Lung Cancer 131 (2019) 147–153

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Stereotactic body radiation therapy with higher biologically effective dose is associated with improved survival in stage II non-small cell lung cancer

Sherry X. Yan[a], Muhammad M. Qureshi[b,c], Michael Dyer[b,c], Minh Tam Truong[b,c], Kimberley S. Mak[b,c,*]

[a] Boston Medical Center, One Boston Medical Center Pl., Boston, MA 02118, USA
[b] Department of Radiation Oncology, Boston Medical Center, 830 Harrison Ave. Moakley LL, Boston, MA 02118, USA
[c] Boston University School of Medicine, 72 E. Concord St., Boston, MA 02118, USA

ARTICLE INFO

Keywords:
Non-small cell lung cancer
SBRT
Survival
BED
National Cancer Database

ABSTRACT

Objectives: The role of stereotactic body radiation therapy (SBRT) in treating stage II non-small cell lung cancer (NSCLC) remains unclear. This study evaluates SBRT dose prescription patterns and survival outcomes in Stage II NSCLC using the National Cancer Database (NCDB).

Materials and methods: Patients diagnosed with Stage II NSCLC and treated with SBRT between 2004–2013 were identified in NCDB. The biologically effective dose with $\alpha/\beta = 10$ Gy (BED_{10}) was calculated. Overall survival (OS) was analyzed using the Kaplan-Meier method and Cox regression models.

Results: Of 56,543 patients with Stage II NSCLC, 451 (0.8%) received SBRT. There were 360 patients (79.8%) with node-negative and 91 patients (20.2%) with node-positive disease. The most common prescriptions were 10 Gy x 5 (35.9%) and 12 Gy x 4 (19.3%). The mean and median BED_{10} were 114.9 Gy and 105.6 Gy, respectively. With median follow-up of 19.3 months, overall median survival was 23.7 months. Median survival was 22.4 months for those treated with $BED_{10} < 114.9$ Gy versus 31.5 months for $BED_{10} \geq 114.9$ Gy ($p = 0.036$). On multivariate analysis, BED_{10} as a continuous variable (hazard ratio [HR] 0.991, $p = 0.009$) and ≥ 114.9 Gy (HR 0.63, $p = 0.015$) were associated with improved survival in node-negative patients. BED_{10} as a continuous variable (HR 0.997, $p = 0.465$) and ≥ 114.9 Gy (HR 0.81, $p = 0.546$) were not significant factors for predicting survival in node-positive patients.

Conclusion: SBRT is infrequently utilized to treat Stage II NSCLC in the United States. Treatment with higher BED_{10} was associated with improved survival, and the benefit was limited to patients with node-negative disease.

1. Introduction

The preferred treatment for patients with Stage II non-small cell lung cancer (NSCLC) is definitive surgical resection [1,2]. However, a minority of patients do not undergo surgery because of comorbidities that render them unsuitable surgical candidates, and some operable patients may prefer not to undergo surgery. There is a rising role for stereotactic body radiation therapy (SBRT) in early stage, typically Stage I NSCLC, delivering ablative doses of highly conformal radiation in a limited number of fractions. In one study, a survey of radiation oncologists in the United States concluded that lung was the most common disease site treated with SBRT [3]. SBRT has been demonstrated to provide high rate of local tumor control in inoperable early stage NSCLC measuring < 5 cm [4]. With the increasing use of SBRT, the STARS and ROSEL trials, as well as RTOG 0618, aimed to evaluate the role of SBRT in operable Stage I NSCLC [5,6]. The National Comprehensive Cancer Network (NCCN) and the American College of Chest Physicians recommend definitive radiotherapy with SBRT treatment for inoperable T 1-2 node-negative NSCLC [1,2]. However, its use in treating Stage II NSCLC with larger primaries and node-positive disease is not as well studied.

Multiple SBRT regimens have been employed in treating early stage NSCLC. The most common regimen of 20 Gy x3 fractions (18 Gy x3 with heterogeneity correction) was initially established in a phase I study at the Indiana University [7] and later served as the basis for the Radiation Therapy Oncology Group (RTOG) phase II study 0236 [4]. RTOG 0236 described an excellent 3-year local control rate of 97.6% with a favorable toxicity profile. Different fractionation schemes delivering

* Corresponding author at: Department of Radiation Oncology, Boston Medical Center, 830 Harrison Ave. Moakley LL, Boston, MA, 02118, USA.
E-mail address: kmak@bu.edu (K.S. Mak).

https://doi.org/10.1016/j.lungcan.2019.03.031
Received 15 November 2018; Received in revised form 14 February 2019; Accepted 30 March 2019

single fraction SBRT and in 3-10 fractions have also been reported [3,8,9]. For centrally located tumors, a five-fraction regimen is generally preferred given increased risk of toxicity [10]. Biologically effective dose (BED) ≥ 100 Gy, assuming α/β of 10 Gy for tumors, has previously been reported to be associated with improved local control and survival [11], and SBRT regimens have generally been prescribed to achieve BED of at least 100 Gy. However, the optimal dose fractionation for treatment of early stage NSCLC is still under investigation.

In this study, using a large national patient registry, we examined the dose fractionations used for SBRT treatment in Stage II NSCLC, with larger primary tumors and node-positive disease compared to Stage I NSCLC, across the United States and determined their impact on survival.

