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Analysis of Fat Necrosis Following Adjuvant High-Dose-Rate Interstitial Brachytherapy for Early-Stage Breast Cancer

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Abstract

Purpose—To report the incidence and potential predictors of fat necrosis in women with early-stage breast cancer treated with adjuvant high-dose-rate (HDR) multicatheter interstitial brachytherapy.

Methods and Materials—Between 2003 and 2010, 238 treated breasts in 236 women were treated with accelerated partial breast irradiation (APBI) using HDR interstitial brachytherapy. Selection criteria included patients with Tis-T2 tumors measuring ≤ 3 cm, without nodal involvement, who underwent breast-conserving surgery (BCS). 99% of treatments were to a total dose of 34 Gy. The presence and severity of fat necrosis was prospectively recorded during follow up. Cosmesis was qualitatively scored in all patients. Cosmesis was quantitatively measured via the percentage breast retraction assessment (pBRA) in 151 cases.

Results—Median follow-up was 56 months. The crude rate of fat necrosis was 17.6%. The rate of symptomatic fat necrosis was 10.1%. In univariate analysis acute breast infection and anthracycline-based chemotherapy, number of catheters, V100, V150, V200 and integrated reference air-kerma (IRAK) were significantly associated with fat necrosis. There was significant collinearity between the brachytherapy related factors, of these V150 was most predictive. In multivariate analysis only V150 was significantly associated with fat necrosis. At 3 years, patients with fat necrosis were more likely to have a fair/poor cosmetic outcome and a larger pBRA.

Conclusions—Mammary fat necrosis is a common adverse event after BCS and HDR interstitial brachytherapy. Fat necrosis is associated with worse qualitative and quantitative

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cosmetic outcomes. Minimizing exposure volumes such as V150 may decrease the incidence of fat necrosis and improve cosmesis.

Keywords

Breast cancer; brachytherapy; fat necrosis; cosmesis; partial breast

Introduction

For several decades breast conserving therapy (BCT) has been a standard treatment for early-stage breast cancer. The use of whole-breast irradiation (WBI) after BCS has been shown to reduce the risk of ipsilateral breast tumor recurrence over BCS alone (1). The observation that the majority of local recurrences after BCS are at or near the lumpectomy site (2) has led to investigation of accelerated partial breast irradiation (APBI) as an alternative to WBI. APBI can be completed within several days as compared to several weeks for conventional WBI. Various dose delivery methods have been used for APBI, including multicatheter interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation therapy, and external beam conformal radiation therapy. Early studies have reported low ipsilateral breast tumor recurrence (IBTR) rates with these techniques (3).

Mammary fat necrosis is a benign, sterile inflammatory process (4) that may be caused by trauma, biopsy, or breast surgery. Fat necrosis after adjuvant radiation therapy has been documented with external beam radiotherapy and interstitial or intracavitary brachytherapy (5–7). Fat necrosis may be an asymptomatic finding detected during breast cancer surveillance imaging. Mammographic findings may include a focal mass or opacity, microcalcifications, or as lipid cysts (8). During follow up fat necrosis may present as some combination of a palpable mass, mastalgia, or overlying skin erythema. Mastalgia may require analgesic medication or surgical intervention for pain control.

In the setting of APBI, evaluation of patient, tumor and treatment characteristics that may be associated with the development of fat necrosis and its clinical significance has been limited (5, 9, 10). In this study, a detailed analysis of fat necrosis has been performed on a large cohort of patients treated with APBI using HDR multicatheter interstitial brachytherapy with a median follow-up of more than 4 years. We examine clinical and treatment-related factors that could contribute to the risk of developing fat necrosis and its impact on cosmesis.

Methods and Materials

Between February 2003 and January 2010, 238 treated breasts in 236 patients with at least 6 months of follow-up were treated with APBI using HDR interstitial brachytherapy at Barnes-Jewish Hospital and Washington University School of Medicine. WBI was not given. Selection criteria included patients with unifocal American Joint Cancer Center Commission (AJCC, 6th edition) Tis-T2N0M0 breast cancers ≤ 3 cm treated with breast-conserving surgery. 181 of 187 patients with invasive disease had pathologic N0 disease assessed mainly by sentinel lymph node biopsy. Nine patients had prior radiation therapy with fields that were adjacent to or included the ipsilateral breast. Three of these patients had prior WBI and received adjuvant APBI for an ipsilateral breast tumor recurrence following a second partial mastectomy. Three of these patients were treated for Hodgkin's lymphoma, two were treated for soft tissue sarcoma of the upper extremity, and one was treated for non-Hodgkin's lymphoma. The Washington University School of Medicine Human Research Protection Office Institutional Review Board approved this retrospective review for Human Subjects.

