Original paper

The incidence of fat necrosis in balloon-based breast brachytherapy

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Abstract

Purpose: To investigate the incidence of and potential risk factors for fat necrosis in high dose-rate (HDR) balloon-based breast brachytherapy (BBB).

Material and methods: Fifty-four patients were treated postoperatively with HDR-BBB between May 2007 and December 2010. Median age was 71 years (range: 50-88 years). Median tumor size was 1 cm (range: 0.1-2.7 cm). Forty-four had invasive histology; 43% were grade 1, 24% grade 2, and 15% grade 3. The median margin size was 0.7 cm (range: 0.1-1.5 cm).

Results: With a median follow-up of 2.9 years (range: 0.5-5.2 years), local control was 98% with one in-breast failure, and overall survival was 89%. Fifty percent of patients experienced fat necrosis. Seven patients were symptomatic, with the remainder detected by mammography alone. Two patients required surgical resection with pathology confirming fat necrosis; 1 required *i.v.* steroids. At 1, 3, and 5 years following treatment, estimated cumulative incidences of fat necrosis were 7.5%, 52.7%, and 60.6%. Breast laterality, location, tumor size, histology, margin size, balloon volume, skin distance, skin dose, and number of dwell positions were not significantly associated with fat necrosis on univariate analysis.

Conclusions: In this retrospective review of HDR-BBB, we found a 50% incidence of both asymptomatic and symptomatic fat necrosis. Only three patients, however, required intervention. None of the risk factors considered were significantly associated with fat necrosis. Further studies evaluating factors associated with fat necrosis for patients undergoing HDR-BBB are necessary to appropriately assess the risks associated with treatment.

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Key words: brachytherapy, breast cancer, high-dose rate, necrosis, survival, toxicity.

Purpose

Since the Food and Drug Administration (FDA) approved the MammoSite® (Hologic Inc., Bedford, MA, USA) balloon-based brachytherapy (BBB) catheter for clinical use in 2002, the use of accelerated partial breast irradiation (APBI) after breast conservation surgery has increased more than 10-fold [1-3]. Prior to the introduction of BBB, the majority of APBI was performed using multi catheter interstitial brachytherapy, which was originally investigated in the era of low-dose-rate (LDR) irradiation but more recently has also been utilized with high-dose-rate (HDR) techniques [2,4,5]. Unlike interstitial brachytherapy, which can be difficult to teach and has significant operator dependence, MammoSite® has been felt by many to be easier to use and more reproducible [2,4,6-8]. A recently completed manufacturer-sponsored registry trial and several institutional reviews have explored the safety, efficacy, and toxicity associated with MammoSite® [2,3,6,9]. Initial results look promising, with outcomes similar to that of whole breast irradiation (WBI), though several randomized trials are currently ongoing, including NSABP B-39/RTOG 0413, international trials under the direction of GEC-ESTRO (The Groupe Européen de Curiethérapie – the European Society for Radiotherapy & Oncology), and randomized studies led by the Hungarian National Institute of Oncology [10,11].

One complication that has been noted in several studies evaluating HDR breast brachytherapy, regardless of the modality utilized has been fat necrosis. A benign inflammatory process, fat necrosis is commonly caused by trauma but has also been a documented complication from radiotherapy [12-16]. Several studies have evaluated its incidence in brachytherapy, which ranges from 2% to 52% [2,3,5,6,9,11-18]. Symptomatic fat necrosis can often require pain medication, steroids, or even surgical inter-

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vention. Often fat necrosis can be asymptomatic; however, some studies have demonstrated that even asymptomatic fat necrosis can be linked to a worsened cosmetic outcome [13-15].

While several studies have evaluated risk factors and incidence of fat necrosis with interstitial brachytherapy, reports dedicated to the evaluation of fat necrosis in BBB are limited [12,14,16,17]. To our knowledge, this is the first study dedicated to the evaluation of fat necrosis specifically in BBB. Although the reports from the registry trial included information regarding fat necrosis, no specific criteria for identifying fat necrosis were defined, and investigators were not required to use any specific testing or imaging to identify fat necrosis [3,6,9]. Additionally, registry trials involve a highly selected patient population and have certain limitations such as lack of standardized and uniform pathologic review, margin status assessment, and criteria for assessing and quantifying toxicity [2]. As such, we sought to retrospectively analyze our patients treated with BBB under the direction of a single treating radiation oncologist, with a primary focus on the incidence of and risk factors associated with fat necrosis.

