Establishing a histology-specific biologically effective dose threshold for lung stereotactic ablative radiotherapy (SABR): Is ≥100 Gy$_{10}$ enough?

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ABSTRACT

Objectives: Squamous cell carcinoma (SCC) is associated with worse local control and overall survival (OS) compared to adenocarcinoma (ADC) in patients with early stage non-small cell lung cancer (ES-NSCLC). Biological effective dose (BED) escalation above 100 Gy$_{10}$ improves tumor control, yet SCC and ADC may respond differentially to BED beyond 100 Gy$_{10}$.
Materials and Methods: We queried the National Cancer Database for ES-NSCLC (T1-2N0, Stage I-IIA) patients with SCC or ADC treated with stereotactic ablative radiotherapy (SABR). Receiver operator characteristic (ROC) curve analysis was used to identify the optimal dose threshold for SCC and ADC. Patients were stratified by histology and BED (≥122 Gy$_{10}$ vs < 122 Gy$_{10}$). Univariable and multivariable analyses identified characteristics predictive of OS. Cox proportional hazard ratios with inverse probability weighting (IPW) were used to mitigate indication bias between the two dose arms.
Results: Ultimately 11,084 ES-NSCLC patients with either ADC (n = 6476) or SCC (n = 4608) were eligible for analysis. Calculated optimal BED threshold for both SCC and ADC was 122 Gy$_{10}$. Univariable analysis demonstrated a median (36 months vs 32 months), 3-year (51% vs 43%), and 5-year (27% vs 22%) OS advantage in SCC patients receiving BED escalation ≥122 Gy$_{10}$ (p = 0.002). No survival difference was observed in the ADC dose escalation arm (p = 0.650). BED escalation ≥122 Gy$_{10}$ remained an independent predictor of improved survival on IPW multivariable comparison (p < 0.0001).
Conclusion: Escalation of BED ≥ 122 Gy$_{10}$ was an independent prognosticator of improved survival in patients with SCC of the lung post-SABR. No survival benefit was observed for ADC, suggesting a differential response to BED escalation.

1. Introduction

Non-small cell lung cancer (NSCLC) represents a heterogeneous group of malignancies characterized by varying molecular aberrancies, as well as, clinicopathologic characteristics. In patients with early stage NSCLC, surgical resection remains the current standard of care. However, many patients with technically resectable disease are deemed inoperable due to co-morbid medical conditions or patient refusal. In these non-operative, early stage patients, stereotactic ablative radiotherapy (SABR) has emerged as the current standard of care. [1,2]

More recently, it is becoming increasingly recognized that squamous cell carcinoma (SCC) histology is associated with worse local control and overall survival compared to adenocarcinoma (ADC)

following treatment with SABR. [3–7] One proposed strategy to mitigate the poorer outcomes observed with SCC is through escalation of the biologically effective dose (NCT03321747). Historically, superior local control and survival outcomes have been observed when BED, defined by where *n* is the total number of fractions, *d* is the dose per fraction, and tumor *α/β* was assumed to be 10) is at least 100 Gy$_{10}$ [8]. However, contemporary analyses have suggested that higher BED thresholds (i.e. > 105 Gy$_{10}$ -110 Gy$_{10}$) may improve local control and survival outcomes in early stage NSCLC. [9–11] While higher BED thresholds have been proposed, the optimal dose threshold has not been established. Herein, we report the association between dose and outcome of early stage SCC and ADC of the lung treated with SABR using the national cancer database (NCDB).

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2. Materials and methods

The NCDB encompasses an estimated 70% of annual cancer cases in the United States and is jointly overseen by the American Cancer Society and American College of Surgeons. As the NCDB contains de-identified data, the study was except from institutional review board supervision. [12] Previous studies have outlined the methodology involved with NCDB analyses; as such, a comparable approach was undertaken [13]. We queried the database (2004–2015) for T1-2N0 NSCLC treated with ablative radiation doses (i.e. BED $\geq 100 \, Gy_{10}$). Starting from 1,393,073 patients, the following were excluded: unknown or stage IIb-IV disease (n = 1,153, 637), surgical resection

Table 1

Sensitivity analysis regarding the impact of biologically effective dose cutoff on Cox multivariable analysis for OS.

