Late chest wall toxicity after MammoSite® breast brachytherapy

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ABSTRACT

PURPOSE: Accelerated partial breast irradiation (APBI) with the MammoSite® breast brachytherapy (MBB) system is being investigated as an alternative to whole breast radiation in breast conservation therapy (BCT) at multiple centers worldwide. The newness of MBB means a complete understanding of long-term toxicity, particularly involving the chest wall, has yet to be completely articulated. We report the first pathologic rib fractures associated with MBB and dosimetric analysis of the original treatment plans.

METHODS AND MATERIALS: As part of ongoing quality assurance, we reviewed the records of 129 sequential patients who underwent MBB for breast cancer and identified those who subsequently had clinically significant and radiographically documented rib fracture(s) involving the ipsilateral chest wall. Equivalent tolerance doses yielding a 5% and 50% risk of rib toxicity within 5 years from treatment with 10 fractions (as with MBB) were previously calculated using the linear quadratic equation based on 2 Gy per fraction treatments delivered to one-third of the rib volume (TD5/5 = 37 Gy; TD50/5 = 44 Gy). The original radiation therapy plans were evaluated vis-à-vis the plane films or PET/CT images documenting the osseous abnormalities and presenting complaints to find the specific fractured ribs. The specific affected ribs were contoured on the planning CT in “bone windows” using the Nucletron MicroSelectron-classic V2 (Nucletron B.V., Veenendaal, The Netherlands) for this analysis and the original patient treatments. With these datasets, we determined the dose-volume characteristics of the affected ribs including maximal dose encompassing the entire rib on one CT slice, V20Gy, V30Gy, V37Gy, V44Gy, D50, D25, and D5 (the mean dose to 50%, 25%, and 5% of the rib).

RESULTS: Between May 2002 and August 2007, three of 105 patients with a minimum of 6-months follow-up who underwent adjuvant APBI by MBB were found to have a total of five treatment-related rib fractures. The average dose-volume characteristics from the original plans were as follows: D50 = 22.1 Gy, D25 = 32.2 Gy, D5 = 41.6 Gy, max dose to 1 cc = 34.8, Dmax (to 0.1 cc) = 45.6 Gy, V25 Gy = 57.4%, V30 Gy = 30.8%, V37 Gy = 15.9%, V44 Gy = 6.6%, and max dose through rib = 35.8 Gy. Two patients sustained two rib fractures and 1 patient had a single rib fracture. Four of five fractures occurred in postmenopausal patients and two of five fractures occurred in a patient with a history of osteoporosis and exposure to adjuvant chemotherapy.

CONCLUSIONS: Fractures occurred in ribs with V37 Gy and V44 Gy each well below 33%. As long-term toxicity data accrue from APBI series, the traditional models for estimating the biologic equivalent dose may benefit from refinements that specifically address the unique radiobiologic and physical properties intrinsic to high-dose-rate brachytherapy for breast conservation therapy.

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Keywords: MammoSite®, Accelerated partial breast irradiation; Rib fracture; Late radiation toxicity; high-dose-rate radiation; Breast cancer

