Research Article

Stereotactic body radiation therapy versus fractionated radiation therapy for early-stage bronchopulmonary carcinoid

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Aim: To compare trends and outcomes in early stage bronchopulmonary carcinoid (BPC) tumors treated nonoperatively with conventionally fractionated radiotherapy (CFRT) and stereotactic body radiotherapy (SBRT). **Methods/materials:** We queried the National Cancer Database for primary (typical) BPC staged cT1-2N0M0 and treated nonsurgically with lung-directed radiation and $\geq$1 month of follow-up. Odds ratios were used to predict likelihood of SBRT treatment and multivariable Cox regression determined predictors of survival. **Results:** Out of 154 patients, 84 (55%) were treated with SBRT and the remainder were treated with CFRT. Although SBRT use was 0% from 2004 to 2007, it varied from 50 to 70% per year thereafter. Propensity-matched Kaplan–Meier analysis revealed improved survival with lung SBRT (median: 66 vs 58 months; p = 0.034). **Conclusion:** SBRT for early stage, primary BPC has increased over time and was associated with higher survival than CFRT.

Background

Low-grade neuroendocrine tumors of the lung, traditionally referred to as typical pulmonary carcinoids, are rare and usually follow an indolent clinical course [1–3]. For patients able to undergo surgery, resection remains the preferred management and standard of care, resulting in excellent local control (>95%) [4–6]. Often, these tumors occur in older patients not amenable to surgical resection due to medical comorbidities. In this situation, radiation is considered a reasonable alternative [7].

In more recent years, stereotactic body radiotherapy (SBRT) has emerged as an efficacious method to deliver ablative doses of radiation to lung tumors, typically in medically inoperable patients with non-small-cell lung cancer (NSCLC) [8,9]. In this setting, as compared with conventionally fractionated radiation therapy (CFRT), SBRT has shown to have improved outcomes and is preferred in appropriately selected patients, resulting in increased utilization over the past 10–15 years [10].

However, the experience with SBRT for pulmonary carcinoids is much more limited, being reported in only a few small series [11,12]. SBRT for these neoplasms may be particularly beneficial owing to the relatively radioresistant nature [13]. As such, we sought to use the National Cancer Database (NCDB) to examine trends and outcomes with the use of SBRT as compared with CFRT.

Methods

The methods for analyzing the NCDB have been previously outlined [14–16]. This retrospective review comprised de-identified data from the NCDB, therefore, an IRB waiver was permitted. Overseen by the American Cancer Society and American College of Surgeons, the NCDB encompasses an estimated 70% of annual cancer cases in the USA. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.
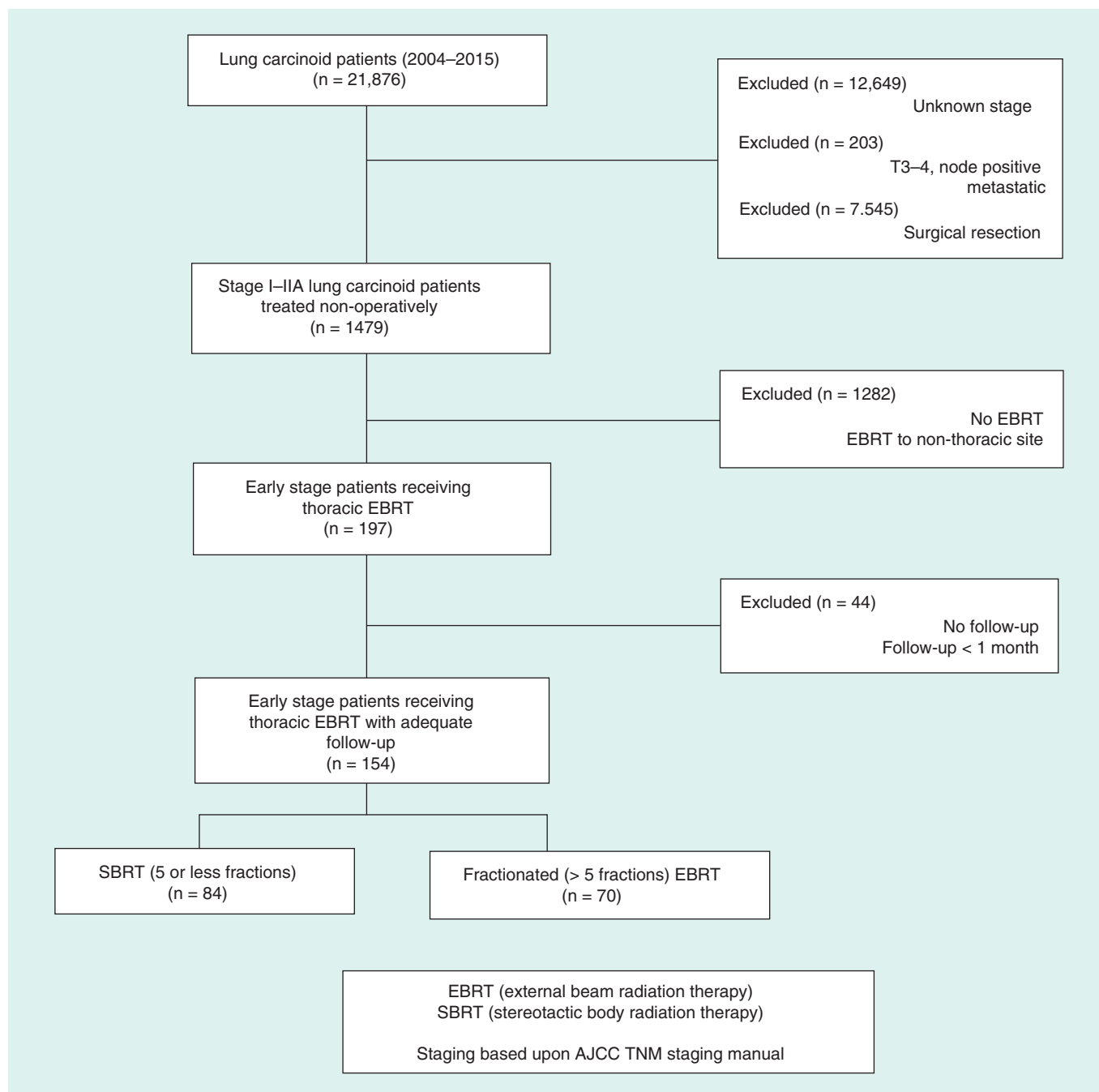
Future Medicine