Material and methods

Study patients

Fifty-four consecutive patients with at least 6 months of follow-up who underwent balloon-based partial breast brachytherapy between May 2007 and December 2010 at a single institution were included in this retrospective study. Information was collected regarding patient and disease characteristics (age, length of time between surgery and partial breast brachytherapy, breast laterality, breast location, tumor size, re-excision, T-stage, estrogen receptor [ER] status, progesterone receptor [PR] status, HER2 status, presence of an invasive tumor, tumor grade, lymphovascular space invasion [LVSI], margin size, multicentricity, pathology), treatment characteristics (computed tomography [CT] injected volume, maximum skin dose, number of dwell positions, skin distance, balloon volume, chemotherapy), and post-treatment outcomes (symptoms, fat necrosis, date of fat necrosis, method of fat necrosis detection, in-breast failure, other complications, date of death, and date of last follow-up). The primary endpoint was occurrence of fat necrosis; secondary endpoints included overall and disease specific survival as well as other toxicities associated with treatment. Fat necrosis was assessed by mammographic evaluation and clinical exam. Symptomatic patients underwent pathologic examination at the discretion of the attending radiation oncologist or surgeon.

Treatment details

All patients were operated on by a fellowship-trained oncologic surgeon at our institution. Patients were required to have negative margins with at least 1 mm of normal tissue. The median margin size was 0.7 cm (range: 0.1-1.5 cm). Sentinel lymph node biopsy was performed at the time of surgical resection for patients with invasive disease. The cavity-evaluation device was placed at the time of surgery and filled with saline in order to ensure the tumor cavity remained patent. The cavity-evaluation device was changed out at the time of simulation for the MammoSite® or Contura® catheter (SenoRx, Inc., Aliso Viejo, CA, USA); all catheter change-outs and treatments were performed under the direction of a single radiation oncologist. Six patients were treated with Contura®, and the remainder were treated with MammoSite®. After an unacceptably high rate of skin infection among patients treated in the first few months, all patients were placed on prophylactic oral antibiotics during treatment and given precautions on keeping the catheter site clean and dry. The median time between initial surgery and initiation of radiotherapy was 6 days (range: 3-35 days). Five patients (9%) underwent re-resection for margin, which explains the high end of the range in this sample. All patients were treated with 34 Gy in 10 fractions twice daily at least six hours apart via Ir-192 prescribed to 1 cm from the balloon-edge. Daily verification CT images were taken to ensure proper balloon placement before treatment; this was done before the morning fraction. A minimum of 5 mm source-to-skin distance was required, and the maximum skin dose was limited to less than or equal to 145% of the prescription dose. The balloon catheter was removed after the final treatment and the wound was allowed to heal by secondary intention. Patients were seen in follow-up every 3-6 months for the first 1-2 years, and then every 6 to 12 months thereafter. Mammography was performed in all patients at 6 and 12 months after the treatment and annually thereafter.

Statistical analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage. The Kaplan-Meier method was used to estimate the cumulative incidence of fat necrosis and the cumulative incidence of mortality after partial breast brachytherapy, censoring at the date of last follow-up. Associations of disease and treatment characteristics with the primary endpoint of fat necrosis after partial breast brachytherapy were evaluated using single variable Cox proportional hazards regression models; relative risk (RRs) and 95% confidence intervals (CIs) were estimated. No adjustment for multiple testing was made in these exploratory analyses, and p-values of 0.05 or less were considered as statistically significant. All statistical analysis was performed using SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina, USA) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria). Due to the small number of patients treated with Contura®, all data was analyzed in aggregate and no attempt was made to compare dosimetric or outcomes parameters between the two groups.