All patients were treated with HDR interstitial brachytherapy using a high activity Iridium-192 source. The interstitial implants (ISI) were placed using a free hand technique with the goal of encompassing the surgical cavity with a 2 cm margin of breast tissue in all directions. It was common for there to be less than 2 cm of breast tissue in the anterior and/or the posterior directions due to the presence of the skin anteriorly or muscle or chest wall posteriorly. In general, an intraplane catheter spacing of 1.2 cm and an interplane spacing of 1.5 to 2.0 cm was used. All implants were multiplanar, and the use of more than two planes was common. ISI were placed intraoperatively with an opened surgical cavity in the first 45 patients with the breast surgeon re-incising the partial mastectomy incision and dissecting down to the surgical cavity. Thereafter predominantly real-time ultrasound guidance was used without reopening the surgical cavity. The partial mastectomy surgical cavities were never surgically obliterated. Real-time ultrasound guided implantation was performed using a strict sterile technique and under a combination of narcotic and anxiolytic sedation with local anesthesia. The direction of catheter planes was determined after considering how best to encompass the targeted breast tissue with the least catheters traversing a minimum amount of non-targeted breast tissue. The deepest plane of catheters, which was often at the level of but not into the pectoralis major muscle, was typically placed first. In some cases the deepest plane was in breast tissue 2 cm posterior to the surgical cavity. The most superficial plane of catheters was created next which was often 5 mm deep to the skin surface but in some cases was 2 cm anterior to the surgical cavity. 1.2 cm intracatheter spacing was used. If the distance between the deepest and most superficial planes of catheters was greater than 1.5–2.0 cm then additional planes were created in the interior of the CTV using a 1.5–2.0 cm intraplane spacing. Catheters in different planes were placed such that a plane passing through the center of the implant, orthogonal to the planes of the catheter applicators showed a triangular shape of the catheter cross sections.

The initial eight patients had surgical clips placed at the time of implantation and underwent two-dimensional brachytherapy treatment planning using multiple sets of orthogonal plain films. In these patients coded, radiopaque dummies were placed in each catheter which was in turn numbered. Several sets of two-dimensional (2D) radiographs of the implant were then taken in a conventional simulator at various gantry angles. Each catheter as well as each surgical clip was identified on each 2D image and then digitized into the Plato treatment planning system. This created a virtual three-dimensional (3D) space which contained the 3D implant structure and the surgical clips without any patient anatomy. The surgical clips were used as guides to determine the active lengths of each catheter. Treatment planning proceeded and exposure volumes such as V150 and V200 could be calculated and optimized in this virtual space but no explicit CTV could be created. All subsequent patients underwent computed tomography (CT) simulation (Brilliance CT Big Bore, Philips, Cleveland, (OH)) and 3D treatment planning. The Plato Brachytherapy planning system (Nucletron BV, Veenendaal, The Netherlands) was used through November 2006, after which treatment planning was done using the BrachyVision treatment planning system (Varian Medical Systems Inc., Palo Alto, CA). The clinical target volume (CTV) was created by adding a uniform 2 cm margin to the surgical cavity contour and subsequently limited to 5 mm away from the skin surface. The pectoral muscles, chest wall, and axilla were excluded from the CTV. No additional margin was added for the planning target volume (PTV), therefore the CTV was identical to the PTV.

The prescription dose in 236 cases (99%) was 3400 cGy delivered in 10 twice daily fractions. One patient who underwent reirradiation received 3000 cGy in 10 bid fractions, and one patient received 3200 cGy in 8 bid fractions. Treatment was given over 5 to 7 days, with a minimum of 6 hours separation between fractions.