BED Cutoff	HR	95% CI	p-value	HR	95% CI	p-value
		SQUAMOUS CELL CARCINOMA			ADENOCARCINOMA	
$100 \, Gy_{10}$	1.050	0.955-1.154	0.316	0.964	0.884-1.050	0.399
$110 \, Gy_{10}$	0.910	0.840-0.990	**0.022**	1.014	0.942-1.091	0.721
$120 \, Gy_{10}$	0.885	0.819-0.957	**0.002**	0.963	0.895-1.036	0.311
$122 \, Gy_{10}$	0.881	0.813-0.954	**0.002**	0.963	0.895-1.036	0.311
$130 \, Gy_{10}$	0.881	0.813-0.955	**0.002**	0.973	0.904-1.048	0.473
$140 \, Gy_{10}$	0.900	0.827-0.979	**0.014**	0.980	0.907-1.058	0.601
$150 \, Gy_{10}$	0.900	0.824-0.979	**0.015**	1.010	0.934-1.092	0.804

Table 2

Clinical Characteristics of the Squamous Cell Carcinoma (SCC) Cohort and Significant Factors Associated with Receipt of Stereotactic Ablative Body Radiotherapy (SABR) at BED $\geq 122 \, Gy_{10}$.

Parameter	SCC (N = 4608)		Multivariable Analysis: SCC Cohort Receiving BED $\geq 122 \, Gy_{10}$	
	BED $\geq 122 \, Gy_{10}$ (N = 2045)	BED $< 122 \, Gy_{10}$ (N = 2563)	OR (95% CI)	*p*-value
Age				
< 75 years	1074 (53)	1279 (50)	REF	REF
≥75 years	971 (47)	1284 (50)	0.975 (0.859-1.107)	0.698
Sex				
Male	1062 (52)	1311 (51)	REF	REF
Female	983 (48)	1252 (49)	0.944 (0.835-1.068)	0.363
Race				
White	1846 (90)	2308 (90)	REF	REF
Black	163 (8)	203 (8)	1.097 (0.863-1.394)	0.450
Other	36 (2)	52 (2)	0.747 (0.472-1.181)	0.212
Charlson Deyo Comorbidity Index				
0	1126 (55)	1317 (51)	REF	REF
1	538 (26)	711 (28)	0.902 (0.780-1.044)	0.166
2	381 (19)	535 (21)	0.907 (0.771-1.067)	0.240
Insurance Type				
Private	244 (12)	277 (11)	REF	REF
Government	1760 (86)	2255 (88)	0.836 (0.361-1.939)	0.677
Uninsured	13 (1)	12 (< 1)	0.771 (0.338-1.760)	0.537
Income (US dollars/year)				
< $30,000	392 (19)	483 (19)	REF	REF
$30,000-$34,999	560 (27)	692 (27)	1.006 (0.819-1.234)	0.958
$35,000-$45,999	606 (30)	736 (29)	1.089 (0.871-1.361)	0.456
≥$46,000	476 (23)	644 (25)	1.046 (0.804-1.360)	0.740
Education				
≥29%	290 (14)	386 (15)	REF	REF
20-28.9%	653 (32)	722 (28)	1.184 (0.957-1.465)	0.120
14-19.9%	690 (34)	908 (35)	1.002 (0.793-1.265)	0.990
< 14%	401 (20)	539 (21)	0.991 (0.750-1.310)	0.950
Patient Residence				
Suburban	1573 (77)	2058 (80)	REF	REF
Urban	363 (18)	404 (16)	1.148 (0.950-1.387)	0.153
Rural	65 (3)	46 (2)	1.730 (1.139-2.627)	**0.010**
Facility Type				
Community	47 (1)	73 (3)	REF	REF
Academic/Comprehensive Cancer Center	1998 (98)	2490 (97)	1.052 (0.707-1.576)	0.812
Distance to Treating Facility				
< 11 miles	924 (45)	1261 (49)	REF	REF
≥11 miles	1121 (55)	1302 (51)	1.107 (0.963-1.273)	0.152
Year of Diagnosis				
2004-2006	46 (2)	33 (1)	REF	REF
2007-2009	400 (20)	237 (9)	1.096 (0.665-1.807)	0.718
2010-2012	876 (43)	1026 (40)	0.572 (0.354-0.924)	**0.022**
2013-2015	723 (35)	1267 (49)	0.371 (0.229-0.599)	**< 0.001**
Tumor Size				
≤1 cm	148 (7)	126 (5)	REF	REF
> 1 cm and ≤ 2 cm	921 (45)	894 (35)	0.879 (0.674-1.146)	0.340
> 2 cm and ≤ 3 cm	641 (31)	826 (32)	0.664 (0.506-0.870)	**0.003**
> 3 cm and ≤ 4 cm	240 (12)	517 (20)	0.382 (0.284-0.513)	**< 0.001**
> 4 cm and ≤ 5 cm	95 (5)	200 (8)	0.378 (0.264-0.541)	**< 0.001**
SABR Delivery				
Daily	619 (30)	1996 (78)	REF	REF
Nondaily	1426 (70)	567 (22)	1.377 (1.120-1.585)	**< 0.001**