Introduction

The role of adjuvant radiation in breast conservation therapy (BCT) has been established gradually over the last several decades in numerous phase III, multi-institutional clinical trials (1). Since most recurrences after BCT are identified within the same quadrant as the primary lesion,
there is debate regarding the optimal target volume (whole vs. partial breast) and by extension, which radiation delivery modalities are most appropriate (2). Although this question is being actively investigated by the National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group (NSABP B-39 and RTOG 0413), numerous techniques are already used to give accelerated partial breast irradiation (APBI) after lumpectomy including three-dimensional conformal external beam radiation, intraoperative electron radiotherapy, single-catheter high-dose-rate (HDR) brachytherapy (often by the MammoSite® Radiation Therapy System; Cytc Corp., Marlborough, MA), multiple catheter HDR brachytherapy, and low dose rate (LDR) brachytherapy (3–7). Of these methods, our institution has significant experience with the MammoSite® product on which we have reported clinical outcomes and techniques in previous publications (8–10). This device is an HDR single source brachytherapy applicator with a dual lumen, closed ended catheter; the eccentric lumen is used to inflate a sphere-shaped balloon with a 1:10 iodine contrast: normal saline mixture to conform to the lumpectomy cavity, whereas the central lumen connects to a remote afterloader with an iridium-192 source (11, 12). Treatment is typically given on a twice-per-day basis for a period of 5 days for a total of 34 Gy in 10 fractions with the dose prescribed to 1 cm beyond the outside of the inflated balloon. Although this system has enjoyed popularity in the radiation oncology community, the newness of the application means that a complete understanding of side effects have yet to be completely described. Reported acute and late toxicities thus far have included: balloon rupture, abscess formation or infection, seroma development, skin erythema or hyperpigmentation (radiation dermatitis), telangiectasias, and fat necrosis (6, 11, 13, 14). In the early experience of several institutions, including our own, a relationship was found between the frequency of cutaneous toxicities/poor cosmetic outcomes and the thickness of tissue between the MammoSite® balloon surface and the skin edge. Accordingly, we changed the guidelines for acceptable skin-to-balloon surface distance from the generally recommended 5 mm to a more generous 7 mm (8, 15). In turn, this has led surgeons to be increasingly aware of the tissue thickness between the lumpectomy cavity and overlying skin, a circumstance that could contribute to a more aggressive mobilization of tissue toward the superficial edge of the cavity at the time of lumpectomy or balloon placement. Consequently, the volume of tissue between the internal edge of the lumpectomy cavity and the chest wall may be less than ideal. This raises concerns regarding the resultant increased biologic equivalent dose (BED) to the chest wall that could result in greater risk of late normal tissue toxicity above that seen with the more traditional external beam techniques targeted to the whole breast. We now report on the first treatment-related fractures associated with the use of the MBB system along with a dosimetric re-analysis of the original treatment plans.

Methods and materials

A detailed review of the techniques and indications for the use of MBB along with our work determining BEDs to the chest wall have been extensively discussed previously and are beyond the scope of the present work (9, 16). APBI is given with 34 Gy in 10 fractions twice-per-day with at least a 6-h interfraction interval. As part of our ongoing quality assurance program, we periodically review outcomes and toxicities associated with MBB including seroma formation and cosmetic outcome (8). For this investigation, we reviewed the records of those patients who underwent treatment with MBB for breast cancer or carcinoma in situ and subsequently had clinically significant and radiographically documented treatment-related rib fracture(s) involving the ipsilateral chest wall. A careful history and physical examination were performed with particular attention to any history of trauma or evidence for disease progression. Further radiologic and laboratory workup were undertaken to rule out other causes predisposing for bone weakness as needed.

After Institutional Review Board approval and securing the consent of the patients for participation by phone, the plane films or PET/CT images documenting the osseous abnormalities were secured and reviewed carefully (see Figs. 1 and 2). Guided by these radiographic images, we identified the affected rib(s) on the original radiation therapy planning CT in “bone windows.” The affected rib was contoured on each 2.5-mm CT section of the breast and the contoured volume included all slices containing the balloon and eight additional slices cranially and caudally to allow for the diversity in anatomical variation between the patients. This method is similar to the method used in our previous work (19). The specific location of the documented rib fracture was also approximated on the planning CT by intercomparison of the planning and postfracture images. We used the Nucletron MicroSelectron-classic V2 (Nucletron B.V., Veenendaal, The Netherlands) program for the original patient treatment and this analysis. With these datasets, we determined the dose—volume characteristics of the effected ribs including \( V_{37} \) Gy, \( V_{44} \) Gy, \( D_{50} \), and \( D_5 \) (the mean dose to 50% and 5% of the rib, respectively). The mean contoured volume for each rib was 6 cm³ (range, 3.6–9.6 cm³). In addition, we carefully analyzed the isodose curves and determined the maximal dose encompassing the entire diameter of the rib on any one axial CT slice. Next, we constructed data tables populated with information from the radiation planning system, current understanding about late normal tissue toxicities, and patient comorbidities to aid in further discussion among other researchers that could lead to the construction of meaningful clinical guidelines in the future.

