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Incidence and prognostic factors for seroma development after MammoSite breast brachytherapy

John M. Watkins¹, Jennifer L. Harper¹, Anthony E. Dragun¹, Michael S. Ashenafi¹, Debajyoti Sinha², Jun Li¹, David J. Cole³, and Joseph M. Jenrette^{1,*}

¹Department of Radiation Oncology, Medical University of South Carolina, Charleston, SC

²Department of Biostatistics and Biometrics, Medical University of South Carolina, Charleston, SC

³Department of Surgery, Medical University of South Carolina, Charleston SC

Abstract

PURPOSE—Describe the incidence and identify risk factors for seroma development after MammoSite breast brachytherapy (MBT).

METHODS AND MATERIALS—MBT patient data were prospectively recorded into a quality assurance database. Departmental and electronic records were reviewed to extract patient-, treatment-, and outcome-specific data. Stepwise logistic regression analysis was performed to identify factors associated with development of any seroma including the subset of clinically significant seroma (CSS). CSS was defined as a symptomatic seroma requiring multiple aspirations, biopsy, and/or excision. Variables analyzed included age, weight, number of excisions, time from resection to catheter placement, placement technique, balloon volume, dosimetric factors, and postbrachytherapy infection.

RESULTS—MBT was performed in 109 patients, of whom 97 had minimum 6 months (median, 36) post-MBT follow-up or earlier development of seroma. All patients received 34 Gy to 1 cm depth from balloon surface, delivered twice daily in 10 fractions. Seroma developed in 41% of patients at a median of 3 months (range, 0.1–25) post-MBT. One-third of seromas (13% of all patients) were CSS. The only factor identified as statistically significant for development of any seroma was catheter placement on day of resection vs. ≥ 1 day later (59% vs. 33%; $p = 0.0066$). Post-MBT infection was highly statistically significant for development of CSS (64% vs. 7%; $p < 0.0001$). Prophylactic antibiotics reduced the risk of post-MBT infection from 37.5% to 6% ($p = 0.011$).

CONCLUSIONS—The incidence of CSS after MBT is low. Post-MBT infection is statistically significantly associated with CSS development, the incidence of which is reduced with prophylactic antibiotics.

Keywords

Breast neoplasms; Intracavitary brachytherapy; MammoSite; Seroma; Breast conservation therapy

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*Corresponding author. Department of Radiation Oncology, Medical University of South Carolina, 169 Ashley Avenue, Charleston, SC 29425. Tel.: + 1-843-792-3271; fax: + 1-843-792- 5498. E-mail address: E-mail: jenretbm@musc.edu (J.M. Jenrette).

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Introduction

MammoSite breast brachytherapy (MBT) is a form of accelerated partial breast irradiation, which is presently being evaluated as an alternative to whole breast radiotherapy in resected early-stage breast cancer. Although a formal multi-institutional randomized trial is underway to compare efficacy and tolerability of partial breast irradiation with whole breast radiotherapy, previously published multi institutional reports of MBT have been promising (1–3). As the collective experience with MBT grows, identification of factors predictive for MBT-specific toxicity remains to be described (4). Seroma development, in particular, has been described as occurring in as few as 9% and up to 76% of patients after MBT, with varying levels of severity (4,5). The present report describes a large cohort of patients treated with uniform dose of MBT at a single institution. Specifically, patient- and treatment-specific variables are assessed to determine factors predictive for development of MBT-associated seroma.

Methods and materials

Between May 2002 and August 2006, 109 patients underwent lumpectomy followed by intracavitary MammoSite catheter breast brachytherapy (MBT) at the Medical University of South Carolina. Of the 109 patients, 12 were excluded from the present analysis due to insufficient follow-up (minimum 6 months unless earlier development of seroma). All patients who initiated MBT are included in this analysis, and all patients but one completed prescribed therapy (did not receive final fraction). After initiation of MBT, only 1 patient experienced balloon rupture requiring replacement MBT was used as the sole radiotherapy modality in the entire population; no patient received external beam therapy to the whole breast.

Eligibility for MBT included patients with unicentric invasive ductal or lobular carcinoma, or ductal carcinoma *in situ* (DCIS) tumors. Extent of disease was pathologic Stage 0 (pTisN0, or DCIS), I (pT1N0), IIA (pT2N0 or pT1N1), or select IIB (pT2N1). Surgical margins were cleared to ≥ 2 mm to invasive or *in situ* carcinoma, occasionally requiring postlumpectomy re-excision. All patients with invasive disease underwent sentinel lymph node biopsy, with subsequent axillary dissection if the sentinel node was positive for malignancy. Timing of MammoSite catheter placement varied from intraoperative (0 days) to up to 66 days postexcision. In general, most catheters were placed within 2 weeks after final excision and verification of margins. Placement approach varied with surgeon and experience, with both scar entry technique and lateral trocar approaches being used. The lateral trocar approach used in most cases in the present population, involves advancing the MammoSite catheter through an approximate 1 cm incision in the lateral breast, toward the ultrasonographically identified resected tumor cavity. The catheter balloon is then filled to expand the cavity.

