Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 September 1; 81(1): 91–96. doi:10.1016/j.ijrobp.2010.04.022.

Obesity Increases the Risk of Chest Wall Pain from Thoracic Stereotactic Body Radiation Therapy

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Abstract

Purpose—Stereotactic body radiation therapy (SBRT) is increasingly being used to treat thoracic tumors. We sought here to identify dose-volume parameters that predict chest wall toxicity (pain and skin reactions) in patients receiving thoracic SBRT.

Methods—We screened a database of patients treated with SBRT between August 2004 and August 2008 to find patients with pulmonary tumors within 2.5 cm of the chest wall. All patients received a total dose of 50 Gy in four daily 12.5-Gy fractions. Toxicity was scored according to the NCI-CTCAE V3.0.

Results—Of 360 patients in the database, 265 (268 tumors) had tumors within <2.5 cm of the chest wall; 104 (39%) developed skin toxicity (any grade); 14 (5%) developed acute pain (any grade), and 45 (17%) developed chronic pain (grade 1 in 22 cases [49%] and grade 2 or 3 in 23 cases [51%]). Both skin toxicity and chest wall pain were associated with the V30 or volume of the chest wall receiving 30Gy. Body mass index (BMI) was also strongly associated with the development of chest pain: patients with BMI ≥ 29 had almost twice the risk of chronic pain ($P = 0.03$). Among patients with BMI over 29, diabetes mellitus was a significant contributing factor to the development of chest pain.

Conclusion—Safe use of SBRT with 50 Gy in 4 fractions for lesions close to the chest wall requires consideration of the chest wall volume receiving 30 Gy and the patient's BMI and diabetic state.

Keywords

Stereotactic Body Radiation Therapy; toxicity

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Meeting presentations: This work was presented at ASTRO annual meeting on November 3, 2009. This work has not been submitted for publication to any other journals.

Conflicts of Interest: There are no conflicts of interest for any of the authors regarding this work in this publication.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, with approximately 162,460 deaths per year in the United States alone. According to American Cancer Society estimates, 219,440 new cases will be diagnosed and 159,390 people will die of lung cancer in the United States¹. Although most patients present with locally advanced or metastatic disease, the increased use of computed tomography (CT) for lung cancer screening or other unrelated reasons such as preoperative imaging, has increased the detection of lung cancer at early stages. Patients with early-stage lung cancer who are not candidates for surgery are often given radiation therapy, typically to total doses of 60–74 Gy. Further escalation of radiation doses to approximately 85 Gy may improve long-term local control to some extent², but that control comes at the cost of severe toxicity to normal tissues. One way of potentially delivering larger doses to pulmonary tumors with less damage to surrounding structures is by using stereotactic body radiation therapy (SBRT)³. SBRT has allowed doses to be escalated and has led to improvements in both local control rates (57%–100%) and survival rates^{4,5}. Onishi and colleagues in Japan have had perhaps the longest experience with using SBRT for this purpose, demonstrating the remarkable 5-year local control rate of 92% when biologically effective doses exceed 100 Gy⁶.

Despite these encouraging results, enthusiasm for the use of SBRT for early-stage lung cancer must be tempered until the appropriate dose limits and dose volume histogram (DVH) constraints to critical normal structures can be established. The initial dose escalation experiments pioneered in the United States by a group at the University of Colorado demonstrated that SBRT doses could be safely escalated to 60 Gy in 3 fractions, with no patients experiencing dose-limiting toxicities during the first 3 months after this treatment⁷. However, as use of SBRT for lung lesions increased, complications started to be reported. Use of SBRT for lesions close to critical structures like the chest wall and mediastinum has been associated with increased risk of complications^{8,9}. Use of SBRT for lesions close to the chest wall can result in both acute and chronic chest wall pain, rib fractures, skin reactions and skin contracture. Increased skin toxicity has also been noted with the use of a three-beam treatment technique that can cause excessive dose build-up¹⁰. However, little is known about the lifestyle and dosimetric factors that are associated with toxicity of SBRT when performed close to the chest wall.

Prior attempts to establish dose constraints for thoracic SBRT have been made by extrapolating BED from the known dose tolerance of various structures for the more conventional daily fractions of 2 Gy. However, normal structures with a low alpha/beta ratio, such as the spinal cord, are known to be more sensitive to fraction size^{2,11}. Little is known as to which dose thresholds are likely to produce which complications in thoracic SBRT. The goal of this project was to establish a identify both lifestyle and dose-volume relationships between the use of SBRT (50 Gy in 4 fractions) and the development of chest wall pain and skin toxicity, the most common side effects seen after SBRT is performed close to the chest wall. With this information we can then make efforts to reduce or eliminate the variables result in complications and help to direct patients to the therapy that not only provides the best tumor control but also the lowest morbidity.