Results

A summary of patient, disease, and treatment characteristics for the 54 study patients is shown in Table 1. Median age was 71 years (range: 50-88). The most com-

Table 1. Summary of patient, disease, and treatment characteristics

Patient and disease characteristics	Summary (n = 54; range, %)
Age	71 (50-88)
Breast laterality	
Left	30 (56)
Right	24 (44)
Breast location	
Central	10 (19)
Lower inner quadrant	3 (6)
Lower outer quadrant	4 (7)
Upper inner quadrant	9 (17)
Upper outer quadrant	28 (52)
Tumor size (cm)	1.0 (0.1-2.7)
Re-excision	5 (9)
T-stage	
T1a	7 (13)
T1b	16 (30)
T1c	16 (30)
T2	5 (9)
Tis	10 (19)
ER status (positive)	50 (93)
PR status (positive)	48 (89)
HER2 status (positive)	3 (7)
Invasive tumor	44 (81)
Tumor grade	
Low	1 (2)
Intermediate	4 (7)
High	5 (9)
1	23 (43)
2	13 (24)
3	8 (15)
LVSI	
Indeterminate	1 (2)
Negative	45 (94)
Positive	2 (4)
Margin size (cm)	0.7 (0.1-1.5)
Multicentricity (positive)	3 (6)
Pathology	
DCIS	10 (19)
IDC	39 (72)
IDC (muci)	3 (6)
ILC	1 (2)
Tubular	1 (2)
Treatment characteristics	
CT injected volume (ml)	50 (25-113)
Maximum skin dose (cGy)	266.3 (67.9-420.0)
Number of dwell positions	3 (1-95)
Skin distance (mm)	15 (7-47)
Chemotherapy	8 (15)

The sample median (minimum, maximum) is given for continuous variables. Information was unavailable regarding tumor size (n = 1), HER2 status (n = 10), LVSI (n = 6), margin size (n = 4), multicentricity (n = 1), and number of dwell positions (n = 8) ER – estrogen receptor, PR – progesterone receptor, LVSI – lymphovascular space invasion, DCIS – ductal carcinoma in situ, IDC – invasive ductal carcinoma, ILC – invasive lobular, CT – computed tomography

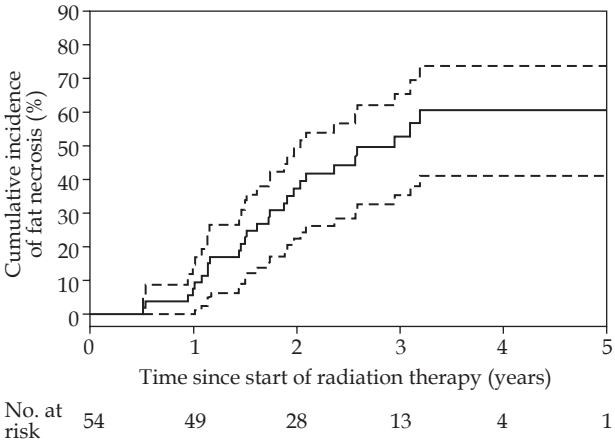

Fig. 1. Cumulative incidence of fat necrosis after the start of partial breast brachytherapy. Dashed lines represent 95% confidence intervals

mon breast location was the upper outer quadrant (52%) and the median tumor size was 1.0 cm (range: 0.1-2.7). Forty-four patients (81%) had an invasive tumor. Median balloon volume as measured by CT was 50 ml (range: 25-113 ml), median maximum skin dose was 266.3 cGy (range: 67.9-420.0 cGy), median number of dwell positions was 3 (range: 1-95), median skin distance was 15 mm (range: 7-47 mm) and 8 patients (15%) underwent chemotherapy in addition to partial breast brachytherapy.

With a median follow-up length of 2.9 years (range: 0.5-5.2 years) only one patient experienced in-breast failure, and this occurred at 3.1 years following the start of partial breast brachytherapy. Six patients (11%) died during the analysis period. Cumulative mortality at 1, 3, and 5 years after treatment was 1.9% (95% CI: 0.0-5.4%), 1.9% (95% CI: 0.0-7%), and 35.1% (95% CI: 1.8-71.7%), respectively (Fig. 1).

