Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 457–462, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.056

CLINICAL INVESTIGATION **Thoracic Cancer**

A DOSE–VOLUME ANALYSIS OF RADIATION PNEUMONITIS IN NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY

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Purpose: To examine the rates and risk factors of radiation pneumonitis (RP) in non–small cell lung cancer (NSCLC) patients treated with stereotactic body radiotherapy (SBRT).

Methods and Materials: Dosimetry records for 251 patients with lymph node-negative Stage I–IIB NSCLC and no prior chest radiation therapy (RT) treated with SBRT were reviewed. Patients were coded on the basis of the presence of at least Grade (G) 2 RP using the Common Toxicity Criteria version 2 criteria. Radiation doses, V5, V10, V20, and mean lung dose (MLD) data points were extracted from the dose–volume histogram (DVH).

Results: Median PTV volume was 48 cc. Median prescribed radiation dose was 60 Gy delivered in three fractions to the 80% isodose line. Median age at treatment was 74 years. Median follow-up was 17 months. RP was reported after treatment of 42 lesions: G1 in 19 (8%), G2 in 17 (7%), G3 in 5 (2%), and G4 in 1 (0.4%). Total lung DVHs were available for 143 patients. For evaluable patients, median MLD, V5, V10, and V20 were 4.1 Gy, 20%, 12%, and 4%, respectively. Median MLDs were 4 Gy and 5 Gy for G0–1 and G2–4 groups, respectively ($p = 0.14$); median V5 was 20% for G0–1 and 24% for G2–4 ($p = 0.70$); median V10 was 12% in G0–1 and 16% in G2–4 ($p = 0.08$), and median V20 was 4% in G0–1 and 6.6% in G2–4 ($p = 0.05$). G2–4 RP was noted in 4.3% of patients with MLD ≤4 Gy compared with 17.6% of patients with MLD >4 Gy ($p = 0.02$), and in 4.3% of patients with V20 ≤4% compared with 16.4% of patients with V20 >4% ($p = 0.03$).

Conclusion: Overall rate of G2–4 RP in our population treated with SBRT was 9.4%. Development of symptomatic RP in this series correlated with MLD and V20. © 2012 Elsevier Inc.

Radiotherapy, SBRT, Lung cancer, Pneumonitis, Toxicity.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) delivers high doses per fraction to a localized area. In medically inoperable patients with non–small cell lung cancer (NSCLC), it is an effective local treatment modality (1–11). Treatment is important because more than half of these patients with untreated disease will eventually die from the cancer (12). At Indiana University School of Medicine, we have undertaken Phase I and II trials investigating SBRT in the treatment of NSCLC. Members from our group have previously reported results from our Phase I and II trials (4, 5, 13). We have described the effects of SBRT on pulmonary function tests, the toxicities associated with treatment of central pulmonary lesions, brachial plexopathy when treating apical lesions, and chest wall toxicity for peripheral tumors (14–17).

Radiation-induced lung injury is a well-described event complicating thoracic radiation in standard fractionation. Many reports have defined risk factors for RP following standard thoracic radiation for NSCLC (18–21). In this report, we discuss the frequency and correlates for RP after SBRT for NSCLC.

METHODS AND MATERIALS

This study was undertaken after approval by the Indiana University School of Medicine Institutional Review Board. Medically inoperable patients with lymph-node-negative American Joint

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This work was presented in part at the American Society for Therapeutic Radiology and Oncology annual meeting, November 1–5, 2009, Chicago, Illinois.

Conflict of interest: none.

Received June 2, 2010, and in revised form July 23, 2010. Accepted for publication Aug 7, 2010.

Committee on Cancer Stage I–IIB NSCLC treated with SBRT were identified (22). The medical records, radiation dosimetry, and treatment plans were reviewed. Medical inoperability was defined by significant medical comorbidities or poor pulmonary function as determined by institutional standards: baseline forced expiratory volume at 1 sec (FEV1) <40% predicted, likely postoperative FEV1 <30% predicted, severely reduced diffusion capacity <40% predicted, baseline hypoxemia (≤70 mm Hg) and/or hypercapnia (>50 mm Hg), and exercise oxygen consumption <50% predicted.