METHODS

Patient Characteristics

We analyzed an institutional database of patients on an IRB approved trial for thoracic SBRT at M. D. Anderson Cancer Center for primary lung cancer or metastatic disease between August 2004 and August 2008. This time frame was chosen as this represented a time where consistent practice of treatment were employed for SBRT, in that all patients were simulated with a 4D CT and treated with cone beam CT. Of the 360 such patients in the database, we selected 265 patients who had had peripheral (as opposed to centrally located) tumors within 2.5 cm of the chest wall and assessed the relationship of patient and tumor characteristics, radiation dosimetry, and volume of chest wall irradiated to the appearance and severity of symptoms. Cases were followed over a period of 1 year from the date of SBRT completion for evidence of pain and skin reactions, according to the National Cancer Institute Common Terminology Criteria for Adverse Events V3.0.

Stereotactic Body Radiation Therapy

All patients in this study were treated at a single institution in a similar fashion, using a supine in a customized vacuum bag chosen for its substantial support and immobilization (BlueBag, Elekta, Stockholm, Sweden). All simulations were done a four-dimensional CT systems (Discovery ST, GE Medical Systems, Milwaukee, WI; or Brilliance 64, Philips Healthcare, Andover, MA) while the patient was in the treatment position. Sets of 10 respiration phase datasets obtained during simulations, along with maximum intensity projections and averaged CT values, were transferred to a Pinnacle V8.0 treatment planning system (Philips Healthcare). For each patient, a structure was created that enveloped the motion of the tumor during respiration (the internal gross tumor volume or iGTV). The iGTV was expanded uniformly by 8 mm, and modified as needed by the treating physician to create the clinical target volume (CTV). The CTV was isotropically expanded by 3 mm to create the planning target volume (PTV). Our planning goal was to treat 95% of the PTV (delineated by the prescribed isodose line) to 50 Gy (to be delivered in 4 fractions). All treatments used 6-MV X-rays delivered in 6–9 treatment fields with heterogeneity corrections. Dynamic wedges were used but intensity-modulated radiation therapy was not. In-room CT images were acquired daily during the treatment with a cone beam CT scanner (21 iX, Varian Associates, Palo Alto, CA). In-house software was used to perform a 3D-3D match allowing setup up on soft tissue targets. Patient shifts were made using the digital couch readouts. For each patient, all four treatments were delivered in 1 week, generally on subsequent days. Each imaging and treatment session took from 25 to 45 minutes.

Evaluation of Chest Wall Dose

As noted in the previous paragraph, the Pinnacle V8.0 treatment planning system (Philips Healthcare) was used for dose calculations with heterogeneity correction for all cases. The chest wall was not manually contoured in the original treatment plans. Rather, the outer edge of each patient's skin/chest wall was automatically outlined; this volume was then subtracted from the total lung contour and the remaining volume was defined as the chest wall volume. Using this new chest wall volume, we calculated the absolute volumes of the chest wall receiving 10 Gy (V_{10}), 20 Gy (V_{20}), 30 Gy (V_{30}), 35 Gy (V_{35}), 40 Gy (V_{40}), or

50 Gy (V_{50}). These dose volumes were then compared with the development of chest pain and skin toxicity.

Statistical Analyses

Data were analyzed with Stata/SE 10.0 statistical software. Pearson's chi square test was used to assess measures of association in frequency tables. The equality of means for continuous variables was assessed with t tests. Logistic regression was used to predict the probability of occurrence of a dichotomous outcome by continuous or categorical independent variables. A p value of 0.05 or less was considered to indicate statistical significance. All statistical tests were based on a two-sided significance level.

RESULTS

Patient and Tumor Characteristics

We identified 265 patients (with 268 tumors) from a database of 360 patients who had been treated with thoracic SBRT for primary or metastatic lung disease between August 2004 and August 2008; the selected patients all had tumors within 2.5 cm of the chest wall. The median age of the 265 patients (142 men, 123 women) was 73 years (range, 43–95 years), and the median distance between the tumor and the chest wall was 0.59 cm (range, 0–2.47 cm) (Table 1). Median follow-up time for all patients was 10.3 months (range, 3–46.6 months), the median GTV was 8.17 mL (range, 0.57–198 mL), and the median PTV was 69 mL. More tumors were located in the posterior thorax (165, or 62%) than in the anterior thorax (103, or 38%).