Figure 1.   CONSORT diagram showing patient selection.
AJCC: American Joint Committee on Cancer; EBRT: External beam radiation therapy; SBRT: Stereotactic body radiotherapy; TNM: Tumor, nodes, metastasis.

Patients with documented clinical stage T1-2N0 typical pulmonary carcinoid who were treated nonoperatively with radiation to the lung were included in this study (atypical carcinoids were not included in this study due to the small number treated with SBRT or even CFRT). Figure 1 is a CONSORT diagram outlining the cohort selection criteria. We excluded patients not receiving radiation, treated with surgery, or having unknown/inadequate (i.e., < 1 month) follow-up to account for immortal time bias.

Race was categorized as Caucasian, African American or other. The Charlson/Deyo comorbidity index quantified the degree of comorbidities [17]. Socioeconomic data in the patients' residence census tract were divided into quartiles

based upon the percentage of persons with less than a high school education and median household income. Facility type was grouped according to the Commission on Cancer accreditation category. Locations were described based on data provided by the US Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page.

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables. Chi-squared tests compared sociodemographic treatment and tumor characteristics between the treatment groups. Overall survival is recorded in the NCDB in months from time of diagnosis to death or censored at last contact. Kaplan–Meier curves were used to calculate cumulative probability of survival [18]. Of note, outcomes like local failure, regional failure, distant failure as well as salvage therapy are not included in the NCDB. Log-rank statistics were used to test for a statistically significant difference in the cumulative proportions across groups. A multivariable survival analysis was conducted using a Cox proportional hazards model [11]. Factors significant on univariable analysis were entered using a stepwise elimination process. Adjusted hazard ratios and 95% confidence intervals are reported, using an alpha level of 0.05 to indicate statistical significance.

To account for indication biases associated with lack of randomization, propensity score-matching was applied to the multivariable survival analysis [19]. Multivariable logistic regression was used to calculate a propensity score indicative of conditional probability of receiving SBRT. The propensity model included observable variables associated with treatment selection on multivariable logistic regression. Patients were then matched based on propensity score and analyzed using Kaplan–Meier curves. The assumption of balance was further validated by stratifying the data into propensity score-based quintiles, and confirming that the difference in propensity score mean per quintile was less than 0.10.