We identified 281 patients treated for NSCLC with SBRT between February 2000 and October 2008. Twenty-eight patients were excluded for having multiple treatments to separate primaries. Two patients were excluded for having no staging information. Of these, 143 patients had complete dosimetry available for review. This series includes patients treated both on and off clinical protocols. Details of the stereotactic body radiation therapy technique have been published previously (13). Briefly, patients were positioned in the Elekta Stereotactic Body Frame (Elekta, Stockholm, Sweden) in a vacuum pillow for patient immobilization. Sternal and tibial external positioning marks were applied after indexing positional lasers to the frame. Abdominal compression was applied and tightened until the diaphragmatic excursion visualized under fluoroscopy was ≤1 cm. CT-guided treatment simulation was performed with 3-mm slices, except through the tumor volume, where 1-mm slices were acquired. Gross tumor volume (GTV) was defined based on the planning CT. Atelectasis, if present, was not included in the GTV, and many times facilitated by PET/CT fusion to the planning CT. A planning target volume (PTV) was created by adding a 0.5-cm expansion in the axial plane and a 1-cm expansion in the longitudinal plane. Treatment planning was performed with various treatment planning systems depending on the year of treatment including Render, CMS, and Eclipse. Tissue inhomogeneity corrections were used in all cases after 2006 and encompass approximately 30% of the reported patients. Patients were usually treated with 6-MV photons. Five to 12 noncoplanar beams were stereotactically directed toward the PTV using three-dimensional planning; 24–72 Gy was delivered in 3–5 fractions prescribed to the 75%–95% isodose line, which covered at least 95% of the PTV (Table 1). Fractions were given once daily and separated by 2–3 days between fractions. Daily setup within the body frame apparatus was confirmed with the sternal and tibial tattoos, and the treatment isocenter was verified before each treatment. Patients were generally seen at 1 month following treatment completion, every 3 months for 2 years, every 4 months for year 3, every 6 months during Years 4–5, and yearly thereafter. History and physical exam, as well as chest imaging with plain radiography or CT scan, were obtained at each visit. Radiation doses were extracted from the dose–volume histograms (DVH). V*n* was defined as the lung volume receiving at least *n* Gy of radiation. Data points extracted from the DVH included mean lung dose (MLD), V5, V10, and V20. Total lung volume was defined as the volume of both lungs minus the GTV volume. Patients were coded on the basis of the presence of Grade 0–1 (asymptomatic) vs. Grade 2–5 radiation pneumonitis (RP) using the Common Toxicity Criteria (CTC) version 2.0 definitions, grade (G) 1 being asymptomatic or requiring no treatment, G2 requiring steroids or diuretics, G3 requiring supplemental oxygen, and G4 requiring mechanical ventilation. Mann–Whitney and Fisher exact tests were used the data analysis.

Table 1. SBRT dose prescriptions

Dose per fraction	Fractions	Total dose	% of patients
20 Gy	3	60 Gy	39%
22 Gy	3	66 Gy	15%
18 Gy	3	54 Gy	13%
12 Gy	4	48 Gy	13%
16 Gy	3	48 Gy	4%
14 Gy	3	42 Gy	4%
8–24 Gy	3	24–72 Gy	
10–14 Gy	4	40–56 Gy	13%
9–10 Gy	5	45–50 Gy	

Abbreviation: SBRT = stereotactic body radiotherapy.

RESULTS

Two hundred fifty-one patients fitting the study criteria were reviewed. Patient and tumor characteristics are shown in Tables 2 and 3. Treatment parameters are given in Table 4. Median follow-up was 17 months (range, 0.3–89). RP was reported after treatment of 42 lesions (17%): G1 in 19 (8%), G2 in 17 (7%), G3 in 5 (2%), and G4 in 1 (0.4%). RP was diagnosed at a median time of 5.6 months after treatment completion (0.5–32.2 months). Grade 1 RP developed at a median time of 8.4 months (1.3–32.2 months) and symptomatic RP (G2–4) developed at a median of 3.5 months (0.5–12 months; $p = 0.002$). Total lung DVHs were available for 143 patients. The 108 patients with incomplete dosimetry were patients treated early in the SBRT experience on old treatment planning systems that were unable to be accessed with newer computer systems. The dosimetry information including total lung DVHs were stored in these data files but not in paper charts. For the patients with available dosimetry, median MLD, V5, V10, and V20 were 4.1 Gy, 20%, 12%, and 4%, respectively. For the 143 patients with DVH data, the rates of RP were 11.1% G1, 8.4% G2, and 2.1% G3 as shown in Table 5, similar to the incidence among all patients. The volumes of normal lung tissue receiving at least *n* Gy of absorbed dose are given in Table 6. Median MLDs

