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Original Article

Stereotactic ablative radiation therapy versus conventionally fractionated radiation therapy for stage I small cell lung cancer

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ABSTRACT

Background: The National Comprehensive Cancer Network (NCCN) recently revised recommendations for inoperable stage I small cell lung cancer (SCLC), having added stereotactic ablative radiotherapy (SABR)/chemotherapy to the historical paradigm of concurrent conventionally-fractionated radiation therapy (CFRT)/chemotherapy. Despite the conformality, convenience, and cost-effectiveness of SABR, the NCCN continues to recommend both CFRT/chemotherapy and SABR/chemotherapy primarily because these approaches have not been comparatively analyzed to date.

Methods: The National Cancer Database was queried for histologically-confirmed T1-2N0M0 SCLC; all patients received chemotherapy. Multivariable logistic regression ascertained factors associated with SABR/chemotherapy. Kaplan–Meier analysis assessed overall survival (OS); multivariable Cox proportional hazards modeling examined factors associated with OS. Survival was also calculated following propensity matching.

Results: Of 2,107 patients, 7.1% underwent SABR/chemotherapy, and 92.9% received CFRT/chemotherapy. The median (interquartile range) dose of SABR was 50 (48–54) Gy in 4 (3–5) fractions, and 55.8 (45–60) Gy in 30 (30–33) fractions for CFRT. Patients receiving SABR/chemotherapy were more often older, had T1 disease, treated at academic/integrated network facilities, and managed in more recent years ($p < 0.05$ for all). Respective median survival figures were 29.2 versus 31.2 months ($p = 0.77$), which persisted following propensity matching (25.4 versus 34.3 months, $p = 0.85$). On multivariable analysis, radiotherapeutic technique was not associated with OS ($p = 0.95$).

Conclusions: For stage I SCLC, SABR/chemotherapy affords statistically equivalent outcomes to CFRT/chemotherapy. Because randomized studies addressing this uncommon scenario would almost certainly suffer from inadequate accrual, these retrospective data should be strongly considered in efforts to institute SABR/chemotherapy as the preferred option for this population.

Historically, the standard of care for limited-stage small cell lung cancer (SCLC) has been concurrent chemotherapy and conventionally-fractionated radiation therapy (CFRT) [1–2]. Uncommonly, SCLC presents as stage I (T1-2aN0) disease, for which the standard of care for operable patients is lobectomy. For inoperable patients (or those refusing surgery), the National Comprehensive Cancer Network (NCCN) previously endorsed either concurrent or sequential CFRT-based chemoradiotherapy (CRT), chemotherapy alone, or supportive care [3].

In 2017, Verma and colleagues published a multi-institutional analysis of stereotactic ablative radiotherapy (SABR) for non-operative stage I SCLC, demonstrating high local control (96% at 3 years) and minimal toxicity (1.3% crude rate of grade ≥3 pneumonitis) [4]. Moreover, although prophylactic cranial irradiation was not in itself associated with development of brain metastases (0% with vs. 7.5% without, $p = 0.57$) or survival endpoints, addition of chemotherapy was associated with improved disease-free and overall survival (OS) (multivariate $p = 0.01$ for both) [5]. As a result, that study directly led to a modification in the NCCN guidelines, which now recommend either SABR/adjuvant chemotherapy or the historical paradigm of concurrent CFRT-based CRT [1].

Despite the successes of SABR for both SCLC and non-SCLC (NSCLC), the NCCN continues to recommend both CFRT/chemotherapy and SABR/chemotherapy primarily because these approaches have not been comparatively analyzed to date. Given the relatively rare incidence of stage I SCLC, it is highly unlikely that a randomized trial comparing both approaches would adequately accrue. As a result, we sought to address this knowledge

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gap by using a large, contemporary national database to compare outcomes in stage I SCLC treated with SABR/chemotherapy versus CFRT/chemotherapy.

Materials & methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society that consists of information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the United States population [6]. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data. As all data, including patient information, in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

The NCDB Participant User File corresponding to SCLC (2004–2014) was utilized for this study. Inclusion criteria for this investigation were newly-diagnosed, histologically-confirmed T1-2N0M0 SCLC that received (multi-agent) chemotherapy. SABR referred to a dose of 45–60 Gy in 3–8 radiotherapy fractions, and CFRT as 45–70 Gy in 25–35 fractions [1,7]. Surgical patients were excluded, in addition to patients not receiving external beam radiotherapy and/or lacking information regarding survival/follow-up. Lastly, in efforts to address administration of salvage SABR following initial chemotherapy (or vice-versa), patients were removed if chemotherapy was started >3 months before (approximating 4–6 cycles of cisplatin/etoposide) or >2 months after (approximating $\leq$35 fractions of CFRT) radiotherapy.