Dosimetric goals prior to November 2003 included: 95% of the PTV receiving the prescribed dose, and prescription dose/mean central dose ≥ 0.7 . Mean central dose was defined as the mean of the local minimum doses between each set of three adjacent source lines within the source pattern (11). Since November 2003, the dosimetric goals were: 95% of the PTV receiving the prescribed dose, V150 $\geq 50 \text{ cm}^3$, V200 $\geq 20 \text{ cm}^3$, and dose homogeneity index, defined as $1 - (V150/V100) \leq 0.7$ (12). Vx is the volume receiving x% of the prescription dose.

Chemotherapy and hormonal therapy were administered at the discretion of the consulting medical oncologist. Chemotherapy was started at least 4 weeks after completion of APBI in all but two patients in whom it was completed prior to radiotherapy. Hormonal therapy was allowed during brachytherapy, but in practice was rarely started prior to APBI.

Follow-up

Patients were seen in follow-up one week after treatment, then every 3 months for one year, every 6 months for the next four years and yearly thereafter. Mammograms were obtained 6 to 12 months after completion of radiation therapy and then yearly thereafter, unless otherwise indicated.

Global cosmetic results were scored as excellent, good, fair or poor by the treating radiation oncologist (IZ) using the Harvard criteria (13). For analysis, the cosmetic results were dichotomized into excellent/good or fair/poor outcomes, and the worst cosmetic outcome was used (14). The breast retraction assessment (BRA) quantitates the amount of retraction by calculating the difference in distance from the sternal notch to the nipple in the treated versus the untreated breast. Nipple positions were measured and BRA was calculated according to the method of Pezner *et al.* (15). The percentage BRA (pBRA) is defined as $(\text{BRA}/\text{reference length}) \times 100$ corrects for variation in anatomy (16). Both BRA and pBRA were determined at each follow-up for 151 of 238 cases.

Fat necrosis was diagnosed by mammogram or clinical findings such as pain, redness, or a palpable mass. Patients with suspected fat necrosis were closely followed. Biopsy was recommended if the mammogram or clinical findings were suspicious for tumor recurrence. Because of a lack of a standard toxicity scoring system for fat necrosis, an institutional scoring system was developed and used to grade fat necrosis (Table 1). In general, symptomatic fat necrosis was initially treated with ketorolac 10 mg po tid for 5 days, followed by a course of naproxen sodium 220 mg po bid. Narcotic analgesics were often prescribed for the first 1–2 weeks. Narcotic analgesics were subsequently prescribed if pain was not adequately controlled with naproxen sodium. Surgery was ideally reserved for severe symptomatic fat necrosis that was not adequately controlled with analgesics. The highest toxicity score, worst cosmetic score, and pBRA value at three years for each patient were used for analysis.

Statistical Analysis

All time intervals were calculated from the date of completion of interstitial brachytherapy. Two cases of synchronous bilateral breast cancers treated with interstitial brachytherapy were treated as independent cases. Fat necrosis-free survival and actuarial rate of fat necrosis were calculated using the Kaplan-Meier method. Univariate logistic regression was used to examine clinical and treatment-related factors that could contribute to the risk of developing fat necrosis. Non-collinear variables with $p < 0.05$ were then included in a multivariate logistic regression analysis. The optimal cutpoint for V150 was determined using the method of Williams *et al.* (17). Fisher's exact test was used to identify the effects of V150 on fat necrosis and of fat necrosis on cosmetic outcome. Student's t-test was used to

analyze the effect of fat necrosis on pBRA. A p value of < 0.05 was considered statistically significant. All tests were two-sided. Statistical analyses were performed using StatView (version 5.0.1; SAS Institute Inc., Cary, NC) and SAS (version 9.2; SAS Institute Inc., Cary, NC).

Results

Patient, cancer, and treatment factors are summarized in Table 2. The median follow-up was 56 months (range, 6–94). The crude rate of fat necrosis was 17.6% ($n = 42$). The median time to diagnosis of fat necrosis was 21 months (range, 5–72 months) with 80% of cases diagnosed within three years of APBI. The 5-year actuarial rate of fat necrosis was 17.5%. The probability of fat necrosis-free survival is presented in Figure 1.