Toxicity

Patients tolerated treatment with MammoSite® quite well, without any reportable acute toxicity. No patient required prescription analgesia, except in the immediate postoperative timeframe. No skin erythema was appreciable during treatment, and patients did not complain of significant fatigue during treatment.

A total of 27 patients (50%) experienced the primary endpoint of fat necrosis. At 1, 3, and 5 years following the start of partial breast brachytherapy, estimated cumulative incidences of fat necrosis were 7.5% (95% CI: 0.2-14.3%), 52.7% (95% CI: 35.3-66.2%), and 60.6% (95% CI: 41.0-84.7%). The method of fat necrosis detection for the majority of these 27 patients was mammogram alone (n = 20, 74%). Only seven patients (14%) were symptomatic of their fat necrosis. Two patients required surgical resection with pathology confirming fat necrosis; one required *i.v.* steroids. The remainder was treated conservatively with oral analgesics and experienced eventual resolution of symptoms.

An exploratory evaluation of risk factors for fat necrosis after partial breast brachytherapy is shown in Table 2.

Table 2. Evaluation of risk factors for fat necrosis after partial breast brachytherapy

Variable	RR (95% CI)	*p* value
Breast laterality (right)	0.92 (0.43-1.99)	0.84
Breast location		0.90
Upper outer quadrant	1.00 (reference)	
Upper inner quadrant	1.15 (0.38-3.53)	
Central	1.13 (0.43-2.94)	
Lower inner/outer quadrant	0.69 (0.20-2.40)	
Tumor size (per 0.5 cm increase)	0.45 (0.02-9.39)	0.61
Invasive tumor	1.38 (0.52-3.67)	0.52
Margin size (per 0.5 cm increase)	1.06 (0.67-1.68)	0.80
CT injected volume (per 25 ml increase)	0.92 (0.50-1.68)	0.78
Maximum skin dose (per 100 cGy)	1.08 (0.71-1.64)	0.72
Number of dwell positions		0.43
1	1.00 (reference)	
2-4	1.39 (0.42-4.66)	
5-95	1.79 (0.74-4.32)	
Skin distance (mm) doubling	0.94 (0.53-1.66)	0.82

Relative risks, 95% confidence intervals, and p-values result from single variable Cox proportional hazards regression models. Number of dwell positions was considered as a three-level categorical variable for easier presentation of results RR – relative risk, CI – confidence interval, CT – computed tomography

None of the risk factors considered were significantly associated with fat necrosis (all $p \geq 0.43$).

Eight patients (15%) experienced other complications after treatment. Four (7%) patients had surgical-site skin infections requiring oral antibiotics; these patients were all treated before the routine administration of prophylactic antibiotics. No patient developed a skin infection after being placed on prophylaxis. Two (4%) patients had a seroma that required incision and drainage, and one patient had recurrent wound healing issues. One patient presented with painless, bloody nipple discharge approximately 12 months after treatment. This resolved without intervention a year later; however, the patient subsequently developed asymptomatic fat necrosis.

Discussion

Initial reports of BBB in the use of partial breast irradiation, coupled with reports from both HDR and LDR interstitial brachytherapy, suggest that APBI may be a safe and effective treatment option for patients with early localized breast cancer who meet certain eligibility criteria. Outcomes appear similar to that of whole breast irradiation, although further long-term follow-up is still needed. As such, much of the focus on recent literature regarding breast brachytherapy has focused on cosmetic outcome and toxicity, given presumed equal efficacy. While numerous reports have analyzed the incidence of and factors contributing to fat necrosis in interstitial brachytherapy, to our knowledge no study has specifically sought to evaluate fat necrosis seen in BBB [12,14,16,17]. Vargo *et al*. found a 10.9% incidence of any fat necrosis and a 3.2% incidence of symptomatic necrosis with the use of MammoSite [5]. This study followed 157 patients treated at a single institution for up to 10 years, with a median of 5.5 years. However, the authors did not report the methods by which fat necrosis was assessed, nor did they indicate the interventions performed for those patients who were symptomatic. Additionally, they did not explore any patient or treatment-related factors that may have contributed to the development of fat necrosis. It is difficult to compare these results to the current study, given that the assessment of fat necrosis was not the primary objective and the aforementioned limitations.