2. Materials and methods

2.1. Study population

Patients diagnosed with NSCLC from 2004 to 2013 were identified in the National Cancer Database (NCDB), a nationally recognized oncology outcomes databank jointly sponsored by the American College of Surgeons and the American Cancer Society. NCDB is estimated to capture 70% of all newly diagnosed cases of cancer from Commission on Cancer-accredited institutions across the United States. Patients diagnosed with clinical Stage II NSCLC from 2004 to 2012 (as defined by the AJCC 6th Edition from 2004 to 2009, and the 7th Edition from 2010 to 2012) were included for analysis. Patients with metastatic disease, carcinoma in situ, history of cancer, missing follow-up information, missing or incorrect AJCC or TNM staging were excluded from analysis. Treatments other than SBRT were excluded, as were treatments with palliative intent. The full exclusion criteria are summarized in Table A.1 in Supplementary data.

The biologically effective dose was calculated using the linear quadratic model [12]. The α/β ratio is assumed to be 10 Gy for rapidly dividing tumor cells (BED_{10}) [11,13,14]. SBRT was defined as radiation prescriptions with a BED_{10} between 72 and 300 Gy delivered in 1, 3, 4, or 5 fractions as previously described [15,16]. Treatment modalities included were external beam, photons, intensity modulated radiotherapy, conformational or 3-D therapy, protons, stereotactic radiosurgery, and Linac radiosurgery. Treatment duration was limited to 33 days, according to RTOG 0236 protocol, with a maximum of 8 days between fractions [4].

2.2. Data analysis

Patient, tumor, and treatment characteristics were examined, including patient age, gender, race, insurance status, median income, Charlson-Deyo comorbidity score, clinical T and N classification, treatment facility type, treatment at > 1 facility, SBRT dose, tumor size, and BED_{10}. The follow up period was defined from the time of cancer diagnosis to date of death or last follow up. Mortality within 30 days of treatment was determined. Survival rates were estimated using the Kaplan-Meier method, and log-rank tests were used to determine statistical significance. Exploratory analyses were performed to examine the impact of BED on survival by dichotomizing SBRT regimens using mean BED_{10} and BED_{10} of 100 Gy, as well as analyzing BED_{10} as a continuous variable.

Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox regression modeling adjusting for patient, tumor, and treatment characteristics. The appropriateness of the proportional hazards assumption was verified using Schoenfeld residual analysis. Schoenfeld's global test was used to evaluate the proportional hazards assumption of the Cox model. All tests were two-sided; p-values of < 0.05 were considered statistically significant. Statistical computations were performed using SAS 9.3 (SAS Institute, Cary, NC) and GraphPad prism software (version 3.0, GraphPad Software).

Table 1
Patient, tumor and treatment characteristics.

	All patients (N = 451) n (percent)
Age (years)	
18 - 64	51 (11.3%)
65 - 74	149 (33.0%)
75 +	251 (55.7%)
Gender	
Males	216 (47.9%)
Females	235 (52.1%)
Race	
White	395 (87.6%)
Black	42 (9.3%)
Other	14 (3.1%)
Insurance status	
Private	53 (11.9%)
Medicaid/Other	27 (6.1%)
Medicare	366 (82.1%)
Median income	
< $30,000	72 (16.5%)
$30,000–$35,999	81 (18.5%)
$36,000–$45,999	117 (26.8%)
$46,000 +	167 (38.2%)
Charlson-Deyo score	
0	233 (51.7%)
1	126 (27.9%)
2 or more	92 (20.4%)
Clinical T and N classification	
T1N1	50 (11.1%)
T2N0	142 (31.5%)
T2N1	41 (9.1%)
T3N0	218 (48.3%)
Facility type	
Community program (CP)	14 (3.5%)
Comprehensive CP	166 (41.4%)
Academic/Research program	221 (55.1%)
Treatment at > 1 facility	
No	338 (74.9%)
Yes	113 (25.1%)

Abbreviations: N: total number of patients; SBRT: Stereotactic body radiotherapy; n: number of patients.

3. Results

3.1. Study population and treatment patterns

Between 2004 and 2013, a total of 56,543 patients were diagnosed with clinical Stage II NSCLC, and 451 (0.8%) patients met study criteria and were included in this analysis. Median age at diagnosis for patients who received SBRT was 76 years (range 48–90). Approximately half of the patients had medical comorbidities, with Charlson-Deyo score of 1 or higher (48.3%). The majority of patients had Medicare health insurance (82.1%). Median and mean tumor size was 3.6 cm and 3.9 cm, respectively. Three-hundred and sixty patients (79.8%) had node-negative disease, and 91 (20.2%) had node-positive (N1) disease. Most of the patients who received SBRT were treated at an academic/research program (55.1%), compared to 41.1% at a comprehensive community program and 3.5% at a community program. Detailed patient and treatment characteristics are shown in Table 1.

3.2. SBRT dose

The most common SBRT dose prescriptions overall were 50 Gy in 5 fractions (35.9%; BED_{10} = 100 Gy) and 48 Gy in 4 fractions (19.3%; BED_{10} = 105.6 Gy). Table 2 lists the most common dose prescriptions and their calculated BED_{10} for all cases and also per nodal classification. There was no statistically significant difference in SBRT dose prescriptions comparing N0 and N1 disease. As shown in Fig. 1, the

Table 2
The most common SBRT prescriptions.

