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Stereotactic ablative radiotherapy (SABR) in early stage non-small cell lung cancer: Comparing survival outcomes in adenocarcinoma and squamous cell carcinoma

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ABSTRACT

Purpose: Recent retrospective studies have demonstrated mixed results regarding the histologic association of squamous cell carcinoma (SCC) with reduced overall survival in patients with early-stage non-small cell lung cancer (ES-NSCLC) treated with stereotactic ablative radiotherapy (SABR).

Methods: We queried the National Cancer Database (NCDB) for ES-NSCLC (T1-2N0, Stage I-IIA) patients with SCC or adenocarcinoma (ADC) treated with SABR. Univariable and multivariable analyses identified characteristics predictive of overall survival. Cox proportional hazard ratios with propensity adjustment were used to mitigate indication bias between the two histologic arms.

Results: Ultimately 15,110 ES-NSCLC patients with either ADC (n = 8,924) or SCC (n = 6,186) were eligible for analysis. Univariable analysis demonstrated a median overall survival of 44 months and 33 months ($p < 0.0001$) and 5-year overall survival of 36% and 24% ($p < 0.0001$) in patients diagnosed with ADC and SCC, respectively. SCC histology, remained an independent predictor of worse survival on propensity score matched multivariable comparison ($p < 0.0001$). Patients with SCC were more likely to have T2 lesions and poorly differentiated grade. Females, African American race, T1 lesions, and age < 75 years were also associated with improved survival.

Conclusion SCC histology was an independent prognosticator of worse survival in patients with ES-NSCLC treated with SABR, thus corroborating the results of previous studies. Randomized, prospective studies are needed to further validate these findings.

1. Introduction

With an incidence of approximately 190,000 annual cases in the United States, non-small cell lung cancer (NSCLC) is the most common primary lung cancer [1]. NSCLC is a heterogeneous disease, with important genetic, molecular, and histological differences that can provide clinicians with both prognostic and predictive information. From a histologic standpoint, NSCLC consists of two principal groupings: adenocarcinoma (ADC) and squamous cell carcinoma (SCC).

Approximately 15–20% of patients with NSCLC present with early-stage (T1-2, N0) disease, in which the standard of care is surgical resection [2,3]. Unfortunately, a number of patients with technically resectable disease have medical co-morbidities (cardiopulmonary disease, diabetes, obesity) that substantially increase the surgical risk or preclude surgery altogether. In these cases of medically inoperable early stage NSCLC, the standard of care is stereotactic ablative radiotherapy (SABR) [3–6].

Recently, three retrospective studies have demonstrated an association between SCC histology and local failure following treatment with SABR [7–9]. However, these studies have reported incongruent results regarding this histologic association of SCC with worse overall survival. A multi-institutional retrospective analysis of 152 patients completed by Baines et al, compared outcomes between ADC and SCC treated with SABR [7]. The authors reported improved 5-year overall

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survival for ADC when compared to SCC. However, previous retrospective studies failed to demonstrate a survival difference between the two histological subsets [8,9]. To further investigate if SCC prognosticates for worse overall survival, we analyzed the national cancer database (NCDB), comparing survival in patients having early stage, node negative ADC and SCC treated with SABR.

2. Methods

2.1. Patient selection

Overseen by the American Cancer Society and American College of Surgeons, the NCDB encompasses an estimated 70% of annual cancer cases in the United States [10]. As the NCDB contains de-identified data, the study was exempt from institutional review board supervision. The methodology involved with NCDB analyses have been described before, as such, a comparable approach was undertaken [11,12]. We queried the database to identify early stage NSCLC patients (T1-2a, N0) treated with an ablative dose (i.e. BED $\geq$ 100 Gy_{10}) of thoracic external beam radiation (EBRT) between the years 2004 – 2015. Patients were excluded if any of the following criteria were met: stage IIb-IV disease, treatment with surgical resection, chemotherapy, or external beam radiotherapy (EBRT) of greater than five fractions or unknown dose/fractionation regimen, patients receiving EBRT exclusively to non-thoracic sites, receiving thoracic radiation at non-ablative doses (i.e. BED $<$ 100 Gy_{10}), or failing to utilize SABR technique. Patients treated with non-ablative doses were excluded as these patients historically had worse survival outcomes [13]. Patients with histologic subtypes other than ADC and SCC were excluded, as were, T2b lesions. A complete CONSORT diagram depicting the cohort selection process is outlined on Fig. 1.

