

Clinical Investigation

Factors Associated with Chest Wall Toxicity After Accelerated Partial Breast Irradiation Using High-dose-Rate Brachytherapy

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Summary

This analysis evaluated the dose-volume relationship between accelerated partial breast irradiation using both single- and multi-lumen brachytherapy and subsequent chest wall pain. In this retrospective analysis a direct correlation was demonstrated between total dose received and volume of rib irradiated. This reinforces the need to keep the volume of rib irradiated and the maximum dose received by the chest wall as low as reasonably achievable.

Purpose: The purpose of this analysis was to evaluate dose-volume relationships associated with a higher probability for developing chest wall toxicity (pain) after accelerated partial breast irradiation (APBI) by using both single-lumen and multilumen brachytherapy.

Methods and Materials: Rib dose data were available for 89 patients treated with APBI and were correlated with the development of chest wall/rib pain at any point after treatment. Ribs were contoured on computed tomography planning scans, and rib dose-volume histograms (DVH) along with histograms for other structures were constructed. Rib DVH data for all patients were sampled at all volumes ≥ 0.008 cubic centimeter (cc) (for maximum dose related to pain) and at volumes of 0.5, 1, 2, and 3 cc for analysis. Rib pain was evaluated at each follow-up visit. Patient responses were marked as yes or no. No attempt was made to grade responses. Eighty-nine responses were available for this analysis.

Results: Nineteen patients (21.3%) complained of transient chest wall/rib pain at any point in follow-up. Analysis showed a direct correlation between total dose received and volume of rib irradiated with the probability of developing rib/chest wall pain at any point after follow-up. The median maximum dose at volumes ≥ 0.008 cc of rib in patients who experienced chest wall pain was 132% of the prescribed dose versus 95% of the prescribed dose in those patients who did not experience pain ($p = 0.0035$).

Conclusions: Although the incidence of chest wall/rib pain is quite low with APBI brachytherapy, attempts should be made to keep the volume of rib irradiated at a minimum and the maximum dose received by the chest wall as low as reasonably achievable. © 2011 Elsevier Inc.

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Introduction

Accelerated partial breast irradiation (APBI) continues to be explored as a method to deliver adjuvant radiation therapy (RT) after lumpectomy for selected patients with early-stage breast cancer treated with breast-conserving therapy (1). Currently, there are several methods for administering APBI, including interstitial brachytherapy and balloon-based brachytherapy and other methods using newer intracavitary devices such as strut-adjusted volume implant (SAVI), three-dimensional conformal external beam irradiation therapy (3D-CRT), and single-fraction intraoperative RT (2). Depending upon the APBI technique used, new and unique types of short- and long-term toxicities have been reported. Recently, there have been isolated reports of potential chest wall/rib toxicity developing as a consequence of this treatment approach using both 3D-CRT and balloon-based brachytherapy (3–7). These studies suggest that there may be a relationship between these hypofractionated doses and a slightly higher rate of chest wall/rib toxicity (e.g., pain and/or fracture) than previously reported with standard doses of RT delivered using conventional fractionation schemes (8). This report attempts to define a relationship between the dose received by the chest wall (ribs) and the subsequent development of toxicity (pain at any point after treatment) secondary to the use of intracavitary brachytherapy devices to deliver APBI.

Methods and Materials

Since March of 2004, over 800 patients have been treated with APBI at our institution. Rib dose data (dosimetric analyses) were available for 89 patients (11%) and correlated with the development of chest wall/rib pain at any point after treatment. These same 89 patients (Table 1) (unselected) were evaluated for the development of chest wall/rib pain at some point in their follow-up examinations. This retrospective analysis was given an exempt determination, granted under 45 CFR 46 101(b) (4) by the Western Institutional Review Board.

Our treatment technique has been previously reported (9). All patients received 34 Gy in 10 fractions delivered over 5 days, using either a single lumen or multilumen device. Dose-volume constraints generally followed National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B39/Radiation Therapy Oncology Group (RTOG) protocol 0413 guidelines. Patients were followed at 3- to 6-month intervals by either their treating radiation oncologist or surgeon. However, the presence or absence of chest wall/rib pain (as evaluated in this analysis) was assessed by only one of the authors (S.B.).

