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CLINICAL INVESTIGATION **Lung**

CHEST WALL TOXICITY AFTER STEREOTACTIC BODY RADIOTHERAPY FOR MALIGNANT LESIONS OF THE LUNG AND LIVER

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Purpose: To quantify the frequency of rib fracture and chest wall (CW) pain and identify the dose–volume parameters that predict CW toxicity after stereotactic body radiotherapy (SBRT).

Methods and Materials: The records of patients treated with SBRT between 2000 and 2008 were reviewed, and toxicity was scored according to Common Terminology Criteria for Adverse Events v3.0 for pain and rib fracture. Dosimetric data for CW and rib were analyzed and related to the frequency of toxicity. The risks of CW toxicity were then further characterized according to the median effective concentration (EC_{50}) dose–response model.

Results: A total of 347 lesions were treated with a median follow-up of 19 months. Frequency of Grade I and higher CW pain and/or fracture for CW vs. non-CW lesions was 21% vs. 4%, respectively ($p < 0.0001$). A dose of 50 Gy was the cutoff for maximum dose (Dmax) to CW and rib above which there was a significant increase in the frequency of any grade pain and fracture ($p = 0.03$ and $p = 0.025$, respectively). Volume of CW receiving 15 Gy - 40 Gy was highly predictive of toxicity ($R^2 > 0.9$). According to the EC_{50} model, 5 cc and 15 cc of CW receiving 40 Gy predict a 10% and 30% risk of CW toxicity, respectively.

Conclusion: Adequate tumor coverage remains the primary objective when treating lung or liver lesions with SBRT. To minimize toxicity when treating lesions in close proximity to the CW, Dmax of the CW and/or ribs should remain <50 Gy, and <5 cc of CW should receive ≥40 Gy.

Chest wall, rib fracture, SBRT.

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is now a well-established modality for the treatment of early stage, inoperable, non–small-cell lung cancer with documented rates of local control as high as 98% at 3 years (1, 2). The utility of SBRT for treating metastatic pulmonary and hepatic lesions has also been reported with equally impressive rates of local control (3, 4). In 2000, a program investigating SBRT was initiated at Indiana University School of Medicine and its associated Veterans Administration Medical Center (VAMC), and as of 2009, more than 300 patients have been treated. In line with our previous publications exploring toxicities attributable to this modality, we now specifically address the issue of chest wall (CW) toxicity (5, 6). This report details our experience at Indiana University, and attempts to provide reasonable guidelines aimed at reducing the risk of CW toxicity when treating peripheral lesions with SBRT.

METHODS AND MATERIALS

The records of all patients treated with SBRT at the Indiana University Department of Radiation Oncology and the Richard L. Roudebush VAMC from 2000 to 2008 were reviewed. All patients were treated with SBRT using strictly defined criteria, which we have previously described (7, 8). Patients received two to five fractions using noncoplanar field arrangements. In general, six to 12 fields were designed to treat the CT-defined gross tumor volume (GTV) with an axial expansion of 0.5 cm and superior–inferior expansion of 1 cm to define the planning target volume (PTV). Patients were immobilized in the Stereotactic Body Frame (Elekta Oncology, Norcross, GA) including a rigid three-sided frame with vacuum pillow as well as abdominal compression for limitation of respiratory motion of the target (7, 8). Virtually all treatments were prescribed to the 80% isodose line covering the surface of the PTV. Equivalent path length heterogeneity corrections via the Anisotropic Analytic Algorithm (Varian Medical Systems) were used for approximately 30% of the treatment plans.