Skin Toxicity

We found that 104 patients (39%) developed some form of skin toxicity as defined by the NCI-CTCAE V3.0. Logistic regression analysis indicated that tumor volume (defined as GTV, CTV, or PTV) correlated with the risk of developing skin toxicity (data not shown). Patients with a GTV of 8 mL or more were at an increased risk of developing skin reactions after treatment (odds ratio [OR], 1.78 [95% confidence interval {CI} 1.07–2.94], $P = 0.025$) (Table 2). The chest wall volumes receiving 20 Gy, 30 Gy, 35 Gy, or 40 Gy also correlated with the risk of skin reactions (Fig. 1). The volume of chest wall receiving at least 30 Gy (V_{30}) had the highest correlation with the likelihood of skin reactions (< 50 mL, 22% versus 51 mL, 44%) (OR 2.8, $P = 0.02$) (Fig. 2). There was a trend towards increased skin toxicity with posterior lesion compared to anterior lesion (OR 1.55, $P = 0.11$).

While all our patients were treated in a similar fashion using a Varian couch and stereotactic immobilization bag, we want to evaluate if our immobilization devices can contribute to an increased skin dose. To test this idea, we compared an unspoiled beam to a beam delivered through the treatment couch, which caused an increased skin dose of up to 49% for the Varian standard couch. The thickness of the stereotactic immobilization bag also affected skin dose, with a 1.5-cm-thick bag increasing the dose by 23%, a 4.5-cm-thick bag by 39%, and a 6-cm-thick bag by 41%¹².

Chest Wall Pain—Overall, 67 patients developed some form of chest wall pain, including 8 patients with rib fractures; the median time to onset of pain was 6 months (range, 0–11 months). Fourteen patients (5%) developed acute pain, and 45 patients (17%) developed chronic pain. Of the patients that developed chronic pain, that pain was grade 1 in 49% (22/45) and grade 2 or 3 in 51% (23/45). There was a correlation between the development of any chest wall pain and the volume of the chest wall receiving 30Gy (V_{30}) (Fig. 3). We compared patients with a V_{30} below or above 30 ml and found a 2.7% rate of chest wall pain versus an 18% rate in patients with a $V_{30} \geq 30$ ml (OR 8.19, $P = 0.04$) (Table 3).

According to logistic univariate regression analysis, of the multiple factors we studied, body mass index (BMI) was also a strong predictor for the development of chest pain. Of the 66 patients with a BMI of 29 or more, 18 (27%) cases developed chest wall pain after SBRT as compared with 26 (13%) of the 196 patients with a lower BMI, which results in an odd ratio (OR) = 2.45 [95% CI 1.24–4.84], $P = 0.01$. The median BMI for the 218 patients without pain was 26.3 vs. 28.3 for the 44 patients with pain ($P = 0.03$).

In patients with BMI ≥ 29 that developed chest wall pain, we could find no differences in the number of beams, or beam angles; only the presence of the diabetic state was correlated. Of the 41 patients with a BMI ≥ 29 , 22 had diabetes mellitus (defined by clinical diagnosis or had at least two random fasting plasma glucose values above 126 mg/dL); of those 22 patients, 11 (50%) developed chest wall pain after SBRT vs. only 3 of the 18 patients (16%) with BMI over 29 but no diagnosis of diabetes ($P = 0.028$). Chest wall pain grade 2 was present in 18% of diabetic patients compared with none of the nondiabetic patients ($P = 0.057$).

DISCUSSION

The use of SBRT as definitive therapy for patients with pulmonary tumors who are not candidates for surgery is increasing, in part because of preliminary evidence of high local control, reduced toxicity, and greater convenience for the patients^{4–6}. While there is great enthusiasm for this technology, the same high doses of focal radiation that provided excellent tumor control can also result in significant toxicity to proximal normal tissues. The findings from this study help to define the volume of chest wall that can be safely treated when SBRT is used for pulmonary lesions close to the chest wall. The risk of both skin changes and chest wall pain were correlated with the volume of chest wall receiving > 30 Gy. Additionally, patients with an elevated BMI may be at further risk of developing pain after SBRT for pulmonary lesions within 2.5cm of the chest wall.