	BED_{10}	No. of cases	% of total cases
All cases			
10 × 5 = 50 Gy	100	162	35.9
12 × 4 = 48 Gy	105.6	87	19.3
20 × 3 = 60 Gy	180	30	6.7
18 × 3 = 54 Gy	151.2	29	6.4
12.5 × 4 = 50 Gy	112.5	29	6.4
12 × 5 = 60 Gy	132	29	6.4
8 × 5 = 40 Gy	72	19	4.2
N0 (T2N0 or T3N0)			
10 × 5 = 50 Gy	100	134	37.2
12 × 4 = 48 Gy	105.6	73	20.3
20 × 3 = 60 Gy	180	23	6.4
18 × 3 = 54 Gy	151.2	21	5.8
12.5 × 4 = 50 Gy	112.5	24	6.7
12 × 5 = 60 Gy	132	21	5.8
8 × 5 = 40 Gy	72	14	3.9
N1 (T1N1 or T2N1)			
10 × 5 = 50 Gy	100	28	30.8
12 × 4 = 48 Gy	105.6	14	15.4
20 × 3 = 60 Gy	180	7	7.7
18 × 3 = 54 Gy	151.2	8	8.8
12.5 × 4 = 50 Gy	112.5	5	5.5
12 × 5 = 60 Gy	132	8	8.8
8 × 5 = 40 Gy	72	5	5.5

majority of patients received treatments with BED_{10} between 100 and 120 Gy, which correspond to prescriptions of 10 Gy x 5 (BED_{10} = 100 Gy), 12 Gy x 4 (BED_{10} = 105.6 Gy), and 12.5 Gy x 4 (BED_{10} = 112.5 Gy). The mean and median BED_{10} were 114.9 Gy and 105.6 Gy, respectively. A total of 92.7% of patients were prescribed an SBRT dose with $BED_{10} \geq 100$ Gy, and 28.4% of patients received SBRT with $BED_{10} \geq 114.9$ Gy. There was a weak negative correlation between BED_{10} and tumor size ($r = -0.17$, $p = 0.0004$).

3.3. Overall survival

With median follow-up of 19.3 months, median overall survival for patients receiving SBRT for Stage II NSCLC was 23.7 months (Table 3). Thirty-day mortality after SBRT was 1.77%. The 3-year and 5-year survival rates were 29.2% and 18.7%, respectively. Median survival for T1N1, T2N0, T2N1, and T3N0 disease was 27.3, 23.7, 19.5, and 24.7 months, respectively (p = 0.315).

3.4. Overall survival by BED

Median survival for patients who received SBRT regimens of

Table 3
Survival analysis by treatment.

	N	Events	Median Survival (months)	Actuarial survival rate 3-year	5-year	p
Overall	451	275	23.7	29.2%	18.7%	
1) BED_{10}						
< 114.9 Gy	323	204	22.4	24.9%	14.5%	0.036
≥114.9 Gy	128	71	31.5	38.9%	27.9%	
–						
< 100 Gy	33	23	21.0	23.3%	.	0.210
–						
≥100 Gy	418	252	24.6	29.6%	19.2%	
2) Clinical T and N classification						0.315
a) T1N1	50	32	27.3	24.3%	20.2%	
b) T2N0	142	90	23.7	24.1%	0.0%	
c) T2N1	41	27	19.5	29.5%	.	
d) T3N0	218	126	24.7	33.3%	22.5%	

Abbreviations: N: number of patients; BED: biologically effective dose.

$BED_{10} \geq 114.9$ Gy was 31.5 months, compared to 22.4 months for patients who received $BED_{10} < 114.9$ Gy (p = 0.036; Table 3 and Fig. 2). Thirty-day mortality after SBRT was similar for patients who received regimens with $BED_{10} < 114.9$ Gy (1.86%) and those who received regimens with $BED_{10} \geq 114.9$ Gy (1.56%, p = 1.0). There was no significant difference in survival for SBRT regimens with $BED_{10} \geq 100$ Gy compared to $BED_{10} < 100$ Gy (median survival 24.6 months vs. 21 months, p = 0.21; Table 3).

On multivariate analysis adjusting for age, gender, race, insurance status, median income, Charlson-Deyo score, clinical T and N classification, facility type, and treatment facility number (Table 4), $BED_{10} \geq 114.9$ Gy continued to be associated with improved survival (HR 0.72; 95% CI, 0.53 − 0.98; p = 0.037). Increasing BED_{10} as a continuous variable was associated with significantly improved survival on univariate analysis (HR 0.995; 95% CI, 0.995–1.0; p = 0.050), but not on multivariate analysis (HR 0.995; 95% CI, 0.990–1.0; p = 0.066). However, on subset analysis of patients with node-negative disease (Table 4), increasing BED_{10} as a continuous variable was associated with improved survival on multivariate analysis (adjusted HR 0.991; 95% CI, 0.984 − 0.998; p = 0.0009). Similarly, $BED_{10} \geq 114.9$ Gy as a dichotomous variable was associated with improved survival on multivariate analysis for patients with N0 disease (HR 0.63; 95% CI, 0.43 − 0.91; p = 0.015). For patients with node-positive (N1) disease, there was no significant survival benefit with higher BED_{10} as a

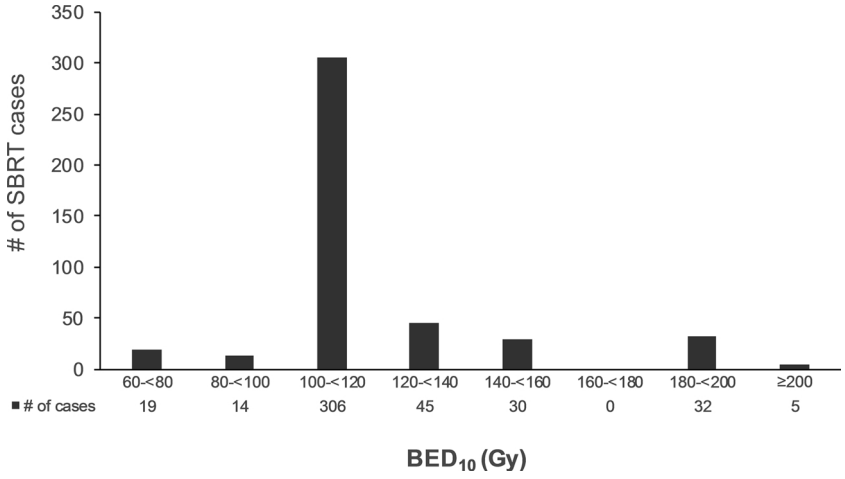

Fig. 1. SBRT prescriptions for Stage II NSCLC by biologically effective dose (BED_{10}).

