 is used to predict the normal tissue response to radiation. The institutional SCLC database used in our analysis uniquely captured several HFRT regimens, including 40 Gy in 15 fractions (BED_{10} = 50.68 Gy, BED_3 = 75.60 Gy), 45 Gy in 15 fractions (BED_{10} = 58.50 Gy, BED_3 = 90.00 Gy), and 45 Gy in 20 fractions (BED_{10} = 55.13 Gy, BED_3 = 78.75 Gy), delivered once daily. Similarly, several CFRT regimens were also captured, such as 60 Gy in 30 fractions (BED_{10} = 72.00 Gy, BED_3 = 100.00 Gy) and 66 Gy in 33 fractions (BED_{10} = 79.20 Gy, BED_3 = 110.00 Gy). Despite important differences in BED values for HFRT and CFRT, their effects on tumor and normal tissues were similar, suggesting that in the context of LS-SCLC, other important factors likely come into play. The high risk of progression and mortality from distant metastases likley outweighs small differences in thoracic radiation therapy doses.

It has been shown that a short time between the start of any treatment and end of radiation therapy (SER) is the most important predictor of outcome in patients with LS-SCLC.[37] SER is associated with improved OS, albeit at the expense of higher rates of esophagitis. An extension of SER by 1 week in a rapidly proliferating tumor such as SCLC is reported to decrease OS by 1.83%.[37] HFRT confers the advantage of a shorter SER compared with CFRT, particularly if administered early with concurrent chemotherapy. HFRT may theoretically reduce the impact of accelerated proliferation of tumor cells during treatment, given its shorter SER. Importantly, rates of esophagitis were not significantly different between HFRT and CFRT cohorts, despite the shorter SER for HFRT. Prospective randomized data are required to further explore HFRT with concurrent chemotherapy as an effective and efficient method of reducing SER and thereby improving OS.

PCI has been shown to improve both OS and disease-free survival among patients with SCLC.[38-40] This finding has been reproduced in this study: PCI was associated with an increase in OS and PFS (HR of 0.51 and 0.53, respectively), thereby supporting the validity of the data collected and the analysis performed. Similarly, concurrent CRT was associated with an improvement in PFS, as in previous studies,[1,7] but did not reach statistical significance for OS. We also observed that in patients undergoing concurrent CRT, CFRT was associated with fewer total cycles of chemotherapy delivered (median 5 vs 6 cycles) compared with those treated with HFRT. Given the retrospective nature of the present study, it is difficult to ascertain the reason for this difference. Possible explanations include the overall lengthier treatment time of CFRT resulting in difficulty tolerating subsequent cycles of chemotherapy or, alternatively, that fewer cycles of chemotherapy were believed to be required with CFRT. Smoking concurrent with radiation therapy treatment was associated with a reduction in OS (HR = 1.85), suggesting that clinicians should counsel their patients on smoking cessation and enroll them in smoking cessation programs.[41,42]

In our study, the median year of diagnosis for patients who received HFRT was 2002, whereas the median year of diagnosis for those who received CFRT was 2010. CFRT is a more modern treatment approach, planned and delivered using more contemporary techniques. As a result, 82.0% of CFRT was delivered using intensity modulated radiation therapy (IMRT), compared with only 5.4% of HFRT cases. Similarly, 4-dimensional (4D) planning, which manages respiration during imaging and planning of radiation therapy, was used in only 14.3% of HFRT cases compared with 90.2% of CFRT cases (Table 1). IMRT and 4D planning allow for more precise sparing of normal tissues, potentially reducing the burden of toxicity. Moreover, positron emission tomography (PET) scanning was only recently incorporated into the SCLC staging investigations.[43] No PET scan was performed for matched HFRT patients as a result, compared with 36.1% of matched CFRT patients who underwent a staging PET scan. Given that a fusion of the PET scan with the planning computed tomography is often used to accurately delineate target volumes, it is plausible that HFRT in the modern era of routine IMRT, PET fusion, and 4D planning may offer an additional advantage of reduced toxicity compared with CFRT, given the lower cumulative dose delivered.

Several limitations of this study warrant mention. After matching, only 72 patients were analyzed. Inferences are therefore restricted by the sample size. However, the estimated HR for OS and PFS closely approximated 1, increasing the likelihood that the results were true nulls. Additionally, using the entire cohort in our multivariable Cox regression sensitivity analysis did not significantly change our estimates or conclusions. The retrospective, observational nature of the data collected may have introduced bias. However, differences in baseline characteristics have been accounted for by using propensity score matching and confirmed using multivariable regression. Although comparative effectiveness methods such as propensity score matching bring us closer to a balanced comparison of cohorts, they do not completely remove bias owing to the potential presence of unmeasured confounders. Lower grades of toxicity could not be reliably distinguished based on chart information, therefore requiring pooling of the data for grade 1 to 3 adverse events. It has been suggested that concurrent CRT confers an OS benefit for elderly patients (age $\geq$70 years).[44] However, no meaningful conclusions specific to the

elderly could be drawn in this study as a limited number of elderly patients were included in the database. It is therefore unknown whether elderly patients would benefit more from HFRT or CFRT in the form of OS, PFS, or reduced toxicity. Finally, long-term complications were outside the scope of the institutional database and were not assessed by the present study.

Conclusions

In patients with LS-SCLC, there appeared to be no significant differences in OS, PFS, or toxicity between the HFRT and CFRT treatment approaches with concurrent chemotherapy. CFRT may be associated with higher rates of skin toxicity. HFRT may therefore be considered an effective and comparably tolerable treatment alternative to CFRT, with the added potential benefit of reduced treatment time and cost. Prospective studies are nevertheless required to confirm the comparative role of HFRT to other more common fractionation regimens for the key endpoints of OS, PFS, and toxicity.

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