The recently-closed manufacturer-sponsored registry trial analyzed 1,440 patients treated with MammoSite® over a 2-year period and reported their outcomes with a median follow-up of 63.1 months [3,6,9]. They found a 2.5% incidence of fat necrosis overall. Fifty percent of cases occurred beyond 18 months. Factors associated with fat necrosis included seroma formation, infection, hormone use, and A/B bra size. No specific criteria for identifying fat necrosis were defined, and investigators were not required to use any specific testing or imaging to identify fat necrosis [3,6,9]. Additionally, registry trials involve a highly selected patient population and have certain limitations, such as a lack of standardized and uniform pathologic review, uncertain margin status assessment, and non-uniform criteria for assessing and quantifying toxicity [2].

Wazer *et al*. evaluated their experience with HDR interstitial brachytherapy and focused specifically on fat necrosis [12]. They found a 27% rate of clinically evident fat necrosis their patients at 24 months of follow-up. Mammography was not used for the diagnosis of fat necrosis. All but one patient was symptomatic; the final patient had a painless palpable mass. Four patients underwent aspiration to rule out concomitant infection. Further treatment with analgesics, antibiotics, vitamin E, and pentoxifylline was pursued in a majority of the patients. Five patients underwent confirmatory core needle biopsy; pathology from those biopsies confirmed the diagnosis of fat necrosis. No patient required therapeutic excision. Wazer *et al*. found that the number of dwell positions used during treatment and the volumes of the breast receiving 340 cGy, 510 cGy, and 680 cGy impacted the development of fat necrosis.

Garsa *et al*. reported their institutional experience with the use of HDR interstitial brachytherapy and analyzed the incidence of fat necrosis among 236 patients [14]. They utilized both radiographic imaging and clinical findings to diagnose fat necrosis. After a median follow-up of 56 months, they found a 17.6% crude rate of fat necrosis with a 10% rate of symptomatic necrosis. Three patients underwent surgery for fat necrosis. Risk factors for the development of fat necrosis in this study included acute infection, anthracycline based chemotherapy, number of HDR catheters used, the volume encompassed by the prescription isodose (V_{100}), the volume encompassed by the 150% isodose line (V_{150}), the volume encompassed by the 200% isodose line (V_{200}), and the integrated refer-

ence air kerma. Of these factors, only the V_{150} was found to be predictive on multivariate analysis. They found a cutoff point of 65 cm^3, with any values for V_{150} above that predictive for a higher risk of fat necrosis. Garsa *et al*. also found that patients who developed fat necrosis went on to have a worse cosmetic outcome than those patients who did not develop necrosis. Patients who developed fat necrosis also had higher BI-RADS (Breast Imaging, Reporting and Data System) scores on follow-up mammography; however, they did not go on to have a higher incidence of ipsilateral breast tumor recurrence. The increased BI-RADS score was likely due to the architectural distortion caused by fat necrosis. Twenty-nine percent of patients with fat necrosis underwent confirmatory biopsy. Symptomatic patients were treated primarily with non-steroidal anti-inflammatory drugs (NSAIDs). Some patients also required short-term narcotics. While 80% of fat necrosis was diagnosed within 3 years, some cases were reported as late as 71 months. The median time to diagnosis was 21 months.