Table 1 presents the incidence and grading of fat necrosis. Asymptomatic (grade 1) fat necrosis occurred in 18 treated breasts (7.6%). Symptomatic (grade 2 to 4) fat necrosis occurred in 24 treated breasts (10.1%). For patients with grade 2 or 3 fat necrosis, the median time to resolution of pain was 3 months (interquartile range, 0.75–5.25). Three patients were scored as having grade 4 toxicity as they did have surgery to remove an area of fat necrosis. However, only one of the three patients had excision of a symptomatic mass after failing more conservative treatment, the second had excision of an asymptomatic mass, and the third had excision of a painful mass without receiving any conservative treatment first. Mammography at diagnosis of fat necrosis was reported using the Breast Imaging-Reporting and Data System (BI-RADS). Of the twelve patients with fat necrosis who had a biopsy, the mammography BI-RADS category was 3 for two patients, 4A for four patients, 4B for four patients, and 4C for two patients. In contrast, in the 27 patients with fat necrosis who did not have a biopsy, mammography was BI-RADS category 2 in 24, category 3 in two and 4A in one. The distribution of BI-RADS scores was significantly different between the patients who had a biopsy and those who did not ($p < 0.001$, Fisher's Exact Test). To date no patient with fat necrosis has subsequently developed an ipsilateral breast tumor recurrence.

Univariate logistic regression (Table 3) demonstrated that acute infection, anthracycline-based chemotherapy, number of catheters, V100, V150, V200 and IRAK were all significant predictors of fat necrosis. Hypertension, diabetes mellitus, smoking history, and prior radiation therapy were not significantly associated with fat necrosis. Treatment-related factors V100, V150, V200, IRAK, and number of catheters were collinear. Of the brachytherapy related factors that were significant in univariate analysis, V150 was most predictive and was used in the multivariate analysis. In a multivariate analysis including V150, acute infection, and anthracycline-based chemotherapy, only V150 was significantly associated with an increased risk of fat necrosis (Table 3). The calculated optimal cutpoint for V150 was 65 cm^3 . The rate of fat necrosis in patients with a V150 less than 65 cm^3 was 15.4%, compared to a rate of 38.5% when the V150 was 65 cm^3 or greater ($p = 0.011$). One of the nine patients who had prior radiation therapy developed asymptomatic fat necrosis.

Physician assessed cosmetic results were available for 235 (99%) of the treated breasts. Cosmesis was scored as excellent/good in 95% of treated. Fat necrosis was significantly associated with a fair/poor cosmetic outcome ($p = 0.009$). 151 patients had pBRA measurement data available. The mean pBRA at three years was 10.2 in the patients who developed fat necrosis, compared to 7.1 in patients who did not develop fat necrosis ($p = 0.02$).

Discussion

Mammary fat necrosis is a benign, sterile inflammatory process that is a well-described complication from post-lumpectomy irradiation of the breast (5–7). The RTOG late radiation morbidity scoring criteria does not make a distinction between symptomatic and asymptomatic fat necrosis; all fat necroses are scored as Grade 4 subcutaneous tissue toxicity. Since the clinical significance of fat necrosis can vary substantially, we created an institutional scoring system to grade fat necrosis (Table 1). This scoring system distinguishes between asymptomatic and symptomatic fat necrosis, with the severity of symptomatic fat necrosis graded by the management required for symptom control. Our scale is similar to that described by Lovey *et al.* (5).

In our study 7.6% of the treated breasts developed asymptomatic (grade 1) fat necrosis, and 10.1% developed symptomatic (grade 2 to 4) fat necrosis. The vast majority of patients with symptomatic fat necrosis were successfully managed with a course of non-steroidal anti-inflammatory drugs (NSAIDs). For patients with grade 2 or 3 fat necrosis, symptoms resolved after a median of 3 months. The rate of grade 4 fat necrosis was low. Of the three patients scored as having grade 4 fat necrosis, only one patient had surgical intervention for symptomatic fat necrosis that was inadequately controlled with analgesics. Based on this clinical experience, we recommend observation for asymptomatic fat necrosis. Symptomatic fat necrosis can be effectively managed with NSAIDs. Short-term narcotic analgesics may be beneficial if symptoms are inadequately controlled with NSAIDs, or if the patient has contraindications to NSAID therapy. Surgery should be reserved for patients who have symptomatic disease that is poorly controlled with analgesics. 28.6% of the patients in our study had a biopsy for histological confirmation, due to clinical and/or radiographic findings suspicious for tumor recurrence. Thus far no patient with fat necrosis has subsequently developed an ipsilateral breast tumor recurrence. Fat necrosis can be diagnosed clinically or radiographically in the majority of cases, without the need for biopsy. Biopsy should be limited to cases where there are suspicious clinical or mammographic finding such that tumor recurrence must be ruled out.