In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. Statistical analysis was performed with MedCalc version 18 (Ostend, Belgium). Tests were two-sided, with a threshold of $p < 0.05$ for statistical significance. First, clinical characteristics of the overall cohort were tabulated. Second, multivariable logistic regression was performed to ascertain factors independently associated with administration of SABR/chemotherapy. Third, Kaplan–Meier curves were calculated to evaluate OS, defined as the interval between the date of diagnosis and the date of death, or censored at last contact. Multivariable Cox proportional hazards modeling (backward stepwise selection) was utilized to evaluate predictors of OS. Fourth, in an attempt to minimize selection and indication biases, patients underwent 1:1 propensity matching. To estimate the propensity score for each patient, the univariate association of each covariate within a particular treatment group was assessed using a simple logistic regression model. Covariates that were significantly associated with treatment type ($p < 0.05$) were included in a multivariable logistic regression model, and backwards stepwise selection was performed with $\alpha = 0.20$; matching was performed with a caliper 0.2 times the standard deviation of the logit propensity score [8–9]. Kaplan–Meier curves were then generated on the propensity matched patients.

Results

A patient selection diagram is illustrated in Fig. 1. Overall, 2,107 patients met study criteria; 149 (7.1%) underwent SABR/chemotherapy, and 1,958 (92.9%) received CFRT/chemotherapy. (Table 1). The vast majority of patients were Caucasian and had governmental insurance; the median (interquartile range) dose of SABR was 50 (48–54) Gy in 4 (3–5) fractions, and 55.8 (45–60) Gy in 30 (30–33) fractions for CFRT. The vast majority (85.4%) of patients received radiotherapy followed by chemotherapy instead of vice-versa.

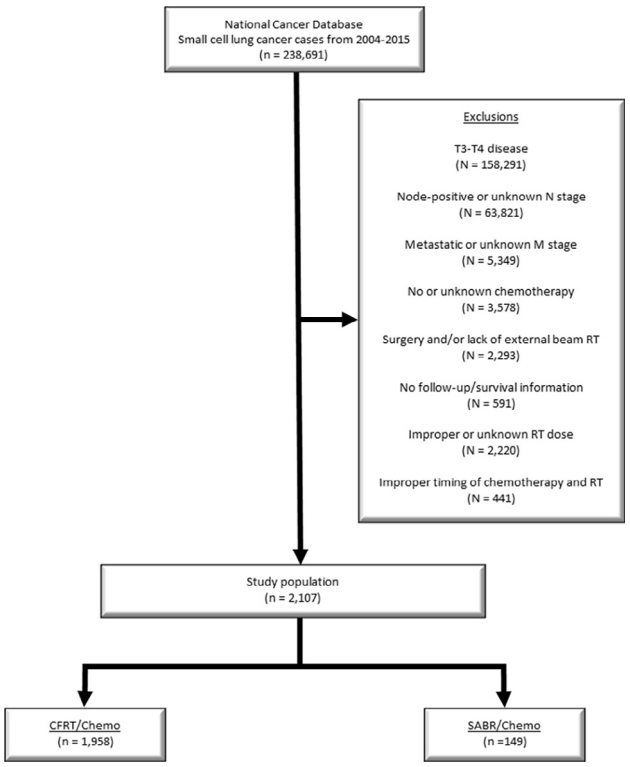

Fig. 1. Patient selection diagram.

Multivariable logistic regression was performed to evaluate independent predictors of receiving SABR/chemotherapy (Table 1). These patients were more often older, had T1 disease, treated at academic/integrated network facilities, and managed in more recent years ($p < 0.05$ for all).

Median follow-up using the reverse Kaplan–Meier method was 66 months (IQR, 31–70 months). Kaplan–Meier estimates comparing OS in patients having received surgery/chemotherapy, chemotherapy alone, and observation are illustrated in Fig. 2A. Respective median survival figures were 31.2 (95% confidence interval (CI), 29.3–33.2) months for CFRT/chemotherapy, and 29.2 (23.7–33.0) months for SABR/chemotherapy ($p = 0.77$). These findings persisted following propensity matching (34.3 (28.5–51.3) months vs. 25.4 (20.3–35.6) months, $p = 0.85$, Supplementary Table 1) (Fig. 2B).