Ultimately, 15,110 patients were eligible for final analysis with 8924 patients having a diagnosis of ADC and 6186 patients having SCC. The median radiation dose-fractionation for the entire cohort was 50 Gy in four fractions. Race was defined as either white, African American or other/unknown. Comorbidity was quantified via Charlson/Deyo comorbidity index, and stage was defined by American Joint Cancer Committee 7th edition clinical staging [14,15]. Income data in the patients' residence census tract were provided as quartiles and reported here as above or below the median. Population classification was based on typology published by the USDA Economic Research Service, facility type was assigned according to Commission on Cancer accreditation category, and insurance status was reported on the admission page [16].

2.2. Statistics

Statistical analysis was performed via MedCalc Version 18 (Ostend, Belgium). Chi square testing was used to compare clinical, socioeconomic, and treatment characteristics between the ADC and SCC groups. Summary statistics were reported for discrete variables and multivariable logistic regression models were used to assess the association between independent variables of interest and histologic grouping. Overall survival (OS) was calculated from the date of diagnosis to the date of last contact or death using Kaplan-Meier curves to present the cumulative probability of survival, and log-rank statistics to assess statistical significance between groups [17]. Univariable survival analysis was performed for all characteristics listed on Table 1, and

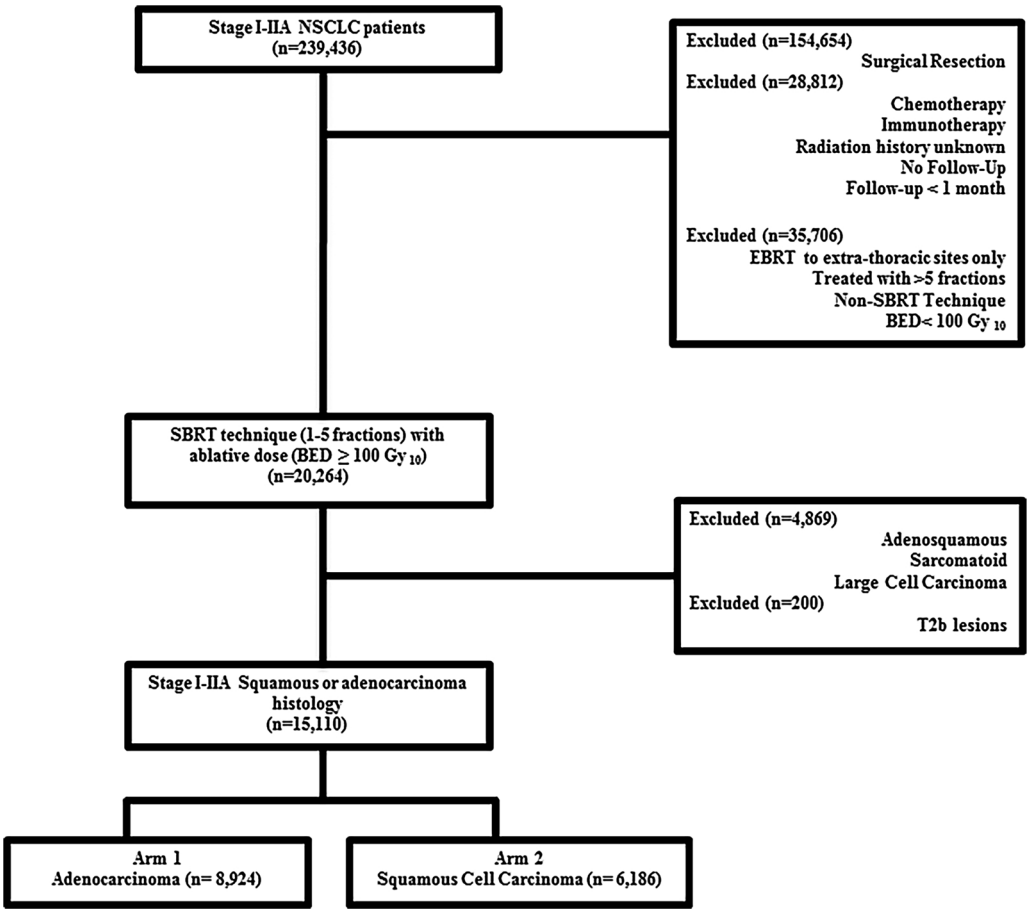

Fig. 1. Overview of the selection criteria for the cohort–non-small cell lung cancer (NSCLC); external beam radiation therapy (EBRT); stereotactic–body radiation therapy (SBRT); biologically effective dose (BED). AJCC TNM Staging Manual was used for staging purposes.

Table 1
Patient and Treatment Characteristics (N = 15,110).

Characteristic	No. (% or range)	Characteristic	No. (% or range)
Demographics		Treatment facility type	
		Community cancer program	483 (3.2)
Sex		Academic/research program	6570 (43.5)
Male	6892 (46)	Comprehensive cancer program/other	8057 (53.3)
Female	8218 (54)	Rural counties	339 (2.3)
Age		Year of Treatment	
Median	75 (40 – 90)	2004 – 2007	526 (3.5)
≤ 75	7766 (51.4)	2008 – 2011	4252 (28.1)
> 75	7344 (48.6)	2012 – 2015	10332 (68.4)
Race		**Disease Characteristics**	
White	13617 (90.1)		
African American	1190 (7.9)	Clinical T stage	
Other/Unknown	303 (2.0)	T1	11,845 (78.4)