Our 5-year actuarial rate of fat necrosis is consistent with the reported rates in other studies which range from 2–52% (Table 4). In some of these studies, only symptomatic or “clinically evident” fat necrosis was reported (9, 18). The wide range of reported rates of fat necrosis may be influenced by differences in patient characteristics, treatment, length of follow-up or diagnostic criteria for fat necrosis. The rate of fat necrosis after ABPI using the MammoSite device was 2.3%, after a median follow-up time of 54 months in the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial (7). No specific criteria defining fat necrosis were given for the registry trial, therefore it is unknown if the lower rate of fat necrosis is due to a difference in diagnosis or treatment technique. The reported rate of fat necrosis after external beam APBI ranges from 6–25% (19–21). Although external beam APBI delivers a more homogenous dose distribution than multicatheter interstitial brachytherapy, fat necrosis is a potential late toxicity.

Although the median time to diagnosis of fat necrosis in our series was less than two years with 80% of cases diagnosed within three years, the incidence of fat necrosis continued to increase with time. New cases of fat necrosis were diagnosed as many as 71 months after treatment. The median time to diagnosis of fat necrosis reported in the literature varies considerably. Lovey *et al.* (5) and Ott *et al.* (6) reported median times of 15.5 months and 30 months, respectively. The median time to occurrence of fat necrosis reported in the William Beaumont series was substantially longer at 66 months, which may reflect the longer 6.5 year median follow-up of that series (22). These findings suggest that long follow-up, in excess of five years, may be necessary to fully evaluate fat necrosis toxicity.

Logistic regression models were used to assess the relationship between multiple patient and treatment characteristics and the development of fat necrosis while adjusting for multiple comparisons. We hypothesized that increasing volumes of increased radiation dose, increasing dose heterogeneity as well as factors that increased local inflammation such as infection and chemotherapy may predict the development of fat necrosis. In univariate analysis, acute infection, anthracycline-based chemotherapy, V100, V150, V200, IRAK and number of catheters were all significantly associated with the development of fat necrosis. Not surprisingly, treatment-related factors V100, V150, V200, IRAK, and number of catheters were collinear. In the multivariate analysis, only V150 was significantly associated with fat necrosis (odds ratio = 1.021; 95% CI 1.007–1.035). It is important to note that the odds ratio is per cm^3 , such that the risk of fat necrosis progressively increases as V150 increases. The rate of fat necrosis was notably higher when the V150 was greater than 65 cm^3 . Limiting high dose volumes, including limiting the V150 to less than 65 cm^3 , may reduce the risk of fat necrosis.

Analyzing the late toxicity of 75 patients treated with APBI using HDR interstitial brachytherapy, Wazer *et al.* (9) found that V150 and V200 were associated with an increased risk of fat necrosis in a univariate analysis. In contrast, Yeo *et al.* (10) reported on 48 patients treated with APBI using HDR interstitial brachytherapy, of whom 5 developed fat necrosis. They found no association of V100, V150 or DHI with fat necrosis. Lovey *et al.* (5) randomized 258 patients to APBI with interstitial brachytherapy or electron irradiation versus WBI and similarly found no correlation between implant parameters (V100, V150, DHI, number of catheters, and implant planes) and the rate of fat necrosis in the interstitial brachytherapy group. The lack of association between fat necrosis and treatment-related parameters in these latter studies may be due to smaller treatment volumes. The mean V100, indicative of treatment volume, was notably larger in our series and the study by Wazer *et al.* (9) (239 cm^3 and 176 cm^3 , respectively) than in the studies reported by Yeo *et al.* (10) and Lovey *et al.* (5) (63 cm^3 and 44.7 cm^3 , respectively). However it is unclear whether the differences in treatment volume are primarily due to a difference in the volume of irradiated breast tissue or in the size of the tumor cavity due to a difference in surgical technique.