Results

We identified 154 patients in the NCDB between 2004 and 2014 meeting the above eligibility criteria, of whom 84 (55%) were treated with SBRT. Table 1 outlines the baseline characteristics of the entire cohort. The median age was 74 years (interquartile range: 65–81), most patients (76%) were stage T1 and very few received systemic therapy (6%). Patients with T2 stage and receipt of chemotherapy were more likely to be treated with CFRT (Table 2). For patients treated with radiation, the rate of SBRT use was 0% from 2004 to 2007, thereafter, it varied from 50 to 70% per year. The median CFRT dose was 54 Gy (interquartile range: 50–60) in 24 fractions (interquartile range: 5–33) and the median SBRT dose was 50 Gy (interquartile range: 50–55 Gy) in four fractions (interquartile range: 4–5).

Median follow-up was 30 months (1–107 months) for the entire cohort. Multivariable analysis identified age < 74 years, SBRT technique, female sex and more recent year of diagnosis as predictive of improved survival (Table 3). Unadjusted Kaplan–Meier analysis demonstrated improved overall survival in patients receiving SBRT compared with patients receiving CFRT (median: 65 vs 58 months, p = 0.0184), as shown in Supplementary Figure 1. Propensity score was generated and incorporated education level and income level following multivariable logistic regression. Fifty-seven pairs were generated based on an exact propensity score match. Propensity-matched Kaplan–Meier analysis revealed improved survival with lung SBRT, median overall survival of 66 months compared with 58 months, p = 0.0344 (Figure 2). We also ran the propensity-matched Kaplan–Meier analysis including only T1 patients with survival benefit still seen with SBRT (median overall survival of 66 months compared with 58 months, p = 0.0171).

Discussion

Pulmonary carcinoid tumors are relatively rare and are second to gastrointestinal sites in terms of location [12]. Surgical resection remains the preferred treatment, yielding local control rates >95% and allowing for sampling of nodal tissue at the time of intervention [20]. As evidenced by the population presented here (median age 74 years), these patients are often older and either cannot tolerate surgical intervention or refuse it. In those instances, radiation offers a reasonable alternative definitive treatment, extrapolating from many years of use of CFRT in NSCLC [21]. Over the past 10–15 years, lung SBRT has emerged as a highly effective and safe alternative to surgery, typically in nonoperable NSCLC patients [8–10,22]. Naturally, the use of SBRT for NSCLC and other lung tumors has sharply expanded over the past 10+ years [9].

The use of SBRT in pulmonary carcinoid, however, has been reported sparingly. A small case series from Yale reviewed outcomes in four patients with pulmonary carcinoid, all treated with SBRT in a safe and effective manner, lending some support to SBRT as an alternative in patients that do not get treated surgically [13]. Of note, in this

Table 1. Patient demographics and clinical characteristics at baseline (n = 154).	
Characteristic	**Number (%)**
Sex:	
– Male	43 (28)
– Female	111 (72)
Race:	
– White	139 (90)
– African–American	14 (9)
– Other	1 (1)
Comorbidity score:	
– 0	97 (63)
– 1	37 (24)
– ≥2	20 (13)
Insurance:	
– Not insured	0 (0)
– Private payer	30 (19)
– Government	122 (79)
– Unrecorded	2 (2)
Education (%):	
– ≥29	22 (14)
– 20–28.9	39 (25)
– 14–19.9	60 (39)
– < 14	33 (22)
Treatment facility type:	
– Community cancer program	2 (1)
– Comprehensive community cancer program	69 (45)
– Academic/research program	82 (54)
Treatment facility location:	
– Metro	121 (80)
– Urban	25 (17)
– Rural	4 (3)
Income, US dollars:	
– < 30,000	30 (19)
– 30,000 to 35,000	37 (24)
– 35,000 to 45,999	44 (29)
– > 46,000	43 (28)
Distance to treatment facility (miles):	
– ≤10	79 (51)
– >10	75 (49)
Age distribution (years):	
– ≤74	81 (53)
– > 74	73 (47)
Year of diagnosis:	
– 2004–2006	4 (3)
– 2007–2009	14 (9)
– 2010–2012	62 (40)
– 2013–2014	74 (48)
T stage:	
– 1	117 (76)
– 2	37 (24)
Chemotherapy:	
– No	144 (94)
– Yes	10 (6)

Table 2. Comparative use of stereotactic body radiotherapy by baseline characteristics in patients receiving lung radiation.