Patients returned for follow-up 1 month after the completion of treatment and then every 3 months for 2 years, and every 6 months

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	Grade				
Short Name	**1**	**2**	**3**	**4**	**5**
Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death

Fig. 1. Scale used for grading of chest wall (CW) pain and rib fracture, as per Common Terminology Criteria for Adverse Events v3.0 (Ref. 9).

thereafter. A chest x-ray or chest computed tomogram was typically obtained before the appointment. At each visit, a complete physical examination was performed including visual inspection and palpation of the chest wall. All incidences of CW pain and rib fracture were recorded, and symptoms were retrospectively scored according to Common Terminology Criteria for Adverse Events v3.0 (9) (Fig. 1). Dates that patients first experienced CW toxicity were recorded and used for analysis.

All lesions were then categorized as either non-CW or CW, defined as lesions in which at least the 50% isodose line or greater abutted any aspect of the adjacent CW. The relevant treatment and demographic data for CW and non-CW lesions was compared using Mann–Whitney tests. The frequency of CW toxicity among these two groups was then analyzed via the Chi-square test. Statistics were not adjusted for the presence of multiple lesions per patient.

Because of changes in departmental treatment planning software, CW and rib volumes were able to be retrospectively contoured for 79 of 203 CW lesions. As a result, data analysis regarding actual dose delivered to the CW and ribs was limited to these lesions (heterogeneity corrections used for 75% [n = 59] of these 79 lesions). Chest wall was contoured as a 3-cm outward expansion from the ipsilateral lung or liver contour, inclusive of both bone and soft tissue, and each rib was individually contoured regardless of the presence or absence of toxicity. Maximum dose (Dmax) delivered to the CW and ribs was recorded, and the significance of Dmax to the development of toxicity was analyzed via the Fisher exact test.

The absolute volume of CW and rib receiving 5 to 60 Gy in 5-Gy increments was recorded. Utilizing the process first described by Dunlap *et al.* (10), the risk of CW toxicity as a function of the absolute CW volume irradiated was fitted to the median effective concentration (EC_{50}) dose–response model:

$$Y = TOP / \left(1 + 10\hat{}[(\log EC50 - X) * HillSlope]\right) \quad (1)$$

where Y is the actual risk of CW toxicity, expressed as a percentage of the maximal risk; TOP is the maximal risk (the minimal risk is zero); Hillslope is the steepness of the curve; and logEC50 represents the irradiated CW volume in which 50% of the maximal risk is observed. The model was applied to the CW volume receiving ≥15 Gy, ≥20 Gy, ≥30 Gy, ≥40 Gy, and ≥50 Gy. Linear regression analysis was performed to correlate the mathematical model for CW toxicity with the observed risk, as determined by the data.

Table 1. Characteristics of patients and lesions treated with stereotactic body radiation therapy between 2000 and 2008

Characteristic	All lesions (n = 347)	Non-CW lesions (n = 144)	CW lesions (n = 203)	p
Age (y)	71 (25–100)	71 (41–93)	72 (25–100)	NS
Male	200	84	116	—
Female	147	60	87	—
Liver lesions	67	24	43	—
Lung lesions	280	120	160	—
GTV (cc)	14 (1-225)	11 (1–112)	15 (1–225)	0.0143
No. of fractions	3 (2-5)	3 (3–5)	3 (2–5)	NS
Dose per fraction (Gy)	18 (6–24)	20 (6–24)	18 (8–24)	NS
Total Dose (Gy)	54 (18–72)	60 (18–72)	54 (20–72)	NS
BED (Gy, α/β = 10)	151 (29–245)	180 (29–245)	151 (40–245)	
Treatment duration (days)	8 (3–35)	8 (4–29)	8 (3–35)	NS
No. of beams	9 (5–12)	9 (5–12)	9 (5–12)	NS
Time to toxicity (mo)	9 (1–50)	14 (6–50)	8 (1–43)	0.0434
Follow-up (mo)	19 (1–100)	24 (1–100)	15 (1–89)	0.0018
% Chest wall toxicity	14% (47)	4% (5)	21% (42)	<0.0001
% Chest wall pain	11% (36)	3% (4)	16% (32)	<0.0001
% Rib fracture	5% (18)	1% (1)	8% (17)	0.0015
Toxicity grade				
I	27	3	24	
II	24	2	22	
III	2	0	2	
IV	1	0	1	

Abbreviations: BED = biologic effective dose; CW = chest wall; NS = not significant ($p > 0.05$).