Percentages may not add to 100% because of rounding.

Note: Education is quartiles of the percentage of persons with less than a high school education in the patients' residence census tract. Income is median household income in the patients' residence census tract.

SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; SABR, stereotactic ablative radiotherapy.

Table 3

:Clinical Characteristics of the Adenocarcinoma (ADC) Cohort and Significant Factors Associated with Receipt of Stereotactic Ablative Body Radiotherapy (SABR) at a BED ≥ 122 Gy_{10}.

Parameter	ADC (N = 6476)		Multivariable Analysis: ADC Cohort Receiving BED ≥ 122 Gy_{10}	
	BED ≥ 122 Gy_{10} (N = 2846)	BED < 122 Gy_{10}(N = 3630)	OR (95% CI)	*p*-value
Age				
< 75 years	1494 (52)	1769 (49)	REF	REF
≥75 years	1352 (48)	1861 (51)	0.902 (0.812-1.005)	0.061
Sex				
Male	1205 (42)	1456 (40)	REF	REF
Female	1641 (58)	2174 (60)	0.927 (0.835-1.029)	0.154
Race				
White	2575 (90)	3242 (89)	REF	REF
Black	221 (8)	299 (8)	0.939 (0.768-1.149)	0.542
Other	50 (2)	89 (3)	0.717 (0.495-1.041)	0.080
Charlson Deyo Comorbidity Index				
0	1674 (59)	2191 (60)	REF	REF
1	754 (26)	950 (26)	1.046 (0.928-1.180)	0.460
2	418 (15)	489 (14)	1.184 (1.016-1.379))	**0.031**
Insurance Type				
Private	368 (13)	476 (13)	REF	REF
Government	2412 (85)	3085 (85)	1.382 (0.777-2.458)	0.270
Uninsured	20 (1)	36 (1)	1.415 (0.807-2.481)	0.225
Income (US dollars/year)				
< $30,000	461 (16)	556 (15)	REF	REF
$30,000-$34,999	737 (26)	881 (24)	0.962 (0.803-1.153)	0.676
$35,000-$45,999	825 (29)	1039 (29)	0.936 (0.771-1.135)	0.501
≥$46,000	809 (28)	1139 (31)	0.885 (0.7111-1.102)	0.275
Education				
≥29%	376 (13)	467 (13)	REF	REF
20-28.9%	746 (26)	891 (25)	1.048 (0.870-1.262)	0.620
14-19.9%	690 (24)	1297 (36)	1.078 (0.886-1.310)	0.454
< 14%	651 (23)	961 (26)	0.935 (0.745-1.173)	0.560
Patient Residence				
Suburban	2321 (82)	3008 (83)	REF	REF
Urban	393 (14)	466 (13)	0.924 (0.778-1.099)	0.373
Rural	66 (2)	65 (2)	1.173 (0.810-1.699)	0.399
Facility Type				
Community	61 (2)	108 (3)	REF	REF
Academic/Comprehensive Cancer Center	2785 (98)	3522 (97)	1.314 (0.935-1.846)	0.114
Distance to Treating Facility				
< 11 miles	1393 (49)	1959 (54)	REF	REF
≥11 miles	1453 (51)	1671(46)	1.214 (1.081-1.363)	**0.001**
Year of Diagnosis				
2004-2006	62 (2)	43 (1)	REF	REF
2007-2009	558 (20)	327 (9)	1.135 (0.737-1.746)	0.566
2010-2012	1185 (42)	1467 (40)	0.525 (0.346-0.794)	**0.002**
2013-2015	1041 (37)	1793 (49)	0.379 (0.250-0.574)	**< 0.001**
Tumor Size				
≤1 cm	213 (8)	212 (6)	REF	REF
> 1 cm and ≤ 2 cm	1338 (47)	1515 (42)	0.859 (0.694-1.063)	0.163
> 2 cm and ≤ 3 cm	879 (31)	1202 (33)	0.698 (0.560-0.869)	**0.001**
> 3 cm and ≤ 4 cm	324 (11)	519 (14)	0.575 (0.449-0.737)	**< 0.001**
> 4 cm and ≤ 5 cm	92 (3)	182 (5)	0.510 (0.367-0.708)	**0.001**
SABR Delivery				
Daily	821 (29)	843 (23)	REF	REF
Nondaily	2025 (71)	2787 (77)	1.237 (1.100-1.392)	**0.001**