Characteristic	CFRT (n = 70) (%)	SBRT (n = 84) (%)	Odds ratio	95% CI	p-value
Sex:					
– Male	20 (29)	23 (27)	1	Reference	
– Female	50 (71)	61 (73)	1.06	0.52–2.15	0.87
Race:					
– White	65 (93)	74 (88)	1	Reference	
– African American	5 (7)	9 (11)	1.58	0.50–4.96	0.43
– Other	0 (0)	1 (1)	2.64	0.11–65.87	0.55
Comorbidity score:					
– 0	43 (61)	54 (64)	1	Reference	
– 1	19 (27)	18 (21)	0.75	0.35–1.61	0.47
– ≥2	8 (12)	12 (15)	1.19	0.45–3.18	0.72
Age (years):					
– ≤74	38 (54)	43 (51)	1	Reference	
– >74	32 (46)	41 (49)	1.13	0.60–2.14	0.70
Insurance:					
– Private payer	18 (26)	12 (14)	1	Reference	
– Government	51 (74)	71 (86)	2.09	0.93–4.71	0.08
Education:					
– ≥29%	13 (19)	9 (11)	1	Reference	
– 20–28.9	15 (21)	24 (29)	2.31	0.80–6.72	0.12
–14–19.9	27 (39)	33 (39)	1.77	0.66–4.75	0.26
– <14	15 (21)	18 (21)	1.73	0.58–5.16	0.32
Facility type:					
– Community cancer program	1 (1)	1 (1)	1	Reference	
– Comprehensive cancer program	31 (45)	38 (45)	1.23	0.07–20.40	0.89
– Academic/research program	37 (54)	45 (54)	1.22	0.07–20.12	0.89
Facility location:					
– Metro	59 (86)	62 (77)	1	Reference	
– Urban	9 (13)	16 (20)	1.69	0.69–4.12	0.25
– Rural	1 (1)	3 (3)	2.85	0.29–28.22	0.37
Income (USD):					
– < 30,000	11 (16)	19 (23)	1	Reference	
– 30,000–35,000	16 (23)	21 (25)	0.76	0.28–2.04	0.59
– 35,000–45,999	17 (24)	27 (32)	0.92	0.35–2.40	0.86
– > 46,000	26 (37)	17 (19)	0.38	0.14–0.99	0.05
T stage:					
– 1	45 (64)	72 (86)	1	Reference	
– 2	25 (36)	12 (14)	0.30	0.13–0.66	**0.0026**
Distant to facility:					
– ≤10 miles	36 (51)	43 (51)	1	Reference	
– >10 miles	34 (49)	41 (49)	1.01	0.54–1.90	0.98
Received chemotherapy:					
– No	62 (89)	82 (98)	1	Reference	
– Yes	8 (11)	2 (2)	0.19	0.04–0.92	**0.0393**
Year of diagnosis:					
– 2004–2006	4 (6)	0 (0)	1	Reference	
– 2007–2009	7 (10)	7 (8)	9.00	0.41–198.22	0.16
– 2010–2012	27 (39)	35 (42)	11.62	0.60–225.09	0.10
– 2013–2015	32 (45)	42 (50)	11.77	0.61–226.50	0.10

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.

Table 3. Multivariable Cox regression for predictors of survival in patients with pulmonary carcinoid treated with radiation therapy.