In the overall cohort, when adjusting for potential confounders, there were three predictors of poorer OS on multivariable analysis (Table 2). These were advancing age, male gender, and treatment in earlier years ($p < 0.05$ for all). Of note, with reference to the CFRT/chemotherapy cohort, receipt of SABR/chemotherapy was not associated with OS ($p = 0.95$).

Discussion

Although SABR/chemotherapy is safe and efficacious for stage I SCLC, the historical paradigm of CFRT/chemotherapy remains a management option per the NCCN because no studies to date have compared both approaches. This investigation of a large, contemporary national database addresses a major knowledge gap by demonstrating statistically equivalent following SABR or CFRT in stage I SCLC. Because randomized studies addressing this relatively rare scenario would almost certainly suffer from inadequate accrual, these retrospective data should be strongly considered in efforts to institute SABR/chemotherapy as the preferred option for this population.

Table 1
Clinical characteristics of the overall cohort and significant factors associated with receipt of SABR/chemotherapy.

Parameter	CFRT/Chemo (*N* = 1,958)	SABR/Chemo (*N* = 149)	Multivariable	
			OR (95% CI)	*p*-Value
Age				
<68 years	926 (47%)	72 (48%)	REF	REF
≥68 years	1032 (53%)	77 (52%)	1.546 (1.026–2.329)	**0.037**
Gender				
Male	888 (45%)	63 (42%)	REF	REF
Female	1070 (55%)	86 (58%)	1.176 (0.813–1.702)	0.390
Race				
White	1763 (90%)	127 (85%)	REF	REF
Black	149 (8%)	18 (12%)	0.812 (0.413–1.597)	0.546
Other/Unknown	46 (2%)	4 (3%)	0.282 (0.035–2.258)	0.233
Insurance type				
Uninsured	44 (2%)	4 (3%)	REF	REF
Private	525 (27%)	35 (23%)	0.949 (0.755–1.146)	0.998
Governmental	1361 (70%)	105 (70%)	1.005 (0.963–1.049)	0.998
Income (US dollars/year)				
<$48,000	961 (49%)	71 (48%)	REF	REF
≥$48,000	967 (49%)	75 (50%)	1.304 (0.822–2.068)	0.259
Unknown	30 (2%)	3 (2%)	–	–
Percentage of adults in zip code without high school diploma				
≥21%	310 (16%)	24 (16%)	REF	REF
13–20.9%	617 (32%)	40 (27%)	1.387 (0.764–2.516)	0.282
7–12.9%	624 (32%)	38 (26%)	0.922 (0.474–1.796)	0.812
<7%	379 (19%)	42 (28%)	0.625 (0.286–1.363)	0.237
Unknown	28 (1%)	5 (3%)	–	–
Patient residence				
Metro	1461 (75%)	72 (48%)	REF	REF
Urban	376 (19%)	29 (19%)	0.809 (0.463–1.413)	0.456
Rural	60 (3%)	18 (12%)	0.876 (0.247–3.109)	0.837
Unknown	61 (3%)	30 (20%)	–	–
Facility type				
Community	274 (14%)	15 (10%)	REF	REF
Comprehensive Community	990 (51%)	64 (43%)	1.579 (0.749–3.329)	0.230
Academic/Research	475 (24%)	57 (38%)	4.030 (1.874–8.668)	**<0.001**
Integrated Network	217 (11%)	13 (9%)	2.662 (1.146–6.183)	**0.023**
Unknown	2 (0%)	0 (0%)	–	–
Facility location				
East Coast	722 (37%)	46 (31%)	REF	REF
Midwest	1045 (53%)	84 (56%)	0.861 (0.578–1.283)	0.463
West Coast	189 (10%)	19 (13%)	1.569 (0.871–2.828)	0.134
Unknown	2 (0%)	0 (0%)	–	–
Years of diagnosis				
2004–2007	503 (26%)	57 (38%)	REF	REF
2008–2011	780 (40%)	46 (31%)	2.349 (1.237–4.461)	**0.009**
2012–2014	675 (34%)	46 (31%)	4.400 (2.380–8.136)	**<0.001**
Tumor laterality				
Left	866 (44%)	66 (44%)	REF	REF
Right	962 (49%)	71 (48%)	0.820 (0.567–1.187)	0.293
Unknown	130 (7%)	12 (8%)	–	–
T classification				
T1	924 (47%)	126 (85%)	REF	REF
T2	1034 (53%)	23 (15%)	0.180 (0.111–0.291)	**<0.001**

Statistically significant *p* values are in bold.
Percentages may not add to 100% because of rounding.
CFRT, conventionally-fractionated radiation therapy; SABR, stereotactic ablative radiotherapy; OR, odds ratio; CI, confidence interval.