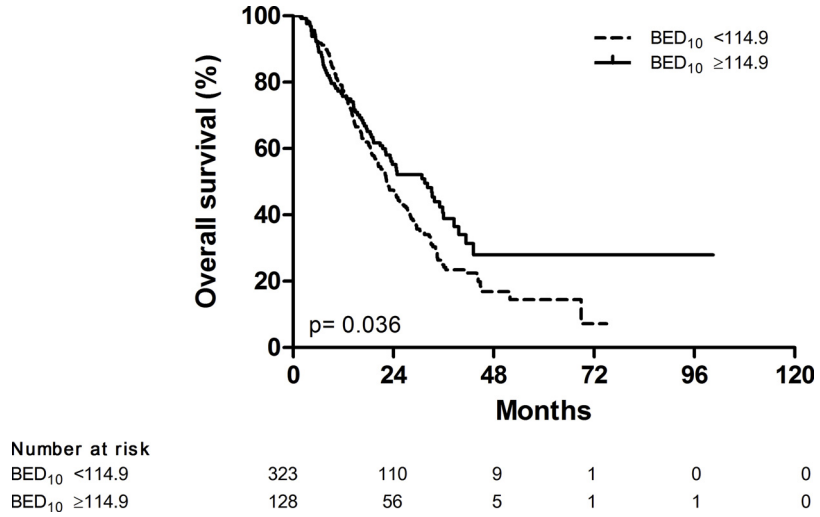

Fig. 2. Overall survival of Stage II NSCLC treated with SBRT regimens with biologically effective dose (BED_{10}) < 114.9 Gy versus ≥114.9 Gy.

continuous variable (HR 0.997, p = 0.465) or as a dichotomous variable using mean value of BED_{10} ≥ 114.9 Gy (HR 0.81, p = 0.546).

4. Discussion

In this analysis of a large population of patients in NCDB with Stage II NSCLC, SBRT was used infrequently. The majority of patients who received SBRT had node-negative disease. They were mainly elderly, with medical comorbidities, and tended to receive SBRT at comprehensive cancer centers or at academic/research programs. Treatment with higher BED_{10} was associated with improved survival, and the benefit was limited to patients with node-negative disease.

Similar to our results, a SEER analysis found that patients older than 65 years with node-negative Stage I-II NSCLC with primary tumor ≤ 5 cm in size, and who received SBRT were older, had higher comorbidity scores, and had larger tumors compared to those receiving surgery [17]. Older patients and those with significant comorbidities may not tolerate surgery, and SBRT is currently indicated for medically inoperable early-stage NSCLC. However, most of the reported prospective studies of SBRT in early-stage NSCLC typically included patients with Stage I and not Stage II NSCLC. The Indiana University phase I SBRT trial, which served as the basis for RTOG 0236, selected patients with early stage node-negative NSCLC with primary tumor up to 7 cm [7,10]. Recently, RTOG 0618 for operable early stage NSCLC included patients with primary tumors up to 5 cm [6]. The STARS and ROSEL trials comparing SBRT to surgery in operable Stage I NSCLC included patients with primary tumor less than 4 cm [5]. Single institution studies also limited SBRT use for patients with Stage I NSCLC and excluded those with Stage II disease, namely those with larger primary tumors (greater than 5 or 7 cm,) or node-positive disease [18–20]. Current NCCN guidelines recommend definitive radiotherapy with SBRT for patients with node-negative NSCLC and primary tumors up to 7 cm, who are not surgical candidates or who refuse surgery [1]. However, surgery or definitive chemoradiation is indicated for node-positive disease or larger primary tumors; SBRT for node-positive disease is not routine clinical practice. Nevertheless, we found that 20.2% of patients with Stage II NSCLC who received SBRT in NCDB had N1 disease, and 48.3% of patients had T3N0 disease.

Nodal involvement is likely be one of the main reasons limiting the use of SBRT in Stage II NSCLC. There is limited literature reporting the use of SBRT in node-positive Stage II NSCLC. Coverage of peribronchial or hilar nodal disease would result in potentially high doses of radiation to central intrathoracic organs at risk (OARs), including the proximal bronchial tree, hilar vessels, and the esophagus [10,21]. However, there

Table 4
Univariate and multivariate analysis of overall survival.

	Univariate			Multivariate		
	N	Events	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Overall[a]						
BED_{10}	382	229	0.995 (0.995–1.0)	0.050	0.995 (0.990–1.0)	0.066
BED_{10} < 114.9 Gy	272	171	Ref		Ref	0.037
BED_{10} ≥ 114.9 Gy	110	58	0.71 (0.53–0.97)	0.028	0.72 (0.53–0.98)	
N0 (T2N0 and T3N0)[b]						
BED_{10}	305	178	0.992 (0.985–0.998)	0.013	0.991 (0.984–0.998)	0.009
BED_{10} < 114.9 Gy	225	140	Ref		Ref	0.015
BED_{10} ≥ 114.9 Gy	80	38	0.65 (0.45–0.93)	0.019	0.63 (0.43–0.91)	
N1 (T1N1 and T2N1)[b]						
BED_{10}	77	51	0.999 (0.992–1.01)	0.777	0.997 (0.988–1.01)	0.465
BED_{10} < 114.9 Gy	47	31	Ref		Ref	0.546
BED_{10} ≥ 114.9 Gy	30	20	0.84 (0.48–1.48)	0.554	0.81 (0.41–1.61)	