Table 2. Summary of all chest wall lesions in study patients

Characteristic	CW lesions with toxicity (n = 42)	CW lesions without toxicity (n = 161)	p
Age (y)	70 (37–94)	72 (24–100)	<0.001
Male	24	95	—
Female	18	66	—
Lung lesions	39	121	—
Liver lesions	3	40	—
GTV size (cc)	15 (1–111)	15 (1–225)	NS
No. of fractions	3 (3–5)	3 (2–5)	NS
Dose per fraction (Gy)	19 (10–24)	16 (8–24)	0.0027
Total dose (Gy)	58 (48–72)	48 (20–72)	0.0008
BED (Gy, α/β = 10)	151 (106–245)	125 (40 -245)	
Treatment duration (days)	8 (6–31)	8 (3–35)	NS
No. of beams	9 (7–12)	9 (5–12)	NS
Follow-Up (mo)	17.5 (1–89)	14.5 (1–89)	NS

Abbreviations: BED = biologic effective dose; CW = chest wall; GTV = gross tumor volume; NS = not significant ($p > 0.05$).

RESULTS

Entire SBRT cohort

A total of 347 lesions were treated in 311 patients. Demographic and treatment characteristics for the entire population are detailed in Table 1. Median follow-up was 19 months. There were no significant differences between CW and non-CW lesions with the exception of GTV size, time to toxicity, and length of follow-up.

The crude frequency of CW toxicity of any grade among the 347 lesions was 14% (47 of 347), with 36 episodes of CW pain and 18 rib fractures. In 23 of 47 instances of CW toxicity, prescription pain relief was required, either with narcotics, gabapentin, or COX-2 inhibitors. For CW lesions, the frequency of rib fracture, CW pain, or either was 8%, 16%, and 21%, respectively, compared with 1%, 3%, and 4%, respectively, for non-CW lesions ($p < 0.0001$, $p < 0.0001$, and $p = 0.0015$ respectively). No episode of Grade III/IV CW toxicity occurred in non-CW lesions. The duration of toxicity was unable to be accurately assessed through retrospective chart review.

The 42 CW lesions with any grade toxicity were then compared to the 161 CW lesions without toxicity (Table 2). Both dose per fraction (1,900 cGy vs. 1,600 cGy) and total dose (5,800 cGy vs. 4,800 cGy) were significantly larger for CW lesions with toxicity compared to those without (p = 0.0027 and 0.0008). Median follow-up was 3 months shorter for lesions without toxicity (14.5 months vs. 17.5 months), but this was not statistically significant ($p = 0.2301$).

Subset of CW lesions with CW and rib contours

For the 79 CW lesions (53 lung and 26 liver) with full dose–volume histogram (DVH) data available, treatment and lesion characteristics are available in Table 3. Among the 18 lesions with any grade CW toxicity, the median Dmax CW and Dmax rib was 6,400 cGy, compared with 5,700 cGy and 5,200 cGy, respectively, among the 61 lesions that did not develop CW toxicity (p = 0.001 and 0.006). A dose of 50 Gy was the cutoff for Dmax CW and Dmax rib above which there was a significant increase in the frequency of any grade CW pain and rib fracture, respectively ($p = 0.03$ and $p = 0.025$).