Table 2. Patient characteristics

		Radiation pneumonitis	
	Entire population *n* = 251	Grade 0–1 *n* = 228	Grade 2–4 *n* = 23
Age	74 (45–100)	74 (45–100)	73 (60–87)
KPS	80 (50–100)	80 (50–100)	70 (50–100)
Sex			
Male	142 (57%)	129 (57%)	13 (57%)
Female	109 (43%)	99 (43%)	10 (43%)
Smoking status			
Never smoker	6 (2%)	5 (2%)	1 (4%)
Quit >30 years	15 (6%)	13 (6%)	2 (9%)
Quit 3 months–30 years	145 (58%)	130 (57%)	15 (65%)
Current or quit <3 months	82 (33%)	78 (34%)	4 (17%)
Unknown	3 (1%)	2 (1%)	1 (4%)
COPD	192 (76%)	173 (76%)	19 (83%)
Oxygen dependent	56 (22%)	52 (23%)	4 (17%)

Abbreviations: KPS = karnofsky performance status; COPD = chronic obstructive pulmonary disease.

Table 3. Tumor characteristics

		Radiation pneumonitis	
	Entire population $n = 251$	Grade 0–1 $n = 228$	Grade 2–4 $n = 23$
Stage			
IA	138 (55%)	128 (56%)	10 (43%)
IB	108 (43%)	95 (42%)	13 (57%)
IIB	5 (2%)	5 (2%)	
Histology			
Squamous	76 (30%)	69 (30%)	7 (30%)
Adenocarcinoma	70 (28%)	62 (27%)	8 (35%)
NSCLC, unspecified	105 (42%)	97 (43%)	8 (35%)
Tumor location			
RUL	74 (29%)	69 (30%)	5 (22%)
RML	15 (6%)	14 (6%)	1 (4%)
RLL	44 (18%)	41 (18%)	3 (13%)
LUL	81 (32%)	74 (32%)	7 (30%)
LLL	37 (15%)	30 (13%)	7 (30%)
GTV	11.7 cc (0.7–225)	10.9 cc (0.7–225)	17.3 cc (1.8–121.7)
PTV	48.3 cc (8–401)	45.4 cc (8–401)	68.8 cc (14.4–208.8)

Abbreviations: GTV = gross tumor volume; LLL = left lower lobe; LUL = left upper lobe; NSCLC = non–small cell lung cancer; PTV = planning target volume; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

were 4 Gy and 4.96 Gy for G0–1 and G2–4 groups, respectively ($p = 0.14$); median V5 was 20% for G0–1 patients and 24% for G2–4 patients ($p = 0.70$); median V10 was 12% in G0–1 and 16% in G2–4 ($p = 0.08$); and median V20 was 4% in G0–1 and 6.6% in G2–4 ($p = 0.05$). Table 7 dichotomizes patients based on median dosimetric values for normal lung and by certain patient/tumor characteristics. G2–4 RP was noted in 4.3% of patients with MLD ≤4 Gy compared with 17.6% of patients with MLD >4 Gy ($p = 0.02$), in 5.7% of patients with V10 ≤12% compared with 15% when V10 >12% ($p = 0.1$), and in 4.3% of patients with V20 ≤4% compared with 16.4% of patients with V20 >4% ($p = 0.03$). PTV volume, tumor location (upper vs. middle/lower lobe), and the presence of preexisting chronic obstructive pulmonary disease were not predictive of G2–4 RP. Crude incidence of G2–4 RP for V20 >4%, 5%, 7%, and 10% was 16%, 18%, 16.6%, and 15.7%, respectively.

DISCUSSION

SBRT with three-dimensional conformal or intensity-modulation techniques for early-stage lung cancer is a proven effective treatment for localized lesions, with local control rates of 85.5%–100% at 2–3 years following treatment (1–11). This technique is also being employed to treat pulmonary metastatic disease, although the survival rates are not comparable to the current population (23). Rates of serious toxicity in most studies are low. Previous reports have described skin, chest wall, and brachial plexus toxicity and associated risk factors (16, 17, 24, 25). This study documents clinically significant RP rates for medically inoperable NSCLC patients treated with SBRT, adding to sparse literature on pulmonary toxicity resulting from hypofractionated radiotherapy.