Patients next underwent a computed tomography scan using thin axial images (2.5–3 mm thickness) for treatment planning and implant quality verification. A minimum overlying skin thickness of 7 mm was required, though 5 mm thickness was permitted on single axial slice. Treatment planning was aborted if there was insufficient overlying skin thickness, excessive intracavitary air, or balloon rupture. Most patients underwent postexcision catheter placement; however, in those patients with intraoperative catheter placement, treatment planning was aborted if surgical margins were unsatisfactory or sentinel lymph node returned positive for disease (requiring axillary dissection). Beginning the first day of treatment and continuing through the final treatment day, patients underwent daily fluoroscopic simulation for balloon volume verification. All patients were prescribed to 34 Gy at 3.4 Gy per fraction to 1 cm depth beyond balloon surface. Treatments were administered twice daily during weekdays, with minimum 6 h between fractions.

Planning was performed using Nucletron Planning System version 3.5 (Nucletron, BV Veenendaal, The Netherlands). Treatments were delivered using high-dose-rate brachytherapy with ^{192}Ir (activity 3.8–9.8 mCi). Dose–volume histograms were constructed for the contoured balloon and for the “target” (balloon + surrounding breast tissue). Plans were evaluated to ensure minimal air cavity artifact (<3 cc). Dosimetric variables were retrospectively calculated, and included the volume (in cubic centimeters; cc) of breast receiving 34 Gy ($V_{100\%}$), 51 Gy ($V_{100\%}$), and 68 Gy ($V_{200\%}$). Volumes were calculated by subtracting the balloon-specific volume (e.g., $V_{100\%}$) from the “target”-specific volume ($V_{100\%}$). Whenever the electronic plans were available, the Nucletron Planning System was used to calculate these parameters. When electronic records were not available, the calculations were performed manually using the hard-copy balloon and target dose–volume histograms. Five cases with electronic plans were randomly selected for manual calculation as a measure of quality assurance, and the mean difference between volumes was 0.9 cc (maximum 3 cc).

After the final fraction of MBT, the balloon is drained and catheter removed. Prophylactic antibiotics were not prescribed to the initial 14 MBT patients treated at our institution. Subsequently, patients have been prescribed cephalexin 500 mg, four times per day from catheter placement through catheter removal. Although the catheter remains in the breast, patients are advised to keep the breast dry and avoid submersion (swimming, tub bathing) until after the catheter has been removed. Immediately after catheter removal, the breast is gently massaged to evacuate fluid and blood, after which antibiotic ointment and gauze are applied with overlying transparent adhesive dressing. Patients are recommended not to remove dressing for 2–3 days after initial placement, then to change regularly until the cavity tract has sealed.

Data were collected on patient-, tumor-, treatment-, and outcome-related factors. Patient factors included age at diagnosis race, history of diabetes, current cigarette smoking, and weight. Tumor-related factors included pathologic T- and N-stage, performance of axillary lymph node dissection, and number of lymph nodes excised and involved. Treatment-related factors included time from biopsy to first lumpectomy, requirement for re-excision, time from final excision to MammoSite catheter placement, MammoSite catheter placement technique and approach, time from lumpectomy to MBT initiation, number of days from MBT start to finish, number of days catheter remained in breast, overlying skin thickness (narrowest), number of MBT plan dwell positions, $V_{100\%}$, $V_{150\%}$, $V_{200\%}$, post-MBT chemotherapy, post-MBT anti-estrogen therapy, administration of prophylactic antibiotics, and development of post-MBT subcutaneous infection. Outcome measures include development of seroma (graded as per Table 1), time to initial seroma development, cosmetic outcome (per the physician-assessed Harvard Cosmesis Scale (6)), and time from MBT completion to last followup. Patients were generally followed 1 month after completion of MBT, then every 3 months for 1 year, every 4 months for 1 year, every 6 months for 3 years, then annually thereafter. Mammograms were generally performed every 6 months for 2–3 years for the involved breast and annually thereafter indefinitely. The contralateral breast was imaged annually post-MBT. The detection of seroma was made by clinical examination with or without ultrasonography.