Given our finding that the volume of chest wall irradiated correlated with chest wall toxicity, it is important to evaluate techniques for reducing chest wall dose when treating lesions within 2.5 cm of the chest wall. Several variables contribute to the chest wall dose, some of which we can influence and others (such as tumor location) we cannot. Of the factors we can influence, it seems that improved dosimetry can reduce the chest wall dose substantially by using a few simple techniques. Plans using 5–10 beams can serve to spread out the chest wall dose compared with plans with 4 or less beams, as has been reported by others as an increase in SBRT-related skin toxicity in plans using 3 or fewer beams¹⁰. Beam angle

optimization can also reduce the chest wall dose by using the lateral edge of the field to improve dose fall-off in the chest wall. The beam angles that are tangential to the chest wall should have increased weighting; use of the field-in-field technique can also help reduce hotspots in the chest wall. For tumors whose motion exceeds 1 cm, lung gating can offer further benefits in eliminating tumor motion, allowing for improved setup reproducibility and a reduced setup margin, which may also serve to reduce chest wall dose.

We considered both acute pain and chronic pain, reasoning that pain that developed less than 2 months after SBRT was likely attributable to local inflammation. In our experience acute pain occurring within that interval is well managed with anti-inflammatory drugs, but pain that develops later is often chronic and rarely responsive to nonsteroidal anti-inflammatory agents. Chronic pain likely represents injury to the intercostal nerve, which can be more challenging to treat, often requiring narcotics or neuropathic specific medications. While all of the patients in our series were treated with an identical fractionation (50 Gy in 4 fractions), this may not hold true for patients treated with other schemas. Since fraction size can have a far greater influence on tissues with low α/β ratio such as the skin and nerves¹³. Thus one might assume that more protracted courses of SBRT, such as the 70 Gy in 10 fractions regimen used by Xia et al.¹⁴, might produce less toxicity when used to treat lesions close to the chest wall. This supposition seems to be supported by a recent comparison of 50 Gy in 5 fractions vs. 60 Gy in 3 fractions that showed comparable local control but increased toxicity when only 3 fractions were used¹⁵.

Although the chest wall dose may be useful as a guideline for estimating how much chest wall can be treated safely, several other factors should be evaluated when attempting to reduce the chest wall toxicity. Factors that may contribute to chest wall pain include tumor invasion into the chest wall, tumor size, tumor motion, and rib fracture. Interestingly, we found that BMI was the strongest predictor of chest wall pain after SBRT, with patients whose BMI was 29 or more being at almost twice the risk of chronic chest wall pain compared with patients with lower BMI. We could not explain this finding by dosimetric factors, but we did find a statistical correlation with diabetes and the development of chest wall pain, which in our series more than tripled the risk of developing chest pain in patients with BMI ≥ 29 after SBRT. Neuropathy is a classic finding in uncontrolled diabetes, but exactly why high glucose levels are toxic to nerves is still being investigated. Most reports suggest that this is a multifactorial process, with contributing biochemical mechanisms including the polyol pathway, advanced glycation end products, and oxidative stress^{16–18}. Moving forward we might speculate that enhanced glucose control both during and after SBRT may also serve as an effective way of reducing morbidity after SBRT, in this patient population.

There are several limitations to this work, first among them being retrospective, with all of the inherent biases and flaws. Second, our findings of skin toxicity were ascertained from medical record review, which can be subjective and vary among different clinicians. Also, as this work was based on a planning system that includes tissue inhomogeneity corrections, clinicians who do not use such systems, will find that their isodose distributions are much tighter, and as such, their estimated V_{30} to the chest wall will likely be underestimated.

Lastly, while our mean follow up was 11 months, outcomes might be slightly different with longer follow up as some cases of rib fracture have been seen 2–3 years after treatment.

In conclusion, the volume of chest wall receiving 30Gy may prove useful as a guideline for estimating the likelihood of chest wall toxicity. However, lifestyle factors such as obesity and diabetes also correlate with toxicity and may be harder to influence. We plan to prospectively use the V30Gy chest wall volume in a randomized phase III trial of SBRT vs. surgery for early-stage lung cancer in which the fractionation scheme (50 Gy in 4 fractions) is the same as that used here. Being aware of the volume of chest wall being treated and taking steps to reduce it, is the first step in reducing complications when performing SBRT close the chest wall. Additionally, we should perhaps be more conservative when treating obese patients, particularly those that also suffer from diabetes mellitus.

Acknowledgments

This work was made possible through the generous support of the MD Anderson Cancer Center, Thoracic Radiation Oncology program, by the family of Mr. M. Adnan Hamed.

Research support: None

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Fig. 1.