Comorbidity score		T2	3,265 (21.6)
0	8558 (56.6)	Histology	
1	4031 (26.7)	Adenocarcinoma	8924 (59.1)
2+	2521 (16.7)	Squamous Cell Carcinoma	6186 (40.9)
Insurance		Grade	
Private	1869 (12.4)	Well differentiated	1453 (9.6)
Government	12951 (85.7)	Moderately differentiated	3033 (20.1)
Unknown	180 (1.2)	Poorly differentiated	2833 (18.8)
Education		Unknown	7791 (51.6)
≥ 29	2113 (14.0)	**Treatment Characteristics**	
20 to 28.9	4138 (27.4)	Radiation dose, Gy	
14 to 19.9	5378 (35.6)	Median (Range)	
< 14	3435(22.7)		50.0 (30.0 – 75.0)
Unknown	54 (0.3)	Interquartile Range (Gy)	
Income, US dollars			5.5
< 30,000	2685 (17.8)	Fractionation	
30,000 to 35,000	3890 (25.7)	Median (fraction number)	
35,000 to 45,999	4343 (28.7)		4(1-5)
≥ 46,000	4132 (27.4)	Biologically Equivalent Dose, Gy_{10}	
Unknown	60 (0.4)	Median (Range)	
Distance to treatment facility, miles			112.5 (100-231.9)
≤ 10	7046 (46.6)	Interquartile Range (Gy_{10})	
> 10	8064 (53.3)		51.2

statistically significant factors were then entered in a hierarchical fashion using "enter" selection of the covariates' likelihood ratios. Given the relatively small total number of candidate covariates in relation to the total patient population, a confirmatory multivariable analysis using a stepwise backward elimination and forward selection procedures were performed and the same results were obtained. Adjusted hazard ratios (HR) and 95% confidence interval (CI) were reported, with $\alpha = 0.05$ used to indicate statistical significance.

Propensity score analysis was used to mitigate indication bias caused by lack of randomization [18–20]. Multivariable logistic regression was used to calculate the propensity score yielding a score reflecting the conditional probability of a patient having a diagnosis of ADC or SCC. The propensity model included observable variables significantly associated with histological subtype on multivariable logistic regression, including clinical T stage, tumor grade, sex, income, education level, insurance, year receiving treatment, distance from treatment facility, and co-morbidity score. After calculation of the propensity score, a Cox proportional hazards model with adjustment for propensity score was developed [21]. Factors included in the propensity score calculation were excluded from the propensity-adjusted Cox proportional hazards model to avoid overcorrection. Assumption of balance between groups was strengthened by stratification into propensity score-based quintiles, which demonstrated a standard intergroup difference of less than 0.10 [22].