Statistical analysis

Patient- and treatment-related factors from the research database were analyzed to determine predictive factors for seroma development. For the purposes of identifying seromas requiring intervention, a specific subset of “clinically significant seroma,” (CSS) was created. CSSs included symptomatic seromas requiring multiple aspirations, biopsy, and/or excision (Grade ≥ 3 per Table 1). Stepwise univariate logistic regression analyses of the patient- and treatment-related factors were performed identify factors statistically significantly associated with development of seroma outcome. Two separate analyses were performed, one each for

development of any seroma as well as CSS. Multivariate analyses were not performed. All p values < 0.05 were considered statistically significant. All analyses were run using Statistical Analysis Systems, version 9.1 (SAS Institute, Cary, NC).

Results

Ninety-seven patients were eligible for the present analysis, with median followup of 36 months (range, 4–57). All patients had DCIS or resectable invasive tumors; sentinel lymph node biopsy was performed in all patients with invasive carcinoma, all patients had three or fewer lymph nodes involved. Patient characteristics are detailed in Table 2.

All patients underwent lumpectomy before MammoSite catheter placement. Treatment-related characteristics are detailed in Table 3. Post-MBT infections developed in 11.5% of patients, at a median of 30 days after catheter removal (range, 0–131). Surgical re-excision was required in 4 of 11 patients who developed infection.

Seromas developed in 41.2% of patients at a median of 3.1 months post-MBT (range, 0.1–24.8). One-third of seromas were considered CSS, occurring in 13.4% of all patients (Table 4). Of 18 patients who underwent fine needle aspiration of seroma, 8 required multiple aspirations (range, 1–5). Four patients underwent excision or biopsy of seroma.

Analysis of patient-, tumor-, and treatment-related factors demonstrated placement of the MammoSite catheter on day of excision to be statistically significantly associated with seroma development (59% vs. 33% when placed one or more days postexcision, $p = 0.0066$). The only factor associated with development of CSSs was post-MBT infection (64% vs. 7% when no infection, $p < 0.0001$). Prophylactic antibiotics significantly reduced the risk of post-MBT infection from 37.5% to 7% ($p = 0.011$).

Cosmetic outcomes were graded as “excellent” in 63.9%, “good” (26.8%), “fair” (7.2%), and “poor” (2.1%) per the Harvard Cosmesis Scale (Table 5). CSS resulted in fair-to-poor cosmetic outcome in 58.3%, as opposed to 3.7% when there was no CSS ($p < 0.001$).

Discussion

Only one previously published series has evaluated prognostic factors for post-MBT seroma development (4). The present series represents the largest single-institution experience reported, with 97 patients followed for a median of 36 months post-MBT. The results show that the incidence of seromas is 41%, similar to previously reported series (5,7). The incidence has been described as high as 76% (4), illustrating the lack of uniformity in clinical detection, documentation and grading of seromas, as well as heterogeneity of surgical interventions. As an example, a recent review of complications after breast surgery described seroma rates of 10–80% (8). Most intervention-based studies and retrospective investigations have focused on reduction of seroma rates after mastectomy and/or axillary dissection. Within all described series, asymptomatic seromas not requiring intervention are the most common experienced by patients. Thus, serial assessment with ultra sonography would seem to be unnecessary in the absence of symptom progression. A symptom- and intervention based late toxicity scoring system, such as that used in the present series, seems most prudent for future delineation of CSSs.

The rate of seroma development seems to be impacted by time from excision to placement of MammoSite catheter. In the Tufts/Brown University series of 39 patients in whom all catheters were placed intraoperatively, the seroma development rate was 76% (4). Within the present series, seromas developed in 59% of patients in whom the catheter was placed intraoperatively, and was the sole prognostic factor for development of any seroma. The etiology for this remains

to be determined; however, this finding would argue for delayed placement of the catheter in the second procedure. An additional benefit of delayed placement is the time required for final pathologic assessment of margins and sentinel lymph node (when performed). Indeed, this is the current recommendation of the American Society of Breast Surgeons (9).

Although the present study overall infection rate of 11.3% is similar to other large single-institution experiences (4,7), the identification of post-MBT infection as statistically significantly associated with development of CSS has not been previously reported. In fact, this finding is in direct contrast to the Tufts/Brown University series, which described a seroma rate of 4% in the setting of post-MBT infection (vs. 25% in absence of infection, $p = 0.05$) (4). The investigators hypothesized that this may have been due to polymorphonuclear cell extravasation into the wound cavity, resulting in decreased fibroepithelial proliferation and thus decreased pro-inflammatory cytokines. Cytokines have been previously implicated in the development of seroma in the postmastectomy setting (10). The present study's finding conflicts with the overall explanation; it seems more likely that infection stimulates, rather than minimizes, local inflammatory cytokines, resulting in the significantly increased rate of CSS.