Skin toxicity after thoracic SBRT for pulmonary lesions within 2.5cm of the chest wall according to chest-wall volumes exposed to 20 Gy (V_{20}), 30 Gy (V_{30}), 35 Gy (V_{35}), or 40 Gy (V_{40}).

Fig. 2.

Percentages of patients experiencing skin toxicity after thoracic SBRT for pulmonary lesions within 2.5 cm of the chest wall. In patients with a V_{30} of the chest wall <50ml there was a 22% rate of skin toxicity which increased to 44% in patients with a V_{30} ≥ 50ml, $p = 0.002$.

Fig. 3.

Percentages of patients experiencing chest wall pain after thoracic SBRT for lesions within 2.5 cm of the chest wall according to chest-wall. In patients with a V_{30} of the chest wall <30ml there was a 2.7% rate of skin toxicity which increased to 18% in patients with a V_{30} 30ml, $p = 0.004$.

Table 1

Patient characteristics and toxicity after thoracic SBRT for pulmonary lesions in 268 tumors

Characteristic	Value
Median age (y)	74 (range, 43–95)
Sex (<i>n</i>)	
M	145
F	123
Median tumor distance from chest wall (cm)	0.59 (range, 9–2.47)
Chronic pain grade (<i>n</i>)	
0	223
1	22
2	21
3	1
4	1
Rib fracture (<i>n</i>)	8
Time to onset of pain (mo)	6 (range, 0–11)
Acute pain grade (<i>n</i>)	
0	254
1	8
2	6
3	0
4	0
Skin toxicity grade (<i>n</i>)	
0	164
1	78
2	18
3	8

Abbreviation: SBRT = stereotactic body radiation therapy.

Table 2

Variables influencing skin toxicity after SBRT in 268 tumors

Characteristic	No. of tumors (%)	Grade 0	Skin toxicity		Logistic regression	
			Grade 1	Grade 2	Odds ratio (95% CI)	p value
Age (y)						
<73	127 (47)	82	34	11	1.24 (0.76–2.03)	0.39
73	141 (53)	82	44	15		
Sex						
M	145 (54)	91	37	17	1.24 (0.76–2.03)	0.39
F	123 (46)	73	41	9		
Tumor location						
Anterior	103 (38)	69	27	7	1.55 (0.91–2.62)	0.11
Posterior	165 (62)	95	51	19		
Tumor distance from chest wall (cm)						
2	249 (93)	151	75	23	1.41 (0.52–3.82)	0.504
>2	19 (7)	13	3	3		
Gross tumor volume (mL)						
8	128 (48)	87	28	13	1.78 (1.08–2.94)	0.025
>8	136 (51)	74	50	12		
Unknown	4 (1)	3	0	1		
Prior thoracic radiation						
Yes	65 (24)	45	16	4	0.63 (0.35–1.14)	0.13
No	203 (76)	119	62	22		
Chest wall V ₃₀ (mL)						
<50	67 (25)	52	10	5	2.8 (1.45–5.22)	0.002
51	201 (75)	112	68	21		

Abbreviations: SBRT = stereotactic body radiation therapy; CI = confidence interval; V₃₀ = absolute volume of chest wall receiving 30 Gy.

Table 3

Variables influencing chest wall pain after SBRT in 268 tumors

Characteristic	No. of tumors (%)	Grade 0	Chronic pain		Logistic regression	
			Grade 1	Grade 2	Odds ratio (95% CI)	p value
Age (y)						
<73	127 (47)	107	8	12	0.88 (0.46–1.67)	0.70
73	141 (53)	116	14	11		
Sex						
M	145 (54)	122	12	11	0.91 (0.48–1.75)	0.79
F	123 (46)	101	10	12		
Tumor location						
Anterior	103 (38)	87	9	8	1.06 (0.54–2.08)	0.86
Posterior	165 (62)	136	13	15		
Gross tumor volume (mL)						
8	128 (48)	111	5	12	1.54 (0.79–3.00)	0.20
>8	136 (51)	110	17	9		
Unknown	4 (1)	2	0	2		
Chest wall V ₃₀ (mL)						
<30	36 (13)	35	1	0		
31	231 (86)	188	21	23	8.19 (1.09–61.42)	0.04
Body mass index						
<29	196 (73)	170	13	13	2.45 (1.24–4.84)	0.01
29	66 (25)	48	9	9		
Unknown	6 (2)	5	0	1		

Abbreviations: SBRT = stereotactic body radiation therapy; CI = confidence interval; V₃₀ = absolute volume of chest wall receiving 30 Gy.