Of note, the Commission on Cancer and American College of Surgeons has not substantiated and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

3. Results

3.1. Patient and disease characteristics

Baseline patient characteristics for the entire cohort are shown in Table 1. In summary, the median age was 75 years with an interquartile range of 12 years. The majority of patients were white race (90.1%) with a slight female predominance (54.4%). Most patients had T1 (78.4%) malignancies. A total of 8924 patients (59.1%) carried a diagnosis of ADC while 6186 patients (40.9%) had SCC. Over two-thirds of patients were treated from 2012-15 (68.4%). Table 2 outlines the differences in demographic and disease–related characteristics between those diagnosed with ADC and SCC. Females were more likely to develop adenocarcinoma compared to males (59% vs 41%). Patients with adenocarcinoma were less likely to have T2 tumors (19% vs 25%), have worse comorbidity scores (14% vs 20%), undergo nodal evaluation (6% vs 13%), and have poorly differentiated histology (13% vs 26%) when compared to SCC ($p < 0.01$ for all). Additionally, patients with adenocarcinoma were less likely to reside further than 10 miles from the treatment facility (51% vs 55%), but were more likely to have an income above $46,000 (30% vs 24%).

3.2. Survival

The median follow-up for all patients was 27 months. Median

Table 2
Comparative Analysis of Adenocarcinoma vs Squamous Cell Carcinoma by Baseline Characteristics in Patients Receiving SABR for ES-NSCLC.

Characteristic	Adenocarcinoma (n = 8924) (%)	Squamous Cell Carcinoma (n = 6186) (%)	Odds Ratio	95% CI	p
Sex					
Male	3678 (41)	3214 (52)	1	Ref	
Female	5246 (59)	2972 (48)	1.54	1.45-1.65	< **0.01**
Race					
White	8022 (90)	5595 (90)	1	Ref	
African American	712 (8)	478 (8)	1.03	0.92-1.17	0.53
Other	190 (2)	113 (2)	1.17	0.93-1.48	0.18
Comorbidity Score					
0	5296 (59)	3262 (53)	1	Ref	
1	2354 (26)	1677 (27)	0.86	0.80-0.93	< **0.01**
≥2	1274 (14)	1247 (20)	0.62	0.58-0.69	< **0.01**
Age					
≤75	4550 (51)	3216 (52)	1	Ref	
> 75	4374 (49)	2970 (48)	1.04	0.98-1.11	0.23
Insurance					
None	71 (1)	39 (1)	1	Ref	
Private Payer	1194 (13)	675 (11)	0.97	0.65-1.45	0.88
Government	7550 (85)	5401 (87)	0.77	0.52-1.14	0.19
Facility Type					
Community Cancer Program	282 (3)	201 (3)	1	Ref	
Comprehensive Cancer Program	4783 (54)	3274 (53)	1.04	0.86-1.25	0.67
Academic/research program	3859 (43)	2711 (44)	1.02	0.84-1.22	0.88
Facility Location					
Metro	7293 (82)	4842 (78)	1	Ref	
Urban	1231 (14)	1068 (17)	0.77	0.70-0.84	< **0.01**
Rural	187 (2)	152 (3)	0.82	0.66-1.02	0.07
Income, USD					
< 30,000	1500 (17)	1185 (19)	1	Ref	
30,000-35,000	2206 (25)	1684 (27)	1.04	0.94-1.14	0.50
35,000-45,999	2537 (28)	1806 (29)	1.11	1.01-1.22	**0.04**
> 46,000	2644 (30)	1488 (24)	1.40	1.27-1.55	< **0.01**
Education					
≥29%	1202 (13.5)	911 (14.7)	1	Ref	
20 to 28.9	2282 (25.6)	1856 (30.0)	0.93	0.84-1.04	0.19
14 to 19.9	3218 (36.1)	2152 (34.8)	1.13	1.02-1.26	**0.02**
< 14	2190 (24.5)	1245 (20.1)	1.33	1.19-1.49	< **0.01**
T Stage					
1	7222 (81)	4622 (75)	1	Ref	
2	1701 (19)	1564 (25)	0.70	0.64-0.75	< **0.01**
N Stage Evaluation					
No	8368 (94)	5676 (68)	1	Ref	
Yes	556 (6)	510 (13)	0.74	0.65-0.84	< **0.01**
Grade					
Well differentiated	1337 (15)	116 (2)	1	Ref	
Moderately differentiated	1615 (18)	1418 (23)	0.10	0.08-0.12	< **0.01**
Poorly differentiated	1198 (13)	1635 (26)	0.06	0.05-0.08	< **0.01**
Distance to facility					
≤10 miles	4356 (49)	2741 (44)	1	Ref	
> 10 miles	4525 (51)	3407 (55)	0.84	0.78-0.89	< **0.01**
Year of Diagnosis					
2004-06	120 (1)	99 (2)	1	Ref	
2007-09	997 (11)	723 (12)	1.14	0.86-1.51	0.37
2010-12	2825 (32)	2031 (33)	1.14	0.87-1.51	0.32
2013-15	4982 (56)	3328 (54)	1.24	0.94-1.62	0.13