Prophylactic oral antibiotics significantly reduced the frequency of CSS. To our knowledge, this represents the first association of antibiotic prophylaxis with reduction of CSS. A limitation of the present study is the chronologic nature of antibiotic administration: after infection in 3 of the first 7 patients, antibiotics have been administered with infrequent exception. Thus, the infection rate could have been an inadvertent manifestation of the early procedural experience at our institution. Review of previously published series demonstrated a lack of definition of antibiotic administration, such that comparison of post-MBT infection rates is not possible (4,5,7). Investigators at Rush University Medical Center observed transdermal catheter mobility of 2–3 cm when patients were repositioned from supine to upright (5). Due to concern for normal flora contamination of the catheter tract and tumor cavity, the recommendation was made for topical antibiotics at the catheter insertion site. An infection rate of 6% was described, though it was unclear how many patients in the series were treated with prophylactic topical antibiotics.

The present series demonstrated CSS as significantly associated with poorer cosmetic outcome. This is consistent with the Tufts/Brown University series, in which development of any seroma resulted in a 21% absolute reduction of “excellent” cosmetic outcome (4). Although the Tufts/Brown series did not delineate between different grades of seroma severity, it seems intuitive that more severe seromas (particularly those requiring intervention) result in suboptimal cosmetic outcomes. Thus, administration of prophylactic antibiotics can both reduce the frequency of CSS and maximize likelihood of optimal cosmetic outcome.

A direct correlation between volume of resection and seroma formation has been previously described, within both postlumpectomy and postmastectomy populations (11,12). Within the present study cohort, volume of resection (as measured by MammoSite balloon volume) did not prove to be associated with formation of either seroma or CSS. This finding may be due to the tamponade effect of the balloon, increasing the hydrostatic pressure within the resected cavity. Within postmastectomy patients, immediate reconstruction of the surgical cavity has been shown to reduce the frequency of seroma formation (13). No recommendations can be made regarding volume of resection or balloon volume, as these are determined by the adequate resection required to achieve negative margins and appropriate balloon volume to minimize peripheral air pocket formation, respectively. Of course, large volume (>100 cc) resections are uncommon within the context of breast conservation therapy, as cosmetic outcome decreases with increasing volume of resection.

Conclusion

Although the development of seromas after MBT may be common, the incidence of CSS is low. Placement of the MammoSite balloon at the time of initial lumpectomy is statistically significantly associated with seroma formation, whereas post-MBT infection is statistically significantly associated with development of CSS. Finally, the incidence of CSS is reduced with prophylactic oral antibiotics while the catheter remains in place.

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Table 1

Post-MammoSite breast brachytherapy Seroma Grading Scale

Grade	Description
0	No seroma
1	Asymptomatic, palpable seroma
2	Symptomatic seroma, ≤ 1 aspiration performed
3	Symptomatic seroma. requiring multiple aspirations
4	Symptomatic seroma, requiring biopsy or excision

Table 2

Patient characteristics

Age	<i>n</i>	%
Median (range)	61 years (25–86)	
Race		
% White	90	93
% Diabetics	12	12
% Current tobacco smokers	14	14
Pathologic T-stage		
DCIS	19	20
pT1a	9	9
pT1b	31	32
pT1c	30	31
pT2	8	8
Pathologic N-stage		
pNx	7	7
pN0	80	82
pN1	10	10
% Axillary lymph node dissection	9	9
Lumpectomy		
Single excision	79	81
Multiple excisions	18	19
Time from lumpectomy to final excision (days)		
Median (range)	8 days (0–66)	

DCIS = ductal carcinoma *in situ*.

Table 3

Treatment characteristics

	<i>n</i>	%
Time from resection to RT start		
Median (range)	6 days (2–24)	
Time RT start to finish		
Median (range)	4 days (4–7)	
RT dose (to 1 cm depth)	34 Gy	
Surgical balloon volume		
Median (range)	60 cc (35–125)	
Overlying skin thickness		
Median (range)	12 cm (5–54)	
Dwell positions ^a		
% Single	81	85
% Multiple	14	15
Dosimetry		
$V_{100\%}$		
Median (range)	73 cc (30–129)	
$V_{150\%}$		
Median (range)	25 cc (4–63)	
$V_{200\%}$		
Median (range)	4 cc (0–22)	
% Post-RT chemotherapy	16	17
% Anti-estrogen therapy [#]	53	54

RT = Radiation therapy.

^aFor 95 patients with available number of dwell positions.

Table 4

Post-MammoSite brachytherapy seroma characteristics

Seroma grade	<i>n</i>	%
0	57	59
1	20	21
2	7	7
3	10	10
4	3	3

Table 5

Cosmetic outcome after MammoSite brachytherapy

Cosmesis score	<i>n</i>	%
Excellent	62	64
Good	26	27
Fair	7	7
Poor	2	2