Results

Between May 2002 and August 2007, 129 patients underwent adjuvant radiation therapy with the MammoSite®
device as part of their BCT and of these 105 had follow-up information of $\geq 6$ months available (median, 41 months). During this period, three of these patients were found to have a total of five treatment-related rib fractures involving the chest wall on the previously radiated side (Figs. 1 and 2). Based on the planning CT, the number and location of the source dwell positions were selected with dwell-time adjusted according to the decay of the Iridium-192 source.

The first patient was a 48-year-old white woman diagnosed with pT1bN0 well-differentiated tubular carcinoma of the right breast after lumpectomy and sentinel lymph node evaluation in early October 2003 (ER+, PR+, HER-2-neu unamplified on dual fluorescence in situ hybridization [FISH]). Placement of the MammoSite® device was performed at the time of re-excision in mid-October for inadequate margins; the balloon was inflated with 35 cc of the saline-contrast mixture. APBI was given from October 13 to October 17, 2003 by a single dwell position. A maximum RTOG grade 3 acute skin toxicity was identified which was managed satisfactorily by hydra-gel dressings and oral antibiotics. The patient declined adjuvant hormone therapy and was not recommended chemotherapy. She had

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**Fig. 1.** Posteroanterior (left) and lateral (right) X-rays of the chest with evidence of the first rib fracture shown by the orange arrows (for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

**Fig. 2.** Digital PET-CT scan showing the second and third rib fractures as indicated by the orange arrow with associated post-MBB seroma (for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).
no history of osteopenia or osteoporosis. In October 2004, the patient complained of intense, pleuritic pain just to the right of the sternum. No history of trauma was elicited and physical examination revealed only a 2 × 3 cm telangectasia on the upper outer quadrant of the breast present since radiation. She was initially managed conservatively and follow-up chest X-ray revealed a fracture of the anterior right fifth rib (Fig. 1). The patient responded well to medical therapy and no further injury to her chest wall structures have been identified.

The second patient was a postmenopausal 46-year-old white woman with a history of osteoporosis and cigarette use, originally diagnosed with pT1cN0M0 infiltrating ductal carcinoma of the left breast after lumpectomy and sentinel lymph node evaluation in December 2005 (Nottingham Grade II/III, ER+, PR+, HER-2-neu amplified on FISH). Placement of the MammoSite™ device was performed at the time of re-excision for inadequate margin; the balloon was inflated with 35 cc of the saline-contrast mixture. APBI was given from January 4 to January 10, 2006 and the plan called for the use of two dwell positions during treatment. No acute—radiation-related toxicity was identified. After radiation, the patient underwent three of eight scheduled cycles of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) and received trastuzumab for 1 year. A dual-energy X-ray absorptiometry (DXA) scan from May 2006 showed a bone mineral density of 0.826 gm/cm² of the lumbar spine (T-score of 3.0) and a bone mineral density of 0.746 gm/cm² of the right femoral neck (T-score of 2.1); both of these findings were consistent with osteoporosis. Since completing chemotherapy, she has been maintained on the oral nonsteroidal aromatase inhibitor letrozole. In July 2006, she noted pleuritic pain in the anterior left chest after hearing two “popping sounds”: once when looking over her shoulder while seated in her car, and the second episode occurred as she picked up her 2-year-old grandchild. Physical examination thereafter revealed exquisite tenderness in the area of the MBB scar, but no palpable rib displacement. Initial plane films showed no evidence of fracture, but CT of the chest one week later revealed a lateral left fifth rib fracture, and PET/CT 2 months later demonstrated another fracture just inferior at the lateral left sixth rib (Fig. 2). Both studies showed a well-defined fluid collection (seroma) consistent with her MBB treatment in close approximation to the fractured ribs and no new pulmonary abnormalities were seen. Although the PET/CT scan showed abnormal radiotracer uptake in the fifth and sixth lateral ribs, no suspicious activity was noted in or around the fluid cavity. Based on the location, presentation, and imaging characteristics of the lesions, the patient was diagnosed with treatment-related healing rib fractures. The patient responded well to medical therapy and reported only minimal tenderness with palpation 5 months after the original injury. Serial imaging of the treated breast have documented gradual resolution of the seroma without evidence of recurrent malignancy, and her ribs were completely healed at 1-year follow-up.