Ribs were contoured on computed tomography (CT) planning scans for patients, and rib dose-volume histograms (DVH) along with histograms for other structures were exported into a text file. Data consisting of device type and DVH were stored in a database. To analyze rib dose, rib DVH data for all patients were sampled for certain volumes of interest. These volumes were at all volumes ≥ 0.008 cc for maximum dose related to pain and at 0.5, 1, 2, and 3 cc. At the time of

follow-up, patients were asked about any skin changes, breast tenderness, and chest wall/rib pain. Patient responses to chest wall/rib pain were marked as yes or no, with no attempt made to grade the responses. Regardless of their answers, a physical examination was performed, during which the area under the cavity was palpated for tenderness. If this was not possible and the surgical cavity was shallow, then the chest wall was palpated through the cavity.

Statistical analysis

Chest wall doses were analyzed for their relationship to the development of chest wall pain by using logistic regression techniques. Pain occurrence yes/no was considered the response variable, and the maximum dose for each patient at rib volumes ≥ 0.008 cc or the dose received at selected volumes (0.5, 1.0, 2.0, and 3.0 cc) was the explanatory variable. Maximum likelihood parameter estimates were calculated and tested for significance using Wald chi-square tests. Odds ratios for each effect parameter were estimated by exponentiating the parameter estimate. At selected rib volumes, doses were calculated from each model to predict different probabilities of a pain response.

Results

At any point after their treatment, a total of 19 patients (21.3%) complained of chest wall/rib pain (Table 2). The presence or absence of rib fractures was not documented. The maximum dose received by the rib at a volume of ≥ 0.008 cc was evaluated in all 89 cases (Table 2). In patients who experienced any chest wall/rib pain at any point in their follow-up, the median maximum dose received by the rib (at volumes ≥ 0.008 cc) was 132% of the prescribed dose (PD) versus 95% of the PD in patients who did not complain of pain. This difference was statistically significant ($p = 0.0035$; odds ratio = 1.007; odds ratio confidence interval = 1.002–1.012). At the selected volumes (0.5, 1, 2, and 3 cc), dose was a significant predictor of pain. Because more dose was required at lower volumes to achieve the same probability of pain, both components were important to understand the probability.

A logistic regression analysis was carried out in order to look for a correlation between dose and volume of the rib irradiated and the probability of developing chest wall/rib pain. There was a correlation. This analysis should be taken with caution considering the limitations of the data.

Discussion

In this analysis, we correlated the risk of developing rib/chest wall pain with the actual dose administered in 89 patients treated at our institution with APBI, using high-dose-rate (HDR) intracavitary brachytherapy. Although the number of events is small, there appears to be a direct relationship between an increasing dose of RT received and volume irradiated of the chest wall/ribs with an increasing risk of developing pain. Preliminary data suggest that the maximum dose should be kept as low as possible, preferably

Table 1 Patient characteristics

Patient characteristics	Measurement
Age range	42–84
No. of patients with clinical stage	
T1a	6
T1b	20
T1c	26
T1S	28
T1mic	1
T2	8
Clinical N stage	
N0	89
Clinical M stage	89
M0	
Stage 0	28
Stage I	53
Stage IIA	8
Chemotherapy after APBI	22
No chemotherapy	67
Median follow-up	6.6 months
Range of follow-up	0.46–43.22

less than 132% of PD for a volume of 0.008 cc (see Table 2 for suggested maximum doses for 0.5, 1, 2, and 3 cc). Fortunately, the reported overall risk of experiencing rib toxicity appears to be quite low. Nonetheless, these data suggest that attempts should be made to further decrease the dose received by these structures whenever reasonably possible.

Historical perspective

Radiation-induced osseous toxicity resulting in rib fracture and/or chest wall pain is a well-recognized, although rare, potential

complication of RT given as part of breast-conserving therapy for early-stage breast cancer. In a comprehensive analysis of 1,117 patients treated between 1968 and 1985 at the Joint Center for Radiation Therapy (Harvard Medical School, Boston, MA), Pierce et al. (10) found a 1.8% incidence of rib fracture after external beam RT. The rate of fracture was higher in patients treated with lower energy irradiation (4-MV versus a 6- or 8-MV linear accelerator; 2.2% versus 0.4%, respectively). An additional series from MD Anderson Cancer Center (Houston, TX) identified an even lower rate of radiation-related rib fracture (1%) by using more contemporary techniques (Table 3). Increasing conformality using modern external beam radiation delivery techniques (e.g., CT planning and application of intensity modulated RT) most likely further diminish the risk of radiation-induced rib fracture.