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.

overall survival was calculated via Kaplan-Meier analysis and found to be 44 months in patients with ADC and 33 months in patients with SCC ($p < 0.001$). Overall survival at 1, 3, and 5 years were 85%, 58%, and 36% respectively in patients with ADC versus 83%, 43%, and 24% respectively in patients with SCC ($p < 0.001$) as shown in Fig. 2. On multivariable analysis increasing age, higher comorbidity score, higher grade, increasing T stage, and squamous cell histology corresponded with worse OS. African American race and female gender were associated with improved overall survival (Table 3). Propensity score adjusted multivariable analysis confirmed that adenocarcinoma histology was a strong independent predictor of improved overall survival (HR: 0.79; 95% CI: 0.75-0.83; $p < 0.001$). In addition, female gender and African American race remained independent predictors of increased overall survival.

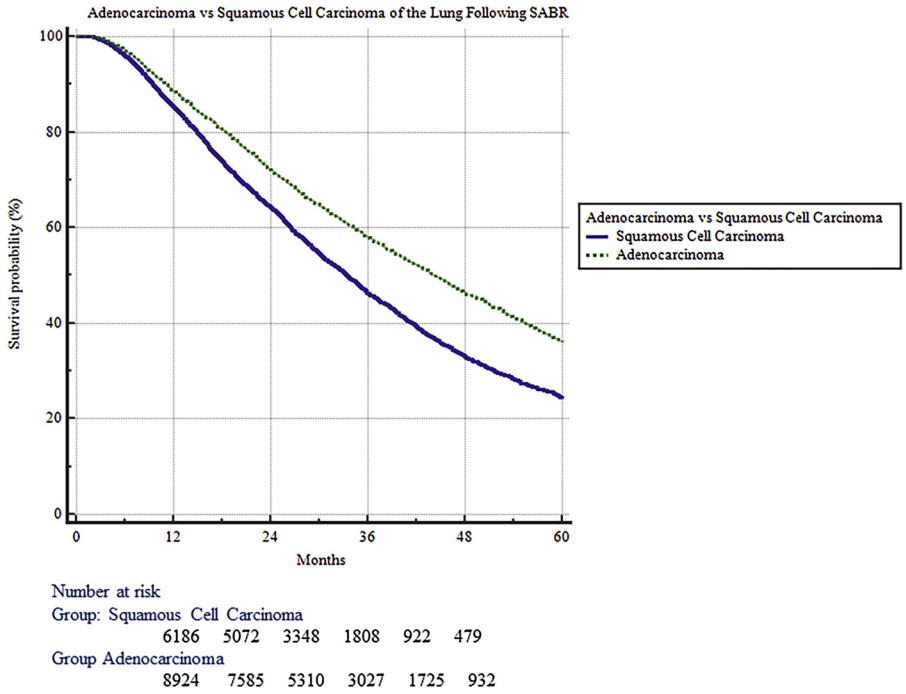

Fig. 2. Kaplan-Meier survival curve comparison in patients with adenocarcinoma versus squamous cell carcinoma of the lung after completion of SABR–stereotactic ablative body radiotherapy (SABR)–.