Percentages may not add to 100% because of rounding.

Note: Education is quartiles of the percentage of persons with less than a high school education in the patients' residence census tract. Income is median household income in the patients' residence census tract.

ADC, adenocarcinoma; OR, odds ratio; CI, confidence interval; SABR, stereotactic ablative radiotherapy.

(n = 154,654), chemotherapy/immunotherapy (n = 500), or external beam radiotherapy of greater than five fractions, unknown dose/fractionation, targeting non-thoracic sites, BED < 100 Gy_{10}, or lack of SABR technique (n = 64,518). Histologic subtypes other than ADC and SCC were excluded (n = 4961), as were lesions > 5 cm or unknown size (n = 654), and follow-up of less than one month (n = 3064) to account for immortal time bias.

Statistical analysis was performed via MedCalc Version 18 (Ostend, Belgium). Receiver operating characteristic (ROC) curve analysis was performed to determine the *a priori* BED threshold producing the greatest difference in overall survival (OS) independently for both SCC

and ADC. [14] For SCC, the resultant Youden's index was ≥122 Gy_{10}, which was further supported by a confirmatory sensitivity analysis (Table 1). [15] Since ROC analysis for ADC did not yield a conclusive threshold, a BED threshold of 122 Gy_{10} was used for comparative purposes. Chi-squared testing was used to compare clinical, socioeconomic, and treatment characteristics between cohorts of BED ≥ 122 Gy_{10} and < 122 Gy_{10} for SCC and ADC groups. OS was calculated using Kaplan-Meier curves, and compared with log-rank statistics. Multivariable Cox regression analysis was performed for all characteristics listed on Table 2 for both SCC (Table 2) and ADC (Table 3).

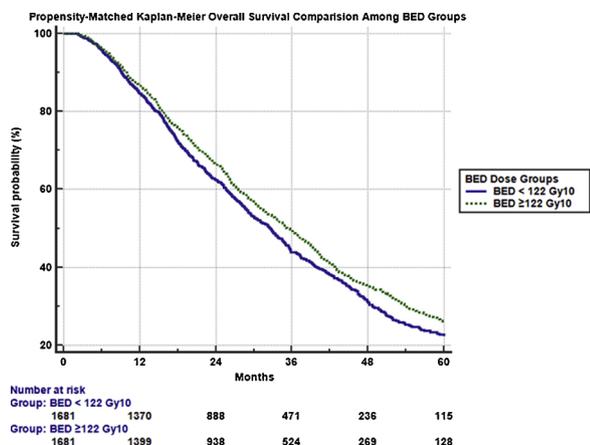Propensity score analysis was used to mitigate indication bias

Fig. 1. Survival Comparison in Patients with Squamous Cell Carcinoma Histology Receiving Stereotactic Ablative Radiotherapy at BED ≥ 122 Gy_{10} vs BED < 122 Gy_{10}.
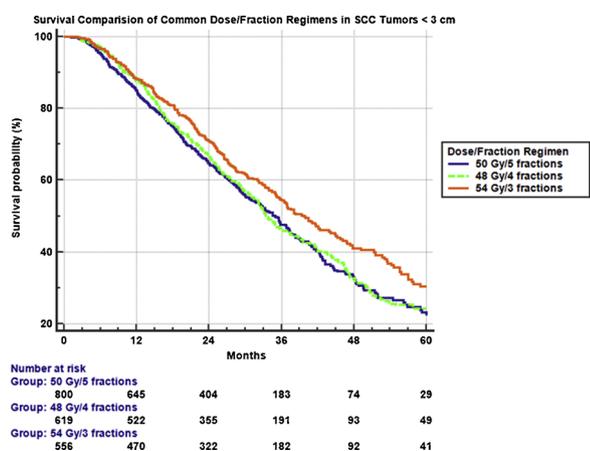