Our results show that the rates of clinically significant RP are low with these techniques: 9.4% of our patients developed G2–4 RP, at least requiring steroid intervention, with the overwhelming majority (7%) of these being self-limited G2 toxicity. No deaths resulted from acute or chronic pulmonary toxicity. These results are comparable to the existing literature on the subject, shown in Table 8. McGarry reported 1 (2%) and 3 (6.4%) patients out of 47 who developed CTC v.2 G2 and G3 RP, respectively, in the updated Indiana University Phase I trial including tumors up to 7 cm in size and not excluding central lesions. The G2 toxicity occurred at a dose of 48 Gy and the G3 toxicities developed

Table 4. Treatment parameters

		Radiation pneumonitis	
	Entire population $n = 251$	Grade 0–1 $n = 228$	Grade 2–4 $n = 23$
Dose/fraction (Gy)	20 (8–24)	20 (8–24)	20 (8–22)
Total dose	60 (24–72)	60 (24–72)	60 (24–66)
Treatment time (days)	8 (4–84)	8 (4–84)	8 (4–13)
No. beams	9 (5–12)	9 (5–12)	8 (7–12)
Fractions	3 (3–5)	3 (3–5)	3 (3–4)
Prescription IDL	80 (75–95)	80 (75–95)	80

Abbreviation: IDL = isodose line.

Table 5. Pneumonitis rates

	All patients $n = 251$	Patients with available dosimetry $n = 143$
None	209 (83%)	112 (78%)
Grade 1	19 (8%)	16 (11%)
Grade 2	17 (7%)	12 (8%)
Grade 3	5 (2%)	3 (2%)
Grade 4	1 (0.4%)	0

Table 6. Dosimetric factors

		Radiation pneumonitis		
Median values	All patients	Grade 0–1	Grade 2–4	*p* value
MLD	414 cGy (75–1,416)	400 cGy (75–1,416)	496 cGy (195–903)	0.14
V5	20% (6.0–45.6)	20% (6.0–40.4)	24% (8.0–45.6)	0.70
V10	12% (2.0–39.9)	12% (2.0–39.9)	15.9% (6.0–32)	0.08
V20	4.1% (1–22)	4% (1–22)	6.6% (1.6–14.0)	0.05

Abbreviations: MLD = mean lung dose; V*n* = volume of lung receiving at least *n* Gy of radiation dose.

after 54 Gy and 72 Gy in 3 fractions prescribed to the 80% isodose line (4). Using similar criteria, Onishi reported 4.1% G2, 1.2% G3, and 1.2% G4 RP in a multi-institutional trial of SBRT in Japan (2). Nagata and colleagues reported no G3-4 RP using a slightly less potent dose of 48 Gy in 4 fractions delivered to the isocenter (3). The updated Indiana University Phase II study showed Grade 3–5 toxicity in 5 of 48 peripheral lesions and 6 of 22 central lesions with pulmonary complication including pneumonia, effusion, decrease in pulmonary function tests, and respiratory failure. No specific radiation pneumonitis was documented in these patients (5). Ricardi reported 3.2% Radiation Therapy Oncology Group (RTOG) G3 RP (requiring steroids or intermittent oxygen) when treating 62 patients to 45 Gy in 3 fractions to the 80% isodose line (6). Stephans reported a comparison of 50 Gy in 5 fractions vs. 60 Gy in 3 fractions and showed a 2.3% incidence of RP requiring steroids (9). Grills recently published a case–control study comparing SBRT to wedge resection. In this report, there was 11% G2–3 RP using CTC v.3 grading system. Only 2% required temporary steroids for management (10). Finally, RTOG 0236 recently reported results with overall G3 RP in 2 of 55 (3.6%) of patients (1).

Table 7. Dosimetric risks for grade 2-4 (symptomatic) pneumonitis

	Grade 2-4 pneumonitis	*p* value
MLD		
≤4 Gy	4.3%	0.02
>4 Gy	17.6%	
V5		
≤20%	4.7%	0.67
>20%	8.9%	
V10		
≤12%	5.7%	0.1
>12%	15%	
V20		
≤4 % (Median)	4.3%	0.03
>4 %	16.4%	
≤10 % (RTOG)	9.6%	0.42
>10 %	15.8%	
PTV		
≤48 mL	6.4%	0.18
>48 mL	13%	
Tumor location		
Upper lobe	9%	0.59
Lower/middle lobe	12%	
COPD		
No	5.7%	0.36
Yes	12%	

Abbreviations: COPD = chronic obstructive pulmonary disease; MLD = mean lung dose; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; V*n* = volume of lung receiving at least *n* Gy of radiation dose.