4. Discussion

It is well recognized that NSCLC constitutes an inhomogeneous disease entity with differential histologic, molecular and genetic profiles, in addition to, subsequent biological behaviors [23]. As such, the therapeutic response and downstream outcomes may also vary depending on the aforementioned factors. Epidemiologically, ADC and SCC constitute the two most common histologic subtypes of NSCLC [1,3]. Previous retrospective investigations assessing histology as a prognosticator in cases of resected early stage NSCLC have suggested an association between local recurrence and squamous histology [24–27]. In the largest series, Kelsey et al. reviewed a total of 975 patients with resected stage I-II NSCLC, and reported a significantly higher rate (HR: 1.98; $p < 0.0001$) of local failure in patients with squamous histology [25]. The authors hypothesized that since SCC often arises in the setting of dysplasia secondary to chronic inflammation, patients with SCC histology were susceptible to field deficits and subsequent local disease recurrence. Of note, overall survival was not assessed in this series.

The histological association between SCC and local recurrence has also been demonstrated in retrospective series involving patients treated with SABR [7–9]. In 2017, a series by Woody et al., analyzed 740 patients with medically inoperable early stage NSCLC who received SABR and found squamous histology as the strongest predictor (HR: 2.4; $p = 0.0008$) of local failure9]. In this series, 3-year actuarial local failure rates were 18.9% and 8.7% in patients with SCC (n = 215) and ADC (n = 243) respectively. Importantly, overall survival was not associated with squamous histology; however increased tumor size was associated with squamous histology on univariable analysis.

A similar retrospective study was completed in Germany by Hörner-Rieber, et al. [8]. In this series, 126 patients with early stage ADC (n = 69) or SCC (n = 57) were treated with SABR. Patients with ADC were subdivided into high-risk (n = 45) and low-risk (n = 24), based upon histologic subtyping. At median follow-up of 22 months, SCC histologic subtype was again identified as a major independent prognostic factor ($p = 0.033$) for local control, with local failure rates of 19%, compared to 4% and 0% in patients with high and low risk ADC respectively. Similar to the results reported by Woody et al, overall survival was not associated with SCC histology; however increasing tumor diameter, T2 lesions, and tobacco abuse were negative prognosticators on multivariable analysis.

Most recently, a retrospective multi-institutional series by Baine et al, analyzed 152 patients with early stage ADC (n = 78) or SCC (n = 74) who were treated with SABR [7]. At median follow-up of 44 months, patients having SCC histology demonstrated an increased risk of local failure, consistent with previously described retrospective reports [8,9,24,25]. In contrast, SCC was associated with worse median overall survival (33 months vs 50 months) and 5-year overall survival (26% vs 41%) when compared to ADC histology. The previous reports of Woody et al. and Hörner-Rieber, et al. did not find an association between SCC histology and reduced overall survival; however these studies may have been limited by a shorter follow-up period. One limitation of the Baine et al. study was failure to account for tumor grade/differentiation, which was found to be an independent predictor of overall survival in our study.

Overall, the results of our study corroborate the findings of Baine, et al in suggesting squamous cell histology as a negative prognosticator of survival. Median and 5-year overall survival in patients with ADC (Median: 44 months; 5-year OS: 36%) and SCC (Median: 33 months; 5-year OS: 24%) were comparable to those reported by Baine et al. Similarly, age was negatively associated with worse survival in both the Baine et al series, as well as, our larger cohort. Similar to previous retrospective studies, additional prognosticators associated with worse survival in our study were male gender [28,29], larger tumor size (i.e. T2 lesions) [29,30,31,32], and poorly differentiated grade [29].

In regard to identification of both SCC histology and poorly differentiated grade as independent prognosticators of worse survival, these findings reinforce the value of obtaining a tissue diagnosis when feasible. As previously mentioned, NSCLC is a heterogeneous disease entity with histologic and histologic subtype variability. Empiric treatment with SABR based upon suspicious clinical and radiographic findings has become increasingly common; however, the results of our study provide further support for pathologic diagnosis given the potential prognostic information derived from tissue biopsy [33–37]. As with many aspects of oncologic care, clinicians and patients alike, must both carefully

Table 3
Multivariable Cox Proportional Hazards Models for Overall Survival in Patients Receiving SBRT for Stage I-II NSCLC.