The volume of CW receiving 25 Gy to 60 Gy was significantly greater for lesions with CW toxicity vs. those without toxicity. For the volume of CW receiving 15 Gy, 20 Gy, 30 Gy, and 40 Gy, there was excellent correlation between the observed risk of any grade CW toxicity and the risk of toxicity as predicted by the EC_{50} model (Table 4). As seen in Fig. 2, there was not a specific threshold volume at which

Table 3. Subset of chest wall lesions included in the EC_{50} dose–response model

Characteristic	CW lesions (n = 79)	Lesions with toxicity (n = 18)	Lesions without toxicity (n = 61)	P
Age (y)	70 (24–93)	70 (46–89)	70 (24–92)	NS
Male	51	12	39	—
Female	28	6	22	—
Lung lesions	53	15	38	—
Liver lesions	26	3	23	—
GTV size (cc)	14 (1–150)	15 (4.5–111)	14 (1–150)	0.017
Distance of GTV from CW (cm)	0.14 (0–2.21)	0.10 (0–1.40)	0.20 (0–2.21)	NS
No. of fractions	3 (2–5)	3 (3–5)	3 (2–5)	NS
Dose per fraction (Gy)	16 (8–20)	18 (10–20)	14 (8–20)	0.025
Total dose (Gy)	48 (20–60)	54 (48–60)	48 (20–60)	0.008
BED (Gy, α/β = 10)	125 (40–180)	151 (106–180)	106 (40–180)	
Treatment duration (days)	9 (3–35)	8 (7–31)	10 (3–35)	NS
No. of beams	10 (6–12)	10 (7–11)	10 (6–12)	NS
Time to toxicity (mo)	7	7	N/A	—
Follow-up (mo)	13 (1–49)	15 (1–34)	13 (1–49)	NS
DMax chest wall (Gy)	60 (25–76)	64 (55–76)	57 (25–74)	0.001
BED (Gy, α/β = 3)	373 (132–717)	500 (391–717)	356 (132–709)	
DMax rib (Gy)	58 (13–75)	64 (50–75)	52 (13–75)	0.0006
BED (Gy, α/β = 3)	356 (32–696)	493 (262–696)	339 (32–696)	

Abbreviations: BED = biologic effective dose; DMax = maximum dose delivered to chest wall/rib; EC_{50} = median effective concentation; GTV = gross tumor volume; N/A = not applicable; NS = not significant ($p > 0.05$).

Table 4. EC_{50} dose–response data for study patients

Dose to CW (Gy)	$LogEC_{50}$	Maximal risk	Correlation between expected and observed results (R^2)
15	233.2	0.56	0.9009
20	118.7	0.54	0.9173
30	26.7	0.42	0.9542
40	10.8	0.43	0.9661
50	11.5	0.60	0.8349

Abbreviations: CW = chest wall; EC_{50} = median effective concentration.

point one observes a dramatic increase in the risk of CW toxicity, but rather a gradual increase in risk as the volume receiving a particular dose increased. For a clinically relevant 30% risk of any grade CW toxicity, the EC_{50} model would limit the volume of CW receiving 15 Gy, 20 Gy, 30 Gy, and 40 Gy to less than 240 cc, 130 cc, 40 cc, and 15 cc, respectively (Fig. 3).

DISCUSSION

Despite the increasing popularity of SBRT, concern persists regarding late normal tissue toxicity. Such concern has been bolstered by reports of increased frequency of rib fracture and chest wall pain after stereotactic treatment of peripherally located lesions when compared to conventionally fractionated therapy (10–12).