Abbreviations: N: total number of patients; ref: referent.
Note: 382 patients had complete information on covariates that were tested in the multivariate analysis.
[a] Multivariate model includes agegender, race, insurance status, median income, Charlson-Deyo score, clinical T and N classification, facility type, and treatment at > 1 facility.
[b] Multivariate model includes agegender, race, insurance status, median income, Charlson-Deyo score, facility type, and treatment at > 1 facility.

are a few reports using SBRT boost to nodal disease in locally advanced NSCLC after definitive chemoradiation [22,23]. In a phase I dose escalation study, Hepel et al. delivered 16–28 Gy in two fractions as an SBRT boost to residual primary and nodal disease (up to 60cc) after chemotherapy with concurrent radiation (50.4 Gy) [22]. One patient had Stage II N1 disease, and 11 patients had Stage III N2-3 disease. Local control at 1 year was 78%, with improved rates of local control with SBRT doses > 24 Gy. Late high grade radiation-related toxicity was observed in one patient, who developed fatal bronchopulmonary hemorrhage. There was no dose constraint for the proximal bronchovascular tree. The authors reported that although higher SBRT doses may contribute to local disease control, strict dose-volume constraints should be established to avoid dose-limiting late toxicity. Using sequential SBRT boost ranging from 20 to 30 Gy in 5 fractions to residual primary and nodal disease after definitive chemoradiation, Karam et al. followed strict normal tissue dose constraints and reported that one patient (6.3%) developed nonfatal hemoptysis requiring hospitalization; there was no higher grade pulmonary toxicity or death [23]. In our study, patients with mediastinal disease were excluded from analysis. However, patients with peribronchial or hilar nodal disease were reportedly treated with SBRT. Due to the lack of data regarding target volume coverage, one might speculate that due to concern for potential increased toxicity, nodal disease near the proximal bronchial tree or hilar vessels could potentially have been outside of the treatment fields or treated to a lower dose than the primary tumor. In addition, dose to OARs, dose heterogeneity and treatment toxicity were not reported in NCDB and thus could not be assessed. Because of the limitations of the dataset, we could not determine why patients with node-positive disease received SBRT without adjuvant therapy, and if they received salvage therapy with disease progression.

Similarly, the use of SBRT for larger primary tumors or organ invasion may be limited by concerns of increased normal tissue toxicity. A few small series using SBRT for Stage II disease have been published and demonstrated safe toxicity profiles, including a report of 13 patients with chest wall invasive NSCLC [24]. SBRT was delivered with median dose of 50 Gy in 5 fractions with 1-year local control rate of 89%, and only 2 patients developed grade 1–2 new or worsening chest wall pain. The same group also reported outcomes in 40 patients with node-negative NSCLC and primary tumor > 5 cm (median size 5.6 cm), who received hypofractionated radiation to 50 Gy in 5 or 10 fractions, or 60 Gy in 8 fractions. With a local control rate of 91.2% at 18 months, there was a 7.5% rate of grade 3–4 and 0% grade 5 pulmonary toxicity [25]. In another single institution retrospective report including patients with primary tumors > 5 cm (24% of patients) treated with 3–5 fractions of SBRT, rates of radiation-related toxicity were low, with 2.1% of patient having high-grade radiation pneumonitis, 1.6% having non-malignant pleural effusion, 2.6% having chronic chest wall pain, and 1.6% having rib fracture [26]. Although these studies describe promising efficacy and low rates of significant toxicity with SBRT treatment for larger primary tumors, our analysis indicates the use of SBRT in this setting is not common practice.

For patients with Stage II NSCLC who received SBRT, our report provides an update on the dose fractionations employed in the United States within the last decade, with the two most common regimens being 50 Gy in 5 fractions followed by 48 Gy in 4 fractions. Published SBRT regimens for early stage NSCLC range from single dose fractions in 30–34 Gy [27,28] to 15–20 Gy x 3 fractions [4,6–8,29], 12 Gy x 4 fractions [9], to 10–12 Gy x 5 fractions [8,30]. A survey of American radiation oncologists conducted in 2010 reported that the most common SBRT prescriptions were 20 Gy x 3 (22%), 18 Gy x 3 (21%), and 12 Gy x 4 (17%), with 95% of reported prescriptions having $BED_{10} \geq 100$ Gy [16]. An NCDB analysis of Stage I NSCLC treated with SBRT identified the most commonly used dose fractionation schemes as 20 Gy x 3, 12 Gy x 4, and 18 Gy x 3 [15]. The overall mean and median calculated BEDs of these regimens were 134.5 and 132 Gy, respectively. Corso et al. found that use of the 3-fraction regimens (20 Gy x 3 and 18 Gy x 3) declined from 47.9% in 2006 to 27.9% in 2011, whereas the use of 10 Gy x 5 increased and became the most commonly prescribed regimen in 2011. The authors also found that smaller tumors tended to be treated with significantly higher BED_{10}. Therefore, it was postulated that the trend toward a 5-fraction, lower-BED regimen was partly due to an increase in the treatment of centrally-located tumors. Similar to Corso et al., we identified a weak negative correlation between BED_{10} and tumor size. Timmerman et al. had identified excessive high-grade toxicity when centrally-located tumors were treated with 60–66 Gy in 3 fractions [31]. This led to RTOG 0813, which investigated doses of 10–12 Gy x 5 fractions for central T 1-2 N0 NSCLC up to 5 cm, within or touching the proximal bronchial tree or adjacent to mediastinal or pericardial pleura [30]. In our study, we could not assess the relationship between dose and peripheral versus central tumor location as this distinction was not captured in NCDB. Our results indicate that dose prescriptions used for Stage II NSCLC were similar to those used for Stage I NSCLC. The more frequent use of 10 Gy x 5 (BED_{10} 100 Gy) and 12 Gy x 4 (BED_{10} 105.6 Gy) as opposed to 20 Gy x 3 (BED_{10} 180 Gy) or 18 Gy x 3 (BED_{10} 151.2 Gy) may reflect the preferential use of lower dose per fraction for larger tumors or those invading adjacent structures, likely to reduce dose to OARs.