SABR is conformal, convenient, and cost-effective for early-stage NSCLC [10], which is likely why it has become the standard of care for that population despite the lack of randomized (only retrospective [11]) evidence supporting its utility over CFRT [12]. Hence, analogizing to stage I SCLC, as technology continues to evolve and the utilization of SABR for stage I SCLC increases [7], we posit that SABR/chemotherapy should be the preferred option for this population based on the results of this study (together with the aforementioned issues regarding prospective assessment).

The results of this study are intuitive in the sense that SCLC – regardless of stage – is a fundamentally systemic disease. Thus, chemotherapy is the most important aspect of management, whereas the specific modality of local therapy has relatively little impact (especially given the radiosensitivity of SCLC). Hence, because all patients received chemotherapy herein, survival was not impacted by radiotherapy modality. Although the NCDB does not record other endpoints other than OS, it is a relatively adequate and robust endpoint for stage I SCLC, based on patterns of failure and because most patients die of disease [4,13–18].

The observed OS herein (83.8% at 1 year) is comparable to previous work, which observed a 1-year OS of 80% in patients undergoing SABR/chemotherapy [4]. Moreover, despite the assumption that the vast majority of this population was inoperable, survival is also favorable compared to historical surgical studies (operable patients), in which 1-year OS ranged from 60-82% and a median of 21–24 months [13–17]. As a result, given the debate of SABR versus surgery for operable stage I NSCLC [19], perhaps this question should also be asked for operable stage I SCLC [20].

This study mostly included patients who received radiotherapy followed by chemotherapy, but a minority (14.6%) underwent

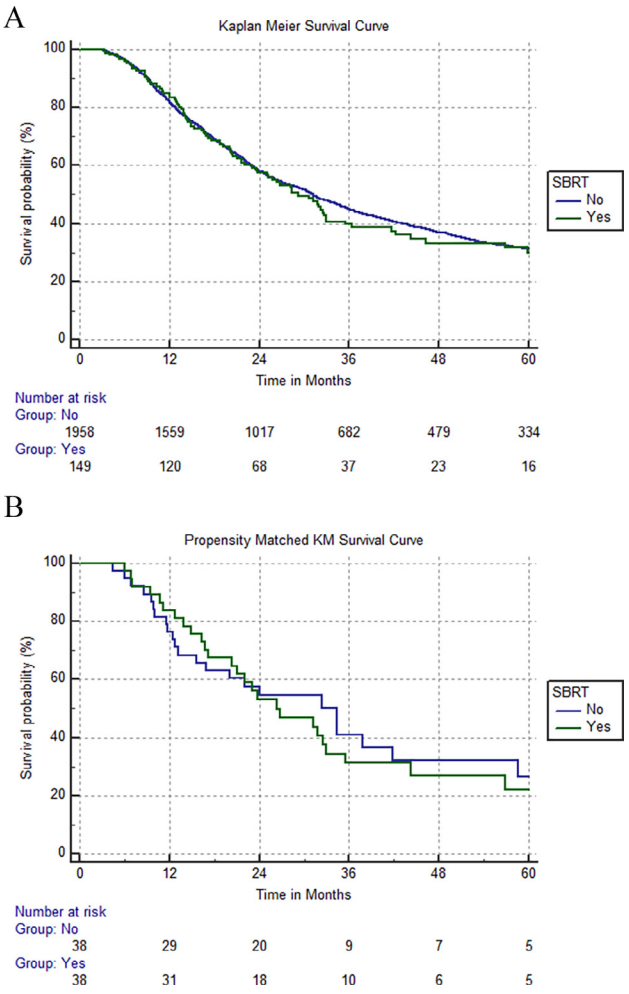

Fig. 2. Comparison of overall survival between treatment paradigms in the overall population (A), and following propensity matching (B).

chemotherapy followed by radiotherapy. We allowed this because (1) there are no known data suggesting differences in outcomes by treatment sequencing in this setting; (2) using either radiotherapy or chemotherapy as salvage was addressed as an inclusion criterion; and 3) this is sometimes performed in large NSCLC lesions in efforts to reduce the high-dose SABR volume. In fact, because most treatment failures in stage I SCLC occur distantly (and chemotherapy is thus most critical for management), it may be argued that earlier administration of chemotherapy may be more advantageous (however, post-chemotherapy SABR target delineation may be more difficult).