The third patient was a 58-year-old white woman diagnosed by abnormal mammogram that underwent lumpectomy with sentinel lymph node dissection in May 2006; findings were consistent with a pT1cNO invasive ductal carcinoma (Nottingham Grade II/III, ER+, PR−, HER-2-neu unamplified on FISH). At the time of re-excision for inadequate margin, the MammoSite™ device was deployed and the balloon was inflated with 60 cc of a saline-contrast mixture. APBI was given from May 10 to May 16, 2006 with five source dwell positions. No acute—radiation-related toxicities were identified. The patient received adjuvant hormone therapy with an aromatase inhibitor, but chemotherapy was not recommended. A DXA scan from May 2006 showed a bone mineral density of 0.921 gm/cm² of the lumbar spine (T-score of 1.1, consistent with osteopenia) and a bone mineral density of 0.746 gm/cm² of the left femoral neck (T-score of 0.9, consistent with normal bone mineral density). In December 2006, she complained of pain in the left anterior chest wall. Workup with a bone scan at that time showed faintly increased radiotracer activity in the anterolateral fourth and fifth ribs; however, plane films of the chest showed no evidence of rib fracture. Clinically, the patient continued to complain of chest wall pain in May 2007 when CT of the chest identified a left chest wall mass measuring 4.8 x 2.6 cm in the area of the MBB treatment. Just below this lesion, a mild convexity along the pleural surface of the underlying lung was identified with blurring of the fat planes consistent with a local soft-tissue mass. Mixed lytic/sclerotic foci in the nearby underlying fourth and fifth ribs consistent with treatment-related fracture or disease involvement were also identified. A May 2007 bone scan demonstrated increased radiotracer activity within the fourth and fifth ribs compared with the December examination. Given these findings, local tumor recurrence was high in the differential so a PET/CT was performed that showed the left chest wall mass with erosion/destruction of the underlying ribs with a maximal SUV of 4.3 that was interpreted as most compatible with spread of malignancy. Next, the patient underwent a CT-guided core biopsy of the chest wall mass in June 2007 that revealed only benign skeletal muscle, scar, and fibrosis. Owing to the risk of sampling error, our multidisciplinary breast tumor board recommended surgical resection of the mass for definitive pathologic diagnosis. In August 2007, a wide local excision of the left chest wall mass was performed and identified benign tissue along with foreign body giant cell reaction. The patient did well postoperatively and reported only minimal pain in the chest wall at her most recent follow-up, although the treatment-related seroma required drainage three times since the wide local excision of her benign chest wall mass.

The radiographic findings of these 3 patients were reviewed and five fractured ribs were identified on the original planning CT (Figs. 3 and 4). These structures were contoured and the dose—volume characteristics of each rib are shown in Table 1. Specifically, we report our dosimetric
findings for each fracture and the averages for the $V_{20Gy}$, $V_{30Gy}$, $V_{37Gy}$, $V_{44Gy}$, $D_{50}$, $D_{25}$, $D_{5}$, the greatest dose to 1.0 and 0.1 cc, as well as the maximal dose encompassing the entire diameter of the rib on a single-axial CT slice. Characteristics of the patients at the time of initial symptoms from their rib fractures are shown in Table 2.