Few studies have compared the efficacy among various dose fractionations. One study comparing 10 Gy x 5 and 20 Gy x 3 in Stage I NSCLC found no significant differences in 1-year local control, distant metastasis, or overall survival [8]. Mild late chest wall toxicity was more common in the group treated with 20 Gy x 3, although the authors stated that without further dosimetric study, it was difficult to determine whether the difference was solely attributable to dose. RTOG 0915 compared tumor control and rate of grade 3 or higher adverse events between single fraction 34 Gy and 48 Gy in 4 fractions in peripherally located T 1-2 N0 NSCLC less than 5 cm [32,33]. Primary tumor control rates at 5 years were similar between the two arms. However, the single fraction arm experienced fewer grade 3 or higher adverse events and was determined to be less toxic compared to the 4-fraction arm. As toxicity data is not available through NCDB, no conclusions can be drawn from this study on the relationship between different dose fractionations and adverse events.

In this study, we identified a dose-response relationship between calculated BED_{10} and survival that was consistent with previously published reports. Koshy et al. found that in patients with Stage I NSCLC treated with SBRT, doses above the median BED_{10} of 150 Gy were associated with improved 3-year overall survival of 55%, compared to 46% if the BED_{10} was < 150 Gy [13]. Specifically, the dose response relationship was significant for T2 tumors (median size 3.7 cm), with a 14% increase in 3-year OS in the group that received "high dose" SBRT. A separate review of the Radiosurgery Society RSSearch® Patient Registry found that $BED_{10} \geq 105$ Gy was associated with improved local control in Stage I NSCLC treated with SBRT, especially for T2 tumors, for which local control translated into an overall survival benefit [34]. Other studies have reported that $BED_{10} \geq 100$ Gy [11] or nominal dose ≥ 54 Gy [35] were associated with improved local control and overall survival. In our study, BED_{10} was associated with significantly improved survival for node-negative patients with Stage II NSCLC treated with SBRT. BED_{10} was also found to predict local relapse on multivariate analysis in over 500 patients with Stage I NSCLC treated with SBRT [36]. It is therefore reasonable to hypothesize that the survival benefit with increased BED is derived from improved local control. However, NCDB does not collect such variables to allow for more extensive analysis. A significant correlation between BED and survival was not identified in node-positive patients. We hypothesize that these patients with lymph node metastases may have had indications to receive and benefit from systemic therapy. Because this analysis included only patients who received SBRT for their newly diagnosed Stage II NSCLC and who did not receive systemic therapy, they might have died from systemic progression prior to experiencing benefit from local control of their primary disease.

Interestingly, a few recent reports suggest that given the rapidly repopulating nature of lung cancer cells, utilization of α/β ratio greater than 10 Gy may more accurately describe the biologically effective dose response relationship in the setting of lung SBRT delivered in ≤ 5 fractions. Liu et al. examined tumor control probability of lung SBRT with six radiobiological models in 46 studies, and fitting of clinical data from all models yielded α/β of about 20 Gy [37]. Chi et al. examined the correlation between BED and various randomly selected α/β ratios from 5 Gy to 50 Gy and found increasing BED was associated with increasing local control, and more significantly for α/β of 20, 30, and 50 Gy [38]. Higher BED was also associated with increased 2-year overall survival, and the correlation was strongest with α/β of 20 Gy. We performed an exploratory analysis using BED_{20} and found that the correlation between BED and survival was preserved with a higher α/β ratio of 20 Gy for lung SBRT (data not shown). As in our analysis using BED_{10}, increasing BED_{20} was associated with improved survival in node-negative patients but not node-positive patients on multivariate analysis. Another advantage of using α/β of 20 Gy is that it has been recently suggested that the use of a greater α/β ratio for calculating tumor BED in SBRT regimens for treating NSCLC may reduce the overestimation of the actual biological effect of the linear quadratic (LQ) model in high-dose regions [39]. Examination of tumor control probability using different radiobiological models has found no deviation from the LQ model in multi-institutional lung SBRT clinical data [37,40]. BED currently remains a standardized method to compare different SBRT dose fractionation schemes despite the theoretical concern of inaccuracies in applying the LQ model for SBRT regimens. As different threshold BED_{10} values have been reported in the literature, our findings in conjunction with previous retrospective analyses are hypothesis-generating, and suggest that dose escalation of SBRT regimens should be considered in Stage II NSCLC to improve survival outcomes, similar to Stage I NSCLC.

Despite the safety of SBRT, as demonstrated by the low 30-day mortality rate, overall survival in patients receiving SBRT for early-stage NSCLC is poor. In retrospective analyses, SBRT was associated with 3-year survival of 45–50% for elderly patients with T 1-2 N0 NSCLC [26,41,42]. Small prospective trials have reported 3-year overall survival at 49–82% after SBRT for Stage I NSCLC [6,10,43–45]. In comparison, our study found a 3-year survival of 29.4%. However, the patients in our registry population had more advanced disease, with 20% having N1 disease, and 48% having T3N0 disease. Studies reviewing outcomes of SBRT for tumors > 5 cm reported median survival between 19.9 months and 25.1 months [25,46,47], similar to the median survival of 23.7 months reported in our study. For patients with T3N0 NSCLC with chest wall invasion treated with SBRT, median survival was lower at 13.3 months [24]. In our study, higher T and N classification were not significantly associated with decreased survival, but our analysis was likely underpowered given the relatively small sizes of the T1N1 and T2N1 groups.