Fig. 2. Survival Comparison in Patients with Squamous Cell Carcinoma Histology and Tumors ≤ 3 cm Receiving Common Dose-Fractionation Regimens in Management of Early Stage NSCLC.

caused by lack of randomization. Multivariable logistic regression was used to calculate propensity scores, reflecting the conditional probability of a patient receiving BED ≥ 122 Gy_{10} or < 122Gy_{10}. The propensity model (i.e. separately constructed propensity models for SCC and ADC) included observable variables significantly associated with receipt of BED ≥ 122 Gy_{10} on multivariable logistic regression. Inverse probability weighting (IPW) was used to account for subject data omitted from the primary analysis. [16] Assumption of balance between groups was strengthened by stratification into propensity score-based quintiles, which demonstrated a standard inter-group difference of less than 0.10. [17]

3. Results

3.1. Patient, disease, and treatment characteristics

Overall, 11,084 patients were eligible for final analysis with 6476 patients having ADC and 4608 patients having SCC. The median radiation dose-fractionation for the entire cohort was 50 Gy (interquartile range (IQR): 50–55 Gy) in four fractions (3–5 fractions) with a median BED = 112.5 Gy_{10} (100–151.2 Gy_{10}). The most common dose-fractionation regimens in the SCC cohort were 50 Gy/5 fractions (n = 1164), 48 Gy/4 fractions (n = 817), and 54 Gy/3 fractions (n = 652), with corresponding BED values of 100 Gy_{10}, 105.6 Gy_{10}, and 151.2 Gy_{10}, respectively. Baseline characteristics for patients having a diagnosis of

SCC (n = 4608) are shown in Table 2. The median tumor size was 2.2 cm (IQR 1.6–3.0 cm), and 44% of cases were treated to a BED ≥ 122 Gy_{10}. Baseline characteristics for patients with ADC (n = 6476) were similar to that of SCC except for a female predominance (59%) [Table 3]. Patients treated on non-consecutive days, residing in rural areas, harboring smaller tumors, and in earlier years (i.e. 2004-06 and 2007-09), were more likely to receive higher BED treatment for both SCC and ADC.

3.2. Survival

Median follow-up for all patients was 43 months, with a median survival of 44 months (95% CI: 43–46) in patients with ADC and 33 months (95% CI: 32–34) in patients with SCC (p < 0.001). On multivariable analysis (MVA) of the entire cohort, increasing age, larger tumor size, higher comorbidity score, and SCC histology associated with worse survival; black race and female sex were associated with longer survival (p < 0.05 for all). On MVA for survival, BED ≥ 122 Gy was an independent predictor for longer survival (p < 0.001) in SCC patients, with and without propensity matching for BED. Conversely, among ADC patients, BED did not correlate with survival on MVA (with and without propensity matching) [Table 3]. For further validation, BED was evaluated as a continuous variable on MVA. The association between higher BED and longer survival in SCC (p = 0.008) was confirmed; as was the lack of association in ADC (p = 0.294). At three and five years, propensity-adjusted survival among SCC treated to BED ≥ 122 Gy_{10} was statistically longer (3-year OS: 50% vs. 44%; 5-year OS: 26% vs. 22% [hazard ratio (HR): 0.839 (95% CI: 0.779-0.904); p = 0.009] (Fig. 1). Because tumors > 3 cm were more likely to receive a lower BED, we conducted a subset analysis comparing tumors ≤ 3 cm with the most commonly used dose-fractionation (reported as BED correlate) regimens in the SCC cohort. Median overall survival was significantly longer (p = 0.001, HR: 0.80; 95% CI: 0.68-0.95) in the BED = 151.2 Gy_{10} (39.7 months) group compared to the BED = 100 Gy_{10} (34.9 months) and BED = 105.6 Gy_{10} (33.6 months) groups (Fig. 2).

4. Discussion

Using a large, contemporary national database, we suggest that for SCC, the optimal BED cutoff should be higher (i.e. ≥ 122 Gy_{10}) than originally anticipated. Interestingly, SABR utilizing this higher BED threshold increased survival in patients with SCC, however did not improve outcomes in patients with ADC when compared to SABR at lower BED values (i.e. 100–121.9 Gy_{10}).