Discussion

Radiation-induced osseous toxicity resulting in rib fracture is a well recognized, if rare, complication of radiation therapy given as part of breast conservation therapy for early stage disease. We previously reported on the theoretic risk posed to the chest wall structures with MBB based on established alpha/beta ratios and DVHs from plans used to treat actual patients (16). In this publication, the classic linear quadratic formula was used with an alpha/beta value of 3 for late effects involving the ribs. MBB tolerance values were extrapolated from conventionally fractionated external beam radiation therapy values with a 5% and 50% risk of late effects (TD5/5 and TD50/5) of 50 and 65 Gy, respectively, given to one-third of the total volume of the rib (20). For 10 fractions of radiation (as typically given by MBB), the doses expected to yield a TD5/5 was 37 Gy and TD50/5 was 44 Gy (to be conservative, no dose modifying factor was used). Of the 17% of patients (16 total) who received a high chest wall dose (≥120% isodose line in contact the rib), the median volumes of the at-risk rib receiving ≥37 Gy ($V_{37Gy}$) and ≥44 Gy ($V_{44Gy}$) were 13.5% and 3.3%, respectively (16). No corresponding osseous radiologic abnormalities were identified at that time. As exemplified by the presented cases, our initial conclusions of only negligible risk of late osseous chest wall toxicity associated with MBB, however, seems to have been premature.

In a review of patients treated between 1968 and 1985 at the Joint Center for Radiation Therapy, Pierce et al found a 1.8% incidence of rib fracture after external beam radiation; the rate of fracture was higher in those treated on a 4 MV rather than a 6 or 8 MV linear accelerator (2.2% vs. 0.4%, respectively, $p = 0.05$) (17). A more recent series from MD Anderson identified an even lower rate of radiation-related rib fracture (<1%) (18). Likely, the increasing conformality of modern external beam radiation delivery systems (e.g., CT-planning and IMRT) will further diminish the risk of radiation-induced rib fracture.

Data from management of head and neck cancer patients show that the rate of osseous toxicity is positively related to the dose rate, volume irradiated, and dose per fraction (19). APBI with HDR breast brachytherapy may lead to an increased risk for rib fracture than seen with external beam radiation by virtue of the former’s increased dose per fraction and hyperfractionated schedule. In addition, the lower energy photons from the iridium-192 source (380 keV average) have a higher linear energy transfer than with megavoltage photons and thus impart a greater RBE (the same
effect may help explain the differences in rib fracture rates in the Joint Center experience (20). These factors may outweigh the decreased volume of rib irradiated with APBI HDR brachytherapy and could argue for considering the rib as more of a “serial” than a “parallel” organ. In this 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 (see Table 1). In addition, the admittedly simplistic linear quadratic model may fail to adequately describe the actual BEDs for MBB and therefore benefit from alteration after more data has accrued. Similarly, 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 radiobiologic properties intrinsic to HDR brachytherapy and relevant patient variables including history of osteoporosis or possibly osteopenia, menopausal status, and exposure to chemotherapy or hormone therapy.

Although this is a small, single-institution series, we believe that this report can engender further discussion and awareness of late tissue complications from APBI by HDR application. It may be prudent to discuss a possible increased risk of rib fracture depending on the location of the brachytherapy device and the patient’s bone health. Previously, we reported that MBB was a safe treatment for appropriate patients with minimal chest wall complication risks even with balloon-to-chest wall distance <5 mm based on accepted BED—volume recommendations (21, 22). Although we are more mindful of the potential for late chest wall toxicity depending on the position of the MBB device and patient history, we continue to offer the treatment because the actual occurrence of rib fractures continues to be rare (<3% of patients thus far) and the long-term morbidity in those few with rib fractures has been acceptable.

Conclusion

After irradiation by the MBB system, fractures occurred in ribs that received doses below accepted tolerance values extrapolated from classic radiobiologic models after APBI; specifically, the $V_{37}$ Gy and $V_{44}$ Gy (the TD5/5 and 50/5, respectively) were each well below 33%. As long-term toxicity data accrue from APBI series, the traditional models for estimating biologic equivalent doses may benefit from refinements that explicitly address the unique radiobiologic and physical properties intrinsic to HDR brachytherapy for BCT.

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References


Table 1

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<th>$V_{57}$ (Gy) (%)</th>
<th>$V_{44}$ (Gy) (%)</th>
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* Two fractures occurred in 1 patient.

Table 2

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* Two fractures occurred in each of these patients.