Significant Characteristic	Hazard of Death (95% CI)	p
	Cox Model without Propensity Score	
Age		
≤75	Reference	
> 75	1.24 (1.18-1.30)	< **0.01**
Sex		
Male	Reference	
Female	0.79 (0.75-0.83)	< **0.01**
Histology		
Squamous Cell Carcinoma	Reference	
Adenocarcinoma	0.79 (0.75-0.83)	< **0.01**
T Stage		
T1	Reference	
T2	1.36 (1.28-1.43)	< **0.01**
Comorbidity Score		
0	Reference	
1	1.11 (1.05-1.18)	< **0.01**
≥ 2	1.36 (1.27-1.46)	< **0.01**
Race		
White	Reference	
African American	0.86 (0.79-0.95)	< **0.01**
Other	0.92 (0.77-1.10)	0.36
Years		
2004-06	Reference	
2007-09	0.93 (0.88-0.99)	**0.03**
2010-12	0.95 (0.82-1.10)	0.50
2013-15	0.95 (0.81-1.10)	0.47
Grade		
Well differentiated	Reference	
Moderately differentiated	1.23 (1.11-1.36)	< **0.01**
Poorly differentiated	1.31 (1.18-1.46)	< **0.01**
Facility Type		
Community Cancer Program	Reference	
Comprehensive Cancer Program	1.06 (1.01-1.12)	**0.01**
Academic/Research Program	1.16 (0.97-1.38)	0.10
	Cox Model with Propensity Score	
Age		
≤75	Reference	
> 75	1.26 (1.20-1.32)	< **0.01**
Prop score	3.25 (2.72-3.89)	< **0.01**
Histology		
Squamous Cell Carcinoma	Reference	
Adenocarcinoma	0.79 (0.75-0.83)	< **0.01**
Facility Type		
Community Cancer Center	Reference	
Comprehensive Cancer Center	1.22 (1.03-1.45)	**0.02**
Academic/Research Program	1.16 (0.98-1.38)	0.08
Race		
White	Reference	
African American	0.87 (0.79-0.96)	< **0.01**
Other	0.92 (0.77-1.09)	0.34

consider the advantages (i.e. gain potentially valuable predictive/prognostic information) and disadvantages (i.e. potential for side effects and reduced quality of life) of performing invasive procedures such as mediastina lymph node exploration and/or biopsy in an inherently frail population.

While these data are strongly powered by large numbers and supported by robust statistical analysis, interpretation of results is limited by several factors including selection bias. In addition, disease recurrence, use of salvage therapy, molecular analysis, histological subtyping of ADC, anatomic location of the tumor, and treatment toxicity are not included in the NCDB, all of which may affect the interpretation of results. For instance, while the histology of ADC was defined by NCDB, the subtype (i.e. non-mucinous vs. mucinous; lepidic, colloid, papillary, etc.) of ADC was not. It is now known that there is significant variation in terms of invasive potential among ADC histologic subtypes, therefore, subtype may impact response to treatment and survival [38–40]. As such, if a large number of non-invasive, indolent ADC histologic subtypes are present within our sample, it may skew the reported overall survival numbers. It is also important to highlight that in our analysis SCC histology was associated with higher T-stage, lower income, less education, higher grade, further distance to treatment facility, and higher co-morbidity scores, all of which may lead to effect modification or confounding. Further, although all patients were treated to a BED $\geq 100_{10}$, total radiation dose was not included in the analysis.

Though efforts were made to account for confounding variables and selection bias with multivariable analysis and the propensity score-matched model there is no substitute for the randomization conducted in phase III trials. Propensity-matching can account for observable variables; however, there are likely a number of unobservable variables which cannot be accounted for with propensity matching. As a result, our conclusions should be validated in a prospective randomized setting.

5. Conclusion

Overall, this is the largest analysis to date comparing survival outcomes in patients with early stage SCC and ADC of the lung treated with SABR. Our results corroborate previous findings; thus suggesting SCC histology as an independent negative prognostic factor for overall survival. These results warrant further investigation in prospective trials as confirmation of SCC as a negative prognosticator may have clinical implications in terms of treatment strategies.

Declaration

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Conflicts of interest

All authors involved have nothing to disclose and no conflicts of interest.

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