A randomized trial was conducted in Hungary that compared patients treated with whole breast irradiation, partial breast irradiation with electrons, and interstitial HDR brachytherapy [15]. At 48 months of follow-up, 37% of patients experienced fat necrosis, with an 11.5% rate of symptomatic necrosis. Those patients with symptomatic fat necrosis were found to have a worse cosmetic outcome. One patient required surgical intervention. While the median time to diagnosis of fat necrosis was 17 months, the incidence of fat necrosis increased over time. Only 66% of the incidence of necrosis was seen by 2 years. Forty-two percent patients with suspected fat necrosis underwent fine needle aspiration (FNA) for confirmation; 80% of these were found to have fat necrosis, while 20% only demonstrated evidence of seroma or fibrosis. Bra size was the only factor found to contribute to fat necrosis, with larger bra size being predictive for necrosis. They found no difference in the incidence of fat necrosis between whole breast radiotherapy and brachytherapy, but a decreased incidence with electron partial breast radiotherapy. This contrasts with a review of medicare claims data by Presley *et al*., which found an increased rate of fat necrosis for patients undergoing brachytherapy when compared to patients undergoing whole breast radiotherapy [10].

Budrukkar *et al*. reported on their experience treating 171 women with APBI using HDR interstitial brachytherapy [16]. At a median follow-up of 48 months, they found a 12% rate of fat necrosis; 80% of these patients were symptomatic. The median time to development of fat necrosis was 24 months. Eight patients required surgical excision. Only the volume of excision was found to correlate with the incidence of fat necrosis.

A multi-institutional phase-II protocol looking at the use of LDR interstitial brachytherapy reported on long-term, 11.2 year follow-up of 50 patients treated with LDR [5]. This study found a 35% incidence of fat necrosis, which was found by either radiography or by clinical exam. The long-term LDR study did not report a breakdown between symptomatic and asymptomatic patients; they mentioned that one patient required surgery for fat necrosis. No mention was made regarding the treatment of the other patients found to have fat necrosis, and no analysis of risk factors was undertaken. While the authors did not report on the median time to onset of fat necrosis, this study supports the idea that long-term follow-up is required because fat necrosis can be a late effect. While many studies found the majority of fat necrosis to be present by 2-3 years, they also found incidences of late necrosis as late as 71 months after treatment [14,15]. This corresponds with our study, which found an increasing incidence of fat necrosis with time. Thus, long term follow-up of MammoSite® patients will be essential in order to accurately define the long-term risk of fat necrosis.

In our study, we found that the incidence of fat necrosis with BBB is similar to that seen with other methods of HDR brachytherapy [12,14,16,17]. While half of our patients were found to have fat necrosis, only 7 patients (14%) were symptomatic. We did not perform confirmatory FNA or biopsy on patients suspected of having fat necrosis, and we would agree with other authors that biopsy or FNA should be only utilized to rule out tumor recurrence in cases where that is in question; they should not be used for routine confirmation of the diagnosis of fat necrosis [14]. Additionally, two patients required surgical intervention, one required intravenous steroids, and the remainder required oral analgesics. Those patients who underwent surgery were found to have pathologic evidence of fat necrosis.

We would recommend that most patients diagnosed with symptomatic fat necrosis should be managed with oral analgesics as the vast majority of these patients will see symptomatic relief; intravenous steroids can also be considered in more advanced cases for patients refractory to analgesics. The diagnosis can typically be made by clinical exam and imaging alone, with biopsy reserved for suspicion of recurrence. Surgery should be limited to those patients whose symptoms progress despite these interventions. We did not find any patient or treatment-related factors that contributed to the development of fat necrosis, and there does not seem to be a consensus in the literature regarding specific factors that predispose patients to developing fat necrosis.

Our study is subject to several limitations, including our relatively small sample size, fairly short follow-up, and the standard limitations related to a retrospective review including possible selection bias. Further studies with longer follow-up and larger patient numbers are necessary to gain an accurate assessment of the incidence of fat necrosis in balloon-based breast brachytherapy.

Conclusions

Balloon-based brachytherapy remains a viable treatment option for a select group of breast cancer patients. Although it is important to accurately assess the toxicity associated with this relatively new treatment, one must not forget the important role that hypofractionated radiotherapy can play in patients who are unable or unwilling to undergo a protracted course of external beam radiotherapy.

Disclosure

Dr. Kim reports disclosures from Medical Tool & Technology, LLC, outside the submitted work.

Authors report no conflict of interest.

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