It is becoming increasingly apparent that histology plays a significant role in post-SABR outcomes. In total, five studies have suggested poorer post-SABR outcomes in patients with SCC compared to ADC. [3–7] The initial series was reported by the Cleveland Clinic in 2017 and involved 740 medically inoperable early stage NSCLC patients who received SABR. In this series, squamous histology was the strongest predictor (HR: 2.4; p = 0.0008) of local failure as 3-year actuarial local failure rates were 18.9% and 8.7% in patients with SCC (n = 215) and ADC (n = 243) respectively. [3] Of note, in this series squamous histology was not associated with decreased overall survival.

Similarly, a retrospective analysis was completed in Germany involving 126 patients with early stage ADC (n = 69) or SCC (n = 57) treated with SABR. [4] At median follow-up of 22 months, SCC histology was identified as an independent predictor (p = 0.033) for worse local control.

Comparatively, a retrospective multi-institutional series by Baine et al, examined 152 patients with early stage ADC (n = 78) or SCC (n = 74) following treatment with SABR. [5] At a median follow-up of 44 months, SCC histology was associated with increased risk of local failure, as well as, worse overall survival (median OS: 33 months vs 50 months). Most recently, a large analysis by Abel et al, compared

Table 4
Multivariable Cox Proportional Hazards Model for Overall Survival.

Parameter	HR	95% CI	p-value
ALL SQUAMOUS CELL CARCINOMA (SCC)			
Age (≥ 75 vs. < 75 years)	1.174	1.087-1.268	< 0.001
Sex (Female vs. Male)	0.845	0.783-0.913	< 0.001
Race (Black vs. White)	0.817	0.702-0.952	0.010
Charlson Deyo score (2 vs. 0)	1.249	1.138-1.372	< 0.001
Patient residence (Urban vs. Suburban)	0.915	0.825-1.015	0.093
Facility type (Community vs. Academic)	1.100	1.018-1.188	0.016
Tumor size (Reference: ≤ 1 cm)			
> 1 cm and ≤ 2 cm	1.208	1.009-1.447	0.040
> 2 cm and ≤ 3 cm	1.426	1.188-1.712	< 0.001
> 3 cm and ≤ 4 cm	1.641	1.352-1.990	< 0.001
> 4 cm and ≤ 5 cm	2.005	1.609-2.499	< 0.001
Biologically Effective Dose (≥ 122 Gy_{10} vs. < 122 Gy_{10})	0.885	0.819-0.957	0.002
INVERSE PROBABILITY WEIGHTED COHORT (SCC)			
Age (≥ 75 vs. < 75 years)	1.222	1.130-1.321	< 0.001
Sex (Female vs. Male)	0.823	0.762-0.888	< 0.001
Race (Reference: White)			
Black	0.833	0.710-0.976	0.024
Other	0.826	0.618-1.104	0.197
Charlson Deyo score (Reference: 0)			
1	1.058	0.967-1.158	0.221
2	1.301	1.180-1.436	< 0.001
Biologically Effective Dose (≥ 122 Gy_{10} vs. < 122 Gy_{10})	0.832	0.769-0.900	< 0.001

Parameter	HR	95% CI	p-value
ALL ADENOCARCINOMA (ADC)			
Age (≥ 75 vs. < 75 years)	1.193	1.107-1.285	< 0.001
Sex (Female vs. Male)	0.749	0.698-0.805	< 0.001
Race (Black vs. White)	0.827	0.720-0.951	0.008
Charlson Deyo score (Reference: 0)			
1	1.160	1.067-1.260	< 0.001
2	1.409	1.271-1.562	< 0.001
Insurance status (Reference: Private)			
Government	1.558	0.982-2.472	0.060
Uninsured	1.669	1.061-2.624	0.027
Education (Reference: $\geq 29\%$)			
20-28.9%	0.899	0.797-1.013	0.080
14-19.9%	0.839	0.748-0.942	0.003
$< 14\%$	0.851	0.753-0.962	0.010
Biologically Effective Dose (≥ 122 Gy_{10} vs. < 122 Gy_{10})	0.983	0.910-1.061	0.650
INVERSE PROBABILITY WEIGHTED COHORT (ADC)			
Age (≥ 75 vs. < 75 years)	1.272	1.184-1.367	< 0.001
Sex (Female vs. Male)	0.742	0.691-0.796	< 0.001
Race (Reference: Black vs White)	0.844	0.746-0.968	0.015
Charlson Deyo score (Reference: 0)			
1	1.165	1.074-1.266	0.003
2	1.484	1.291-1.581	< 0.001
Education			
14-19.9%	0.839	0.749-0.940	0.003
$< 14\%$	0.851	0.754-0.961	0.009
Biologically Effective Dose (≥ 122 Gy_{10} vs. < 122 Gy_{10})	0.933	0.839-1.038	0.202