Characteristic	HR (95% CI)	p-value
Age (years):		
– ≤74	Reference	
– >74	2.06 (1.16–3.67)	0.0134
Radiation technique:		
– CFRT	Reference	
– SBRT	0.48 (0.28–0.85)	0.0110
Sex:		
– Male	Reference	
– Female	0.51 (0.27–0.94)	0.0305
Year of treatment:		
– 2004–2006	Reference	
– 2007–2009	0.36 (0.14–0.95)	0.0396
– 2010–2012	0.52 (0.16–1.66)	0.2723
– 2013–2014	0.52 (0.27–1.04)	0.0628
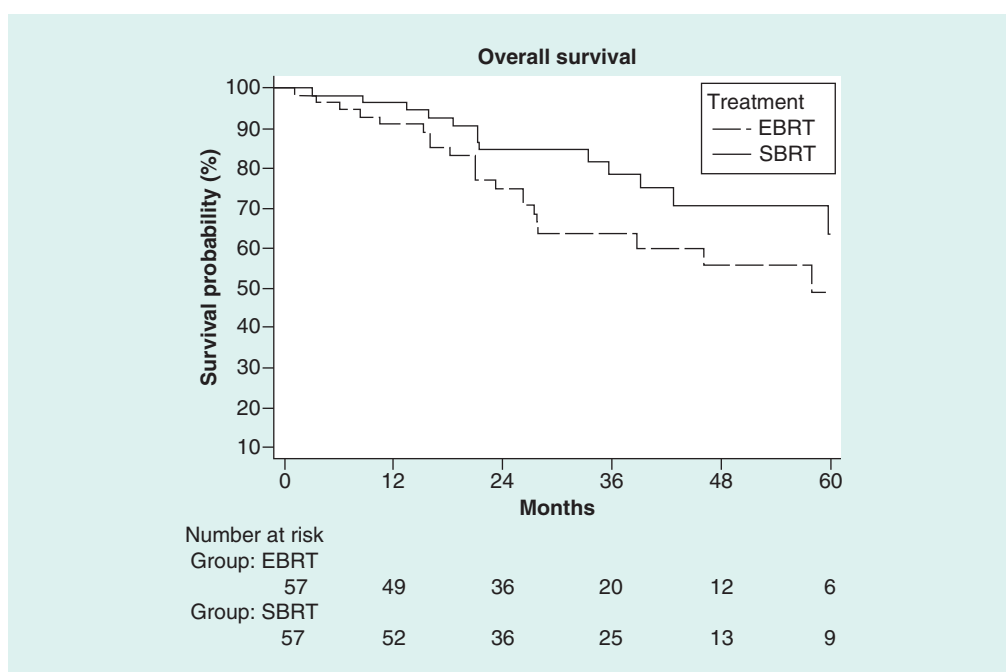
Figure 2. Overall survival comparison between patients with typical carcinoid treated with either conventionally fractionated radiation therapy or stereotactic body radiotherapy. Median survival was 66 months compared with 58 months, in favor of SBRT, p = 0.0344.
EBRT: External beam radiation therapy; SBRT: Stereotactic body radiotherapy.

analysis we did not directly compare surgical resection to SBRT, instead focusing on the difference in radiation techniques. We did show, after propensity matching that the patients treated with SBRT had better survival, suggesting a benefit compared with CFRT. One must keep in mind that patients with T2 tumors and those receiving chemotherapy were more likely to receive CFRT. Granted, the receipt of chemotherapy for stage T1-2N0 typical pulmonary carcinoid does not follow recognized guidelines, and likely implies some other undocumented clinicopathologic factors contributing to worse outcome. In addition, the tumor location was not reported and centrally located tumors may not be as amenable to SBRT and are more likely to cause symptoms or potential patient demise [23–25]. Another consideration is the ability of SBRT to deliver a higher biologically effective dose,

which one would expect to result in better outcomes given the relative radioresistance of carcinoids [13]. Taking all of the above into account, SBRT may be the preferred technique in nonoperative candidates with pulmonary carcinoid.

The limitations of the current study include its retrospective nature and inherent selection bias as a result. The NCDB also lacks critical data as it relates to operability such as performance status, extent of work up, pulmonary function testing and tumor location as mentioned above. The NCDB also does not record outcomes outside of survival, such as local failure, regional failure and any salvage therapy, which are all important and interrelated to survival in this patient population.

Conclusion

This analysis of the NCDB shows a steady increase in the use of SBRT for typical pulmonary carcinoids managed in a nonoperative fashion. There was a survival benefit seen with SBRT compared with CFRT, which persisted on propensity matching. In light of the sharply expanding use of SBRT over CFRT for other early stage lung tumors, SBRT may be considered as the preferred option for T1-2N0 pulmonary carcinoids.

Summary points

- Historically, early stage bronchopulmonary carcinoid has been treated with surgery or conventionally fractionated radiotherapy (CFRT).
- Stereotactic body radiotherapy (SBRT) has emerged as the preferred treatment approach in inoperable cases of non-small-cell lung cancer; however, data in cases of primary typical lung carcinoid are limited.
- We performed a retrospective review of a large, contemporary database, analyzing 154 patients with early stage lung carcinoid treated with CFRT (n = 70) or SBRT (n = 84) from 2004 to 2014.
- SBRT use was 0% from 2004 to 2007, but increased to 50 to 70% per year thereafter and overall survival was longer (median: 66 months versus 58 months; p = 0.034) in those receiving SBRT compared with CFRT.
- SBRT may be considered as the preferred treatment option for nonoperative early stage patients.

Author contributions

RE Wegner performed project conception and design, statistical analysis and manuscript drafting. S Abel, ZD Horne and A Colonias did manuscript revisions. S Hasan performed statistical analysis and manuscript revisions. V Verma performed manuscript revision, project conception and design.

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