Data from the management of patients with head and neck cancer indicate that the rate of osseous toxicity is positively related to dose rate, volume of tissue irradiated, and dose per fraction of RT. Based upon all the above information, APBI using HDR intracavitary or interstitial brachytherapy may theoretically lead to a higher risk of rib fracture/toxicity than has traditionally been seen and/or predicted with conventional external beam treatment (e.g., standard fractionation schedules). This hypothesis is related to the APBI technique's increased dose per fraction and accelerated delivery schedule. In addition, lower energy (3) photons from an iridium-192 source (380 KeV, average) have higher linear energy transfer than megavoltage photons and thus can impart a greater relative biological effect (RBE; the same effect may help explain differences in rib fracture rates in the Joint Center experience).

Although the development of rib fracture does not always occur in patients who experience chest wall pain, it is our belief that factors that may precipitate each event may be similar. Therefore, investigating variables associated with each outcome should prove beneficial in reducing the incidence of each of these toxicities. Brashears et al. (3) previously reported the theoretical

Table 2 Maximum doses for 0.5-, 1-, 2-, and 3-cc volumes of ribs

Parameter	Statistic	Number of Patients with No pain	Number of Patients with Pain	Odds ratio	Odds ratio CI	<i>p</i> value
Maximum dose at volumes ≥ 0.5 cc	N	70	19	1.009	1.003–1.016	0.0039
	Mean	233.7	323.6			
	Std	108.83	97.82			
	Median	256.5	355.0			
	Min, Max	22.0, 462.0	68.0, 485.0			
Maximum dose at volumes ≥ 1.0 cc	N	70	19	1.010	1.003–1.017	0.0047
	Mean	210.0	287.2			
	Std	96.97	83.93			
	Median	233.0	315.0			
	Min, Max	21.0, 422.0	65.0, 411.0			
Maximum dose at volumes ≥ 2.0 cc	N	70	19	1.011	1.003–1.019	0.0053
	Mean	177.6	240.6			
	Std	81.73	66.74			
	Median	184.0	250.0			
	Min, Max	21.0, 367.0	61.0, 328.0			
Maximum dose at volumes ≥ 3.0 cc	N	70	19	1.013	1.004–1.022	0.0046
	Mean	154.3	209.1			
	Std	69.69	59.01			
	Median	157.0	211.0			
	Min, Max	20.0, 313.0	58.0, 299.0			

Abbreviations: Max = maximum; Min = minimum; Std = standard deviation; CI = confidence interval.

Table 3 Studies addressing chest wall late toxicities from radiation therapy

Series (ref.)	No. of cases	Type of RT/doses	Major findings
Medical University Of South Carolina (4)	93	MammoSite, 340 cGy × 10 fractions; High dose, >120% of PD	16 cases considered to have received high rib doses had one-third of their primary rib volumes exposed to the estimated TD 5/5 and TD 50/5 doses
Medical University Of South Carolina (3)	105	MammoSite, 340 cGy × 10 fractions; High dose, >120% of PD	Rib fractures occurred in ribs with V(37) Gy and V(44) Gy, each well below 33%
Joint Center for Radiation Therapy (10)	1,117	External beam RT	1.8% incidence of rib fracture
Current analysis (WellStar Kennestone)	89	Balloon-based brachytherapy, SAVI, 340 cGy × 10 fractions	Direct correlation between dose of RT received and volume of rib irradiated with the development of chest wall pain

Abbreviations: PD = prescribed dose; TD = tolerance dose.