Statistically significant p values are in bold. Significant parameters are those included in the final multivariable model.
HR, hazard ratio; CI, confidence interval.

survival outcomes in patients with early stage ADC (n = 8924) and SCC (n = 6186) treated with SBRT [7]. SCC histology was identified as an independent predictor of decreased overall survival (median OS: 33 months vs 44 months; p < 0.001) compared to ADC. Though SCC was independently associated with poorer outcomes in the aforementioned studies, it is noteworthy to mention that SCC was also associated with less favorable clinicopathologic covariates such as higher T stage.

Considering the growing body of evidence suggesting inferior outcomes for SCC, treatment strategies to mitigate these poorer outcomes are needed. One proposed strategy is to increase the BED beyond the historically accepted 100 Gy_{10} as assessed in our study. Two retrospective studies have supported our findings in that the "optimal" BED threshold of ≥ 100 Gy_{10} should be increased (> 105-100 Gy_{10}). [9,10] However, those studies did not stratify by histology, potentially masking the overall benefit. Interestingly, our data suggests that an

even higher threshold may be required for SCC (Table 4). That said, delivery of ≥ 122 Gy_{10} may be difficult considering the proclivity of SCC to present with (ultra)central disease. Nevertheless, RTOG 0813 has demonstrated similar safety outcomes in patients with centrally located tumors treated to a maximum tolerated dose of 12.0 Gy/fraction for five fractions (i.e. BED: 132 Gy_{10}) compared to peripheral located tumors. [18] Furthermore, the limited number of recommended SABR dose-fractionation schemes can make treatment planning exceedingly challenging. To this extent, novel schemes should be investigated that yield high BED values while also respecting normal tissue dose constraints. Importantly, as the oncologic treatment paradigm continues to shift toward personalized medicine, optimization of histologic-based BED thresholds may not only improve oncologic outcomes, but also reduce toxicity in select patients.

Reasons for poorer outcomes for SCC include reduced

radiosensitivity and increased immunosuppression by means of higher PD-L1 expression. [19] These findings (together with results of our analysis) have potential therapeutic implications and provide a basis to ongoing trials investigating high-BED treatment schedules (NCT03321747), as well as those assessing the role of immunotherapy and SABR (NCT03110978).

Interestingly, radiation regimens in which the BED was increased beyond 122 Gy_{10} seemed to have a variable impact on survival based upon the histology of the tumor. Whereas treatment with high BED regimens seemed to have little to no effect on survival outcomes in patients with ADC (Supplementary Fig. 1), escalation beyond a BED of 122 Gy_{10} was associated with improved overall survival in SCC patients. Although there is no clear explanation as to why this was observed, it may be a result of differential tumor biology and/or radiosensitvity between the two histologic subtypes. Specifically, biological differences may influence the manner in which these tumors tend to progress (i.e. locally vs distantly); as such escalation of dose may benefit one histology (i.e. those that tend to fail locally) considerably more than another (i.e. those that tend to fail distantly).

Although well powered, this study is limited by the selection bias inherent to all observational studies, despite the robust statistical methods utilized to mitigate this effect. In addition to its retrospective nature, the NCDB does not contain information on performance status, clinical workup including positron emission tomography and mediastinal nodal staging, tumor location (central vs. peripheral), pulmonary function tests, and salvage therapies, all of which may confound conclusions of the current investigation. It also does not record other relevant endpoints, such as local, regional, or distant recurrence, cancer-specific survival, or toxicity. Therefore, while our findings are compelling and hypothesis generating, continued prospective investigation of histologic-based dose thresholds is merited.

5. Conclusion

Escalation of BED (i.e. $\geq 122 Gy_{10}$) was associated with improved survival outcomes post-SABR in patients with SCC of the lung. This association was not evident in ADC patients; perhaps suggesting a histologic differential response. Given the inherent limitations of this study, prospective validation is warranted.

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Declaration of Competing Interest

The authors have no conflicts of interest or disclosures.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.07.014.

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