Our study was subject to the limitations associated with analyses using large retrospective datasets such as the NCDB. In addition to the aforementioned lack of data on local control, toxicity, and tumor location, NCDB does not capture cause of death, pulmonary function, medical operability, and patient preferences, such that selection biases in treatment decision cannot be excluded. We also could not explain why node-positive patients received SBRT without other therapy. Furthermore, SBRT details including prescription isodose and target volume coverage are not collected. We also acknowledge that the strict definition of lung SBRT in the United States does not include hypofractionated regimens. We queried NCDB for treatments that were considered SBRT up to eight fractions and found only 13 patients treated with 6–8 fractions (data not shown). While other hypofractionated regimens may be employed as definitive treatment for early stage NSCLC, we limited our analysis to five fractions since any course of radiation treatment extending beyond five fractions is generally not considered SBRT in the United States and is not billed as such per the American Society for Radiation Oncology (ASTRO) Model Policy [48]. This report nevertheless provides novel information on the patterns of practice of SBRT in up to five fractions in Stage II NSCLC across the United States, identifying a large number of Stage II NSCLC patients treated with SBRT in a recent timeframe.

Lastly, with the implementation of the new AJCC 8th edition Lung Cancer Stage Classification adopted in 2018, there will be stage migration with some Stage I cancers now defined as Stage II NSCLC, and some Stage II cancers now Stage III. This could potentially impact the treatment approach and decision to use SBRT, and survival outcomes as a result. We hypothesize that the new staging system will affect practice trends and survival, and look forward to updating these analyses for patients diagnosed in 2018 and afterwards.

5. Conclusions

To our knowledge, this is the first study to describe a dose-response relationship in patients treated with SBRT for Stage II NSCLC. We found that increasing BED_{10} was associated with improved survival, with this benefit significant in node-negative but not node-positive disease on multivariate analysis. As Stage II NSCLC represents a heterogeneous group of diseases, patient selection is important in identifying those who may benefit from SBRT. Prospective studies are warranted to further explore the role of SBRT in management of Stage II NSCLC, as well as determining the optimal dose fractionation of these regimens.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

None declared.

Acknowledgement

None.

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.2019.03.031.

References

[1] National Comprehensive Cancer Network (NCCN), NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2018, (2018) (Accessed 22 February 2018), https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
[2] J.A. Howington, M.G. Blum, A.C. Chang, et al., Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) e278S–313S.
[3] H. Pan, D.R. Simpson, L.K. Mell, et al., A survey of stereotactic body radiotherapy use in the United States, Cancer 117 (19) (2011) 4566–4572.
[4] R. Timmerman, R. Paulus, J. Galvin, et al., Stereotactic body radiation therapy for inoperable early stage lung cancer, JAMA 303 (11) (2010) 1070–1076.
[5] J.Y. Chang, S. Senan, M.A. Paul, et al., Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials, Lancet Oncol. 16 (6) (2015) 630–637.
[6] R.D. Timmerman, R. Paulus, H.I. Pass, et al., Stereotactic body radiation therapy for operable early-stage lung cancer: findings from the NRG Oncology RTOG 0618 trial, JAMA Oncol. 4 (9) (2018) 1263–1266.
[7] R. Timmerman, L. Papiez, R. McGarry, et al., Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer, Chest 124 (5) (2003) 1946–1955.
[8] K.L. Stephans, T. Djemil, C.A. Reddy, et al., A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience, J. Thorac. Oncol. 4 (8) (2009) 976–982.

[9] Y. Nagata, K. Takayama, Y. Matsuo, et al., Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame, Int. J. Radiat. Oncol. Biol. Phys. 63 (5) (2005) 1427–1431.

[10] A.J. Fakiris, R.C. McGarry, C.T. Yiannoutsos, et al., Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study, Int. J. Radiat. Oncol. Biol. Phys. 75 (3) (2009) 677–682.

[11] H. Onishi, T. Araki, H. Shirato, et al., Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study, Cancer 101 (7) (2004) 1623–1631.

[12] D.J. Brenner, The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction, Semin. Radiat. Oncol. 18 (4) (2008) 234–239.

[13] M. Koshy, R. Malik, R.R. Weichselbaum, et al., Increasing radiation therapy dose is associated with improved survival in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 91 (2) (2015) 344–350.

[14] M.V. Williams, J. Denekamp, J.F. Fowler, A review of alpha/beta ratios for experimental tumors: implications for clinical studies of altered fractionation, Int. J. Radiat. Oncol. Biol. Phys. 11 (1) (1985) 87–96.

[15] C.D. Corso, H.S. Park, A.C. Moreno, et al., Stage I lung SBRT clinical practice patterns, Am. J. Clin. Oncol. 40 (4) (2017) 358–361.

[16] H. Pan, B.S. Rose, D.R. Simpson, et al., Clinical practice patterns of lung stereotactic body radiation therapy in the United States: a secondary analysis, Am. J. Clin. Oncol. 36 (3) (2013) 269–272.

[17] N. Ezer, R.R. Veluswamy, G. Mhango, et al., Outcomes after stereotactic body radiotherapy versus limited resection in older patients with early-stage lung cancer, J. Thorac. Oncol. 10 (8) (2015) 1201–1206.

[18] T.D. Crabtree, C.E. Denlinger, B.F. Meyers, et al., Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 140 (2) (2010) 377–386.