risk of toxicity posed to chest wall structures with balloon-based brachytherapy (HDR-based brachytherapy) using established alpha/beta ratios and DVHs from plans used to treat actual patients at their institution (3). After patients underwent irradiation with balloon-based brachytherapy, fractures occurred in ribs that received doses below previously accepted tolerance values extrapolated from classic radiobiological models after APBI. Specifically, the target volume receiving more than 37 Gy (V37 Gy) and V44 Gy (the Tolerance Dose (TD) 5/5 and 50/5, respectively) were each well below 33%. The authors of that study believed the traditional models for estimating biologic equivalent doses might benefit from refinements that explicitly addressed the unique radiobiological and physical properties intrinsic to HDR brachytherapy with APBI. Those authors also stated that other factors might outweigh the decreased volume of rib irradiated with APBI using HDR brachytherapy and could argue (as they suggest) for considering the rib more of a “serial” rather than a “parallel” organ. In that case, the maximum dose that extends through the rib or the maximum dose to 1 cm³ of the rib is analogous to the case of the spinal cord. In addition, the authors believed that the admittedly simplistic linear quadratic model failed to adequately describe actual biologically effective doses for balloon-based brachytherapy.

Brashears et al. (3) also felt that the alpha/beta ratio of 3 for late osseous toxicity may be too low and likewise require revision. Regardless, as long-term toxicity data accrue from APBI series, the traditional models for estimating RBE may benefit from refinements that specifically address both the unique radiobiological properties intrinsic to HDR brachytherapy and the other relevant patient variables including a history of osteoporosis or possibly osteopenia, menopausal status, and/or exposure to chemotherapy or hormone therapy. Unfortunately, in their analysis, Brashears et al. (3) did not establish a threshold dose for the development of this toxicity using their balloon-based brachytherapy experience. We are not aware of any other published series that has extensively addressed this issue.

Study limitations and applicability

In the current analysis, we found a direct correlation between dose delivered to/received by the rib, volume of rib irradiated,

and subsequent development of rib/chest wall pain, despite a relatively small number of patients and few events. Although one cannot assume that these findings can also be extrapolated to the development of rib fractures as well, hypothetically, similar dose-volume mechanisms may be responsible for precipitating each type of toxicity. However, the dose associated with rib fractures is unknown and is likely (as discussed above) to be associated with additional other variables (some of which are patient related). As data from these analyses mature, it is hoped these issues can be further clarified in order to provide more robust recommendations for clinicians. As pointed out above, our analysis should be interpreted with caution (considering the limitations of our data) and requires confirmation from a larger data set, preferably with grading of pain in order to draw meaningful dosimetric constraints (i.e., NSABP B39/RTOG 0413 [14] and/or Contura Registry Trial [15]). Because our data suggest a very low dose-volume constraint for rib/chest wall pain, further assessment is warranted (i.e., prospective documentation for this potential toxicity from balloon APBI brachytherapy, incorporating precise recording of the dose (and volume) to ribs and chest wall.

Because this was not a prospective analysis and information was not available (collected) for all patients, the overall risk of developing chest wall/rib pain and/or rib fractures after HDR-based APBI cannot be determined from this review. However, our data also seem to support the idea that different radiobiological models may be needed to help explain our findings more precisely (as suggested above). In addition, data also clearly support measures designed to reduce chest wall/rib dose when applying HDR brachytherapy to deliver balloon-based APBI. Fortunately, data are accumulating to suggest that second-generation balloon devices (with multiple lumens) and other APBI systems can effectively and substantially reduce rib and chest wall doses (9, 11–13). Based upon our limited analysis here, we would suggest limiting the chest wall dose to as low as possible and preferably less than 132% of the PD at a volume of 0.008 cc (this recommendation should also apply to other catheter-based APBI devices now currently in use and to traditional interstitial breast brachytherapy). However, whenever possible, further reductions in chest wall dose should be attempted if other critical dosimetric variables (e.g., skin dose, PTV_EVAL (as described in the NSABP

Protocol B-39), V150 and V200, etc.) are not significantly and negatively impacted.

Conclusions

Despite a small number of patients, our results indicate that there is a direct relationship between the dose received by the ribs/chest wall (and the volume receiving that dose) with toxicity using balloon-based brachytherapy. These data also suggest a very low dose-volume constraint for rib/chest wall pain that requires further assessment to generate specific dose-volume limitations.

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