In this series, we have a similarly low incidence of RP requiring therapy. Our median MLD, V10, and V20 were 4.1 Gy, 12%, and 4%, respectively. Our median V20 is well below the limits required in recent RTOG protocols (V20 of <10%), and our results are similar to those in the prospective 0236 protocol with respect to pneumonitis rates. In that trial, median V20 was likely below the stated cutoff as allowed in the protocol. We did not find a major difference in crude RP rates when using V20 cutoffs of 4%, 5%, 7%, and 10%, possibly because of the low total number of events. Because of the relatively small number of overall events, we used a cutoff point near the median values of the dosimetric variables to assess pneumonitis risks. We found that patients who developed Grade 2–4 RP had higher V*n* parameters and MLD than the group without toxicity; however, only V20 (4% vs. 6.6%) approached statistical significance. When dividing the toxicity groups based on median MLD and dose–volume metrics, only MLD and V20 were significant predictors. It is difficult to draw definitive conclusions from this finding because one limitation is the retrospective nature of the study. These dosimetric variables have also been shown to be highly correlated in past studies of RP in standard fractionation (20).

We were not able to find a significant difference in symptomatic radiation pneumonitis among patients dichotomized by the current RTOG recommended V20 limit of 10%. This may be because of small patient numbers in this series with V20 >10% (only 13% of the entire patient population). The data shows that the development of RP as a symptomatic toxicity may be within acceptable limits with V20 as high as 10%, but we recommend that the overall percentage of normal lung tissue receiving radiation be a low as possible. The clinician should weigh the risks and benefits of treating and determining these limits for each individual patient. In this series, V20 was predictive of toxicity, but not GTV or PTV size. This finding could represent the importance of high-dose conformality with SBRT treatments, which we achieve with multiple intersecting non-coplanar beams.

The limitations of this study include its retrospective nature and that several treatment planning systems were used during the era in question. Median follow-up was 17 months,

Table 8. Comparison to other series

Author	SBRT dosing schema	Symptomatic radiation pneumonitis (requires intervention)	Scoring criteria
Barriger	Multiple (Table 1)	9.4% 7% Grade 2 2% Grade 3 0.4% Grade 4	CTC v2
McGarry Phase I trial	8 Gy × 3 = 24 Gy 10 Gy × 3 = 30 Gy 12 Gy × 3 = 36 Gy 14 Gy × 3 = 42 Gy 16 Gy × 3 = 48 Gy 18 Gy × 3 = 54 Gy 20 Gy × 3 = 60 Gy 22 Gy × 3 = 66 Gy 24 Gy × 3 = 72 Gy	8.4% 2% Grade 2 6.4% Grade 3	CTC v2
Onishi	Various 18–75 Gy in 1–25 fractions*†	6.5 % 4.1% Grade 2 1.2% Grade 3 1.2% Grade 4	CTC v2
Nagata	12 Gy × 4 = 48 Gy*	4% No Grade 3–4	CTC v2
Ricardi	15 Gy × 3 = 45 Gy	3.2% Grade 3 (Required steroids or intermittent oxygen)	RTOG
Stephans	20 Gy × 3 = 60 Gy 10 Gy × 5 = 50 Gy	2/86 Grade 2 (Required steroids)	Not stated in paper
Grills	12 Gy × 4 = 48 Gy 12 Gy × 5 = 60 Gy	11% 9% Grade 2 2% Grade 3	CTC v3
Timmerman RTOG 0236	20 Gy × 3 (without heterogeneity corrections) 18 Gy × 3 (with heterogeneity corrections)	3.6% Grade 3	CTC v3

Abbreviations: CTC = common toxicity criteria; RTOG = radiation therapy oncology group; SBRT = stereotactic body radiotherapy.
* Dose prescribed to isocenter, not an isodose line encompassing the planning target volume.
† 27 patients also received 30–44 Gy in 15–20 fractions of conventional fractionation before SBRT.

but several patients had follow-up times less than the median time to develop RP, possibly artificially decreasing the true rate of RP because patients may have been censored before developing this toxicity. Most patients in this series were treated with one of a few dose schemes (Table 1), which minimizes biological effective dose differences among the patients. However, the inherent variation of dose fractionation and biological effective dose due to many patients being treated as part of a Phase I clinical trial could be considered a shortcoming of this data. Being a retrospective study, there was no central data review, and the determination of radiation pneumonitis can be subjective and challenging. The distinction between tumor progression and development of pulmonary sequelae following SBRT can be difficult (26). Also, RP is a clinical diagnosis and can be confounded by preexisting or comorbid disease, including chronic obstructive pulmonary disease exacerbations, cardiac disease, tumor progression, or infection (27).

CONCLUSIONS

The overall rate of G2–4 RP in our population treated with SBRT was 9.4%. Development of symptomatic RP in this series correlated significantly with MLD and V20 but not with V5, V10, PTV volume, or tumor location. Given the overall low rate of RP in this and other published RTOG trials, the guideline of keeping V20 <10% is likely adequate. With modern treatment planning and experience, the total lung dose can be kept low; we recommend this.

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