[19] I.S. Grills, V.S. Mangona, R. Welsh, et al., Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer, J. Clin. Oncol. 28 (6) (2010) 928–935.

[20] S. Mokhles, N. Verstegen, A.P. Maat, et al., Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis, Lung Cancer 87 (3) (2015) 283–289.

[21] A. Modh, A. Rimner, E. Williams, et al., Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 90 (5) (2014) 1168–1176.

[22] J.T. Hepel, K.L. Leonard, H. Safran, et al., Stereotactic body radiation therapy boost after concurrent chemoradiation for locally advanced non-small cell lung cancer: a phase 1 dose escalation study, Int. J. Radiat. Oncol. Biol. Phys. 96 (5) (2016) 1021–1027.

[23] S.D. Karam, Z.D. Horne, R.L. Hong, et al., Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer, Radiat. Oncol. 8 (2013) 179.

[24] C. Berriochoa, G.M. Videtic, N.M. Woody, et al., Stereotactic body radiotherapy for T3N0 lung cancer with chest wall invasion, Clin. Lung Cancer 17 (6) (2016) 595–601.

[25] N.M. Woody, K.L. Stephans, G. Marwaha, et al., Stereotactic body radiation therapy for non-small cell lung cancer tumors greater than 5 cm: safety and efficacy, Int. J. Radiat. Oncol. Biol. Phys. 92 (2) (2015) 325–331.

[26] C.J. Haasbeek, F.J. Lagerwaard, M.E. Antonisse, et al., Stage I nonsmall cell lung cancer in patients aged > 75 years: outcomes after stereotactic radiotherapy, Cancer 116 (2) (2010) 406–414.

[27] P. Fritz, H.J. Kraus, W. Muhlnickel, et al., Stereotactic, single-dose irradiation of stage I non-small cell lung cancer and lung metastases, Radiat. Oncol. 1 (2006) 30.

[28] R. Hara, J. Itami, T. Kondo, et al., Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors, Cancer 106 (6) (2006) 1347–1352.

[29] J. Nyman, K.A. Johansson, U. Hulten, Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer—mature results for medically inoperable patients, Lung Cancer 51 (1) (2006) 97–103.

[30] A. Bezjak, R. Paulus, L.E. Gaspar, et al., Efficacy and toxicity analysis of NRG Oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC), Int. J. Radiat. Oncol. Biol. Phys. 96 (2) (2016) S8.

[31] R. Timmerman, R. McGarry, C. Yiannoutsos, et al., Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer, J. Clin. Oncol. 24 (30) (2006) 4833–4839.

[32] G.M. Videtic, C. Hu, A.K. Singh, et al., A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927), Int. J. Radiat. Oncol. Biol. Phys. 93 (4) (2015) 757–764.

[33] G.M. Videtic, R. Paulus, A.K. Singh, et al., Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 99 (2) (2017) S15–16.

[34] J.N. Davis, C. Medbery 3rd, S. Sharma, et al., Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry, J. Radiat. Oncol. 4 (1) (2015) 55–63.

[35] R. McCammon, T.E. Schefter, L.E. Gaspar, et al., Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 73 (1) (2009) 112–118.

[36] I.S. Grills, A.J. Hope, M. Guckenberger, et al., A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy, J. Thorac. Oncol. 7 (9) (2012) 1382–1393.

[37] F. Liu, A. Tai, P. Lee, et al., Tumor control probability modeling for stereotactic body radiation therapy of early-stage lung cancer using multiple bio-physical models, Radiother. Oncol. 122 (2) (2017) 286–294.

[38] A. Chi, S. Wen, Z. Liao, et al., What would be the most appropriate alpha/beta ratio in the setting of stereotactic body radiation therapy for early stage non-small cell lung cancer, Biomed Res. Int. 2013 (2013) 391021.

[39] J.F. Fowler, Linear quadratics is alive and well: in regard to Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847–852), Int. J. Radiat. Oncol. Biol. Phys. 72 (3) (2008) 957 author reply 958.

[40] M. Guckenberger, R.J. Klement, M. Allgauer, et al., Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer, Radiother. Oncol. 109 (1) (2013) 13–20.

[41] M. Koshy, R. Malik, U. Mahmood, et al., Stereotactic body radiotherapy and treatment at a high volume facility is associated with improved survival in patients with inoperable stage I non-small cell lung cancer, Radiother. Oncol. 114 (2) (2015) 148–154.

[42] G.M. Videtic, K. Stephans, C. Reddy, et al., Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control, Int. J. Radiat. Oncol. Biol. Phys. 77 (2) (2010) 344–349.

[43] P. Baumann, J. Nyman, M. Hoyer, et al., Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy, J. Clin. Oncol. 27 (20) (2009) 3290–3296.

[44] C.J. Haasbeek, F.J. Lagerwaard, B.J. Slotman, et al., Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer, J. Thorac. Oncol. 6 (12) (2011) 2036–2043.

[45] D.J. Hoopes, M. Tann, J.W. Fletcher, et al., FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer, Lung Cancer 56 (2) (2007) 229–234.

[46] V. Verma, M.T. McMillan, S. Grover, et al., Stereotactic body radiation therapy and the influence of chemotherapy on overall survival for large (≥5 cm) non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 97 (1) (2017) 146–154.

[47] V. Verma, V.K. Shostrom, S.S. Kumar, et al., Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors, Cancer 123 (4) (2017) 688–696.

[48] American Society for Radiation Oncology (ASTRO), Model Policies: Stereotactic Body Radiation Therapy (SBRT), (2014) (Accessed 23 January 2019), https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROSBRTModelPolicy.pdf.