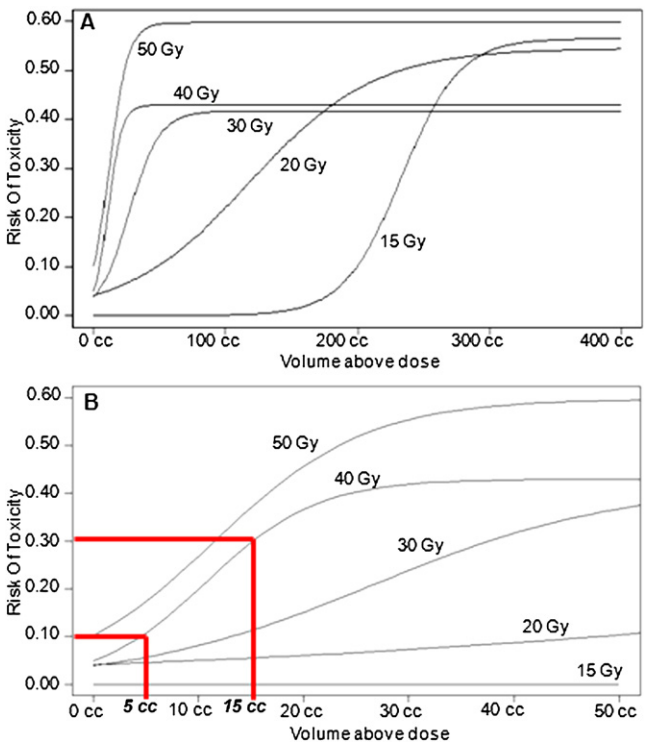

Fig. 2. Volume–risk analysis based on median effective dose–response model for development of any severity chest wall (CW) toxicity at designated dose levels: (a) risk for 0 to 400 cc and (b) 0 to 50 cc of CW receiving particular dose.

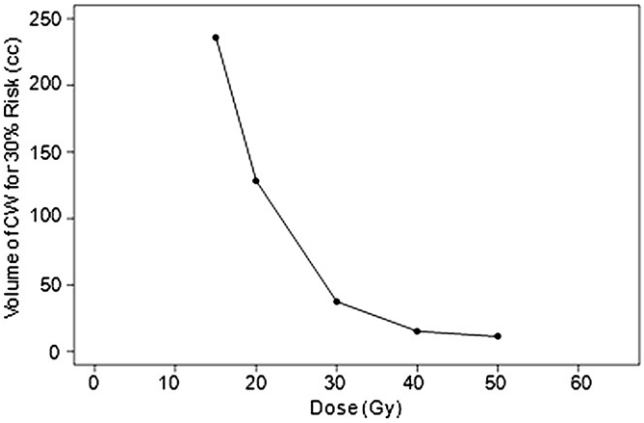

Fig. 3. Dose–volume relationship for a 30% risk of chest wall toxicity of any severity.

Historical series consisting mainly of breast cancer patients report an incidence of CW pain and/or rib fracture of 1% to 6% after conventionally fractionated therapy. Pierce *et al.* observed a 2% incidence of rib fracture among 1,624 early-stage breast cancer patients after conventional radiation therapy (13). With a median follow-up of 79 months, the crude incidence was even lower (0.4%) for patients who received treatment with 6 MV photons compared with 2% among patients treated with 4 MV photons. Overgaard *et al.* reported a 6% incidence of spontaneous rib fracture after conventionally fractionated RT for breast cancer, with rates as high as 19% for more hypofractionated treatment (14).

Comparing these series with the overall body of literature regarding SBRT, the incidence of CW toxicity is not dissimilar. Nagata *et al.* reported on a series of 45 patients with Stage I non–small-cell lung cancer who all received 48 Gy in 4 fractions via SBRT. With a median follow-up of 30 months, the authors did not cite a single incidence of CW toxicity (2). Similarly, with a median follow-up of 31 months, Videtic *et al.* reported one case of Grade 2 chest wall pain among 28 pulmonary lesions treated with SBRT (15).

However, when looking specifically at lesions in close proximity to the chest wall, the rates of CW pain and rib fracture rise dramatically. Voroney et al., reporting on a series of 42 peripherally located lung lesions, cite a 21% and 26% incidence of rib fracture and CW pain respectively, with a median time to occurrence of 17 months (12). With a median follow-up of 11 months, Dunlap *et al.* report 17 cases of Grade III CW pain among 60 patients receiving SBRT for primary or oligometastatic lung malignancy (10). The median distance between GTV and chest wall was 0.15 cm, and the median dose schedule was three fractions of 20 Gy per fraction.