Along the same lines, the goal of this study was not to address the question of chemotherapy alone versus CRT for stage I SCLC. Although no longer endorsed by the NCCN [1], the former remains a treatment option for multiple reasons. First, SCLC responds well to chemotherapy, and thus it is theoretically possible that chemotherapy alone provides adequate local control for non-bulky disease. Additionally, it is unlikely that local control would translate to survival endpoints, given that stage I SCLC remains a systemic disease. That being said, we recommend local therapy for multiple reasons. First, the treatment paradigm for limited-stage SCLC – which also encompasses stage I disease – has nearly always involved some form of local therapy [2]. Second, surgery – another form of local therapy – remains the standard of care for the operable population. Third, many SCLC cases do not develop a complete response (CR) following chemotherapy alone; even if CR occurs, there is a relatively high likelihood of local failure (even though most data are for larger lesions) [21]. Fourth, in light of this, there are few practical "risks" associated with SABR, including an extremely low rate of toxicities despite a comorbid population [4], and thus the benefit:risk ratio is logically quite high (however, there are no prospective data evaluating the safety of combined SABR-chemotherapy in this setting).

The NCDB provides a valuable and unique resource with which to evaluate this clinically important question, but this study does not come without shortcomings. In addition to its retrospective nature, the NCDB does not contain information on performance status, clinical workup including positron emission tomography

Table 2
Multivariable Cox proportional hazards model for overall survival.

Parameter	Cox multivariate	
	HR (95% CI)	*p*-value
Age		
<68 years	REF	REF
≥68 years	1.298 (1.141–1.476)	**<0.001**
Gender		
Male	REF	REF
Female	0.787 (0.703–0.881)	**<0.001**
Race		
White	REF	REF
Black	0.810 (0.643–1.021)	0.074
Other/Unknown	0.751 (0.512–1.104)	0.145
Insurance type		
Uninsured	REF	REF
Private	1.010 (0.664–1.538)	0.962
Governmental	1.352 (0.892–2.048)	0.156
Income (US dollars/year)		
<$48,000	REF	REF
≥$48,000	0.995 (0.865–1.145)	0.947
Unknown	-	-
Percentage of adults in zip code without high school diploma		
≥21%	REF	REF
13–20.9%	0.971 (0.813–1.159)	0.744
7–12.9%	0.897 (0.739–1.088)	0.269
<7%	0.835 (0.666–1.048)	0.120
Unknown	–	–
Patient residence		
Metro	REF	REF
Urban	0.993 (0.853–1.156)	0.923
Rural	1.019 (0.733–1.417)	0.912
Unknown	–	–
Facility type		
Community	REF	REF
Comprehensive Community	0.969 (0.816–1.151)	0.718
Academic/Research	1.057 (0.869–1.285)	0.579
Integrated Network	0.935 (0.710–1.182)	0.576
Unknown	–	–
Facility location		
East Coast	REF	REF
Midwest	1.012 (0.894–1.145)	0.854
West Coast	1.077 (0.879–1.319)	0.477
Unknown	–	–
Years of diagnosis		
2004–2007	REF	REF
2008–2011	0.916 (0.801–1.047)	0.198
2012–2014	0.838 (0.716–0.981)	**0.028**
Tumor laterality		
Left	REF	REF
Right	1.022 (0.913–1.144)	0.708
Unknown	–	–
T classification		
T1	REF	REF
T2	1.080 (0.963–1.212)	0.190
Treatment group		
CFRT + chemotherapy	REF	REF
SABR + chemotherapy	1.007 (0.801–1.267)	0.951

Statistically significant *p* values are in bold.
HR, hazard ratio; CI, confidence interval; CFRT, conventionally-fractionated radiation therapy; SABR, stereotactic ablative radiotherapy.

and mediastinal nodal staging, pulmonary function tests, chemotherapy agents, and salvage therapies, all of which could confound conclusions of the current investigation. It also does not record other relevant endpoints, such as local failure, cancer-specific survival, or tolerance of therapy (including premature cessation of chemotherapy).

Conflicts of interest

All authors state that conflicts of interest do not exist.

Declaration

There are no acknowledgements. There was no funding for this study. This study has not been presented or published in part or full form elsewhere. All authors declare no conflicts of interest.

Disclaimers

None. This has never been presented or published before in any form. All authors declare that conflicts of interest do not exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.006.

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