Within the past year, various institutions have attempted to model the risk of CW toxicity after SBRT. Petterssen *et al.* performed a dose–volume analysis on a population of 33 patients with non–small-cell lung cancer after SBRT with a median follow-up of 29 months and 13 rib fractures (11). The authors predict a 5% risk of rib fracture for 2 cc of rib receiving 27 Gy and a 50% chance of fracture when 2 cc of rib

receives 50 Gy. Dunlap *et al*., the first to use the EC_{50} model, predict a 30% risk of severe CW toxicity when 30 cc of CW receives 30 Gy (10).

In our series of 347 lesions, the rates of CW toxicity of any severity for CW and non-CW lesions, 21% and 3.5% respectively, are similar to those reported from other institutions. We observed 3 Grade III/IV toxicities for 203 CW lesions, and 10% of all CW lesions required prescription pain relief. Among the subset of 79 CW lesions for which we could measure the distance between parietal pleura and GTV, the median distance was 0.14 cm, validating the criteria chosen at the outset for designation of a lesion as ''chest wall.''

Applying the EC_{50} model to our data, we did not observe a threshold dose or volume above which one is assured of developing CW toxicity of any grade, but rather observed a gradual increase in risk as dose and volume receiving said dose increases. Volume of CW receiving 15 to 40 Gy showed excellent correlation with expected risk as per the EC_{50} model. Based on this model, we predict a 10% risk of Grade I and greater CW toxicity when 15 cc and 5 cc of CW receives 30 Gy and 40 Gy, respectively. Similarly, we predict a 30% risk of toxicity when 40 cc and 15 cc of CW receives 30 Gy and 40 Gy, respectively. We are not able to specifically address the risk of severe toxicity secondary to the low incidence of Grade III/IV toxicity observed. Although Dmax of 50 Gy is by no means a threshold beyond which one is guaranteed of developing CW toxicity, we did observe a significant increase in both pain and fracture when Dmax of CW and Rib was above this dose. These dose–volume guidelines were not appreciably different when specifically analyzing only those lesions for which heterogeneity corrections were performed.

In addition to providing the above dosimetric guidelines, our data further elucidate the etiology of CW toxicity after SBRT. In all, 61% (11 of 18) of rib fractures were asymptomatic, revealed solely through routine imaging, and only 19% (7 of 36) of all episodes of CW pain coincided with a documented rib fracture. These findings suggest that peripheral nerve damage, rather than direct rib injury, is the primary mechanism responsible for CW discomfort following SBRT. This assertion is supported by the intraoperative radiotherapy research by Kinsella *et al*., who found peripheral nerve injury to be the dose-limiting toxicity when attempting to deliver large doses of radiation in a single fraction (16).

There are some limitations to our study. Although the median follow-up is nearly twice as long as the median time to toxicity, 19 months of follow-up may be too short to make definitive statements regarding late toxicities. Indeed, Johansson *et al*. have shown that at least 5 years, if not longer, are required to fully assess late toxicity after radiation therapy involving the chest wall (17). Another possible shortcoming is the fact that our cohort contains a variety of fractionation schemes, some with and some without heterogeneity corrections, which may make it difficult to interpret the dose–volume guidelines suggested herein. However, SBRT is performed throughout the world with a variety of fractionation schemes, and a heterogeneous cohort may in fact be most appropriate for providing generalized guidelines to practitioners as a whole.

Nonetheless, we feel that this study provides a valuable contribution to the body of knowledge regarding toxicities attributable to SBRT. Although these findings should be kept in mind, proximity to the chest wall, in and of itself, should not serve as justification for avoiding SBRT or underdosing the target. Despite observing Grade I and above toxicity for 21% of the 207 CW lesions treated, only three adverse events qualified as Grade III or Grade IV. Although treatment-related toxicity should be avoided if at all possible, one must weigh the clinical significance of Grade I/II toxicity against possible treatment failure. With proper modification of beam angles and dose spillage, CW lesions can be both safely and effectively treated.

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