Wazer *et al.* (9) reported that anthracycline-based chemotherapy given after APBI was associated with an increased risk of fat necrosis in a univariate analysis. Similar to our study, patients received chemotherapy an average of 4 weeks after completion of APBI. Chemotherapy nearly reached significance ($p = 0.06$) as a predictor of fat necrosis in our study. Analyzing the subgroup of patients who received anthracycline-based chemotherapy revealed a significant association with fat necrosis in univariate analysis; however there was not a significant association in multivariate analysis when V150 was included in the model. Our results suggest that anthracycline-based chemotherapy is not an independent predictor of fat necrosis when adjusted for other hypothesized factors.

Fat necrosis in this study was associated with worse cosmetic outcomes based on qualitative, dichotomized physician evaluation, and fat necrosis was also associated with greater breast retraction at three years as measured by pBRA. An association with worse cosmesis was also demonstrated by Lovey *et al.* (5). These results suggest that the architectural distortion and retraction caused by fat necrosis may lead to significant perceptible and measurable adverse changes in breast cosmesis, in addition to the commonly described radiographic and clinical findings.

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Glossary

HDR	high dose rate
APBI	accelerated partial breast irradiation.
BCS	breast-conserving surgery
pBRA	percentage breast retraction assessment
BCT	breast conserving therapy
WBI	whole-breast irradiation
IBTR	ipsilateral breast tumor recurrence
AJCC	American Joint Cancer Center Commission
ISI	interstitial implants
CT	computed tomography
PTV	planning target volume
BRA	breast retraction assessment
NSAIDs	non-steroidal anti-inflammatory drugs
V100	volume encompassed by the prescription isodose
V150	volume encompassed by the 150% isodose
V200	volume encompassed by the 200% isodose
DHI	dose homogeneity index = $1 - (V150/V100)$
IRAK	integrated reference air kerma
NR	not reported

Fig. 1.
Probability of fat necrosis free survival

Table 1

Fat necrosis toxicity scoring and incidence

Grade	Definition	No. of treated breasts (%)
Grade 0	No fat necrosis	196 (82.3)
Grade 1	Asymptomatic fat necrosis (painless palpable mass, radiologic or cytological findings)	18 (7.6)
Grade 2	Symptomatic fat necrosis requiring non-narcotic analgesics	19 (8.0)
Grade 3	Symptomatic fat necrosis requiring narcotic analgesics for more than 2 weeks	2 (0.8)
Grade 4	Symptomatic fat necrosis requiring surgical intervention	3 (1.3)

Table 2

Distribution of patient and treatment-related variables

Characteristic	Findings
Age (y)	
Mean (range)	59.6 (35–84)
Pathologic tumor stage	
Tis	51 (21.4%)
T1mic	3 (1.1%)
T1a	28 (11.8%)
T1b	81 (34%)
T1c	58 (24.3%)
T2	17 (7.1%)
Sentinel lymph node biopsy (for patients with invasive cancer)	
Yes	181 (96.8%)
No	6 (3.2%)
Margin status	
Negative (≥ 2 mm)	237 (99.6%)
Focally Positive	1 (0.4%)
Chemotherapy	
Yes	39 (16.4%)
Anthracycline-based chemotherapy	33 (13.9%)
No	199 (83.6%)
Hormonal therapy	
Yes	190 (79.8%)
No	48 (20.2%)
Hypertension	93 (39.1%)
Diabetes mellitus	25 (10.5%)
Smoking history	
Current smoker	29 (12.2%)
Former smoker	59 (24.8%)
Nonsmoker	150 (63%)
Cavity volume (cm ³)	
Mean (SD)	23.1 (19)
Number of catheters	
Mean (range)	20 (7–37)
V100 (cm ³)	
Mean (SD)	239 (100)
V150 (cm ³)	
Mean (SD)	47.5 (21.9)

Characteristic	Findings
V200 (cm ³)	
Mean (SD)	16.6 (6.6)
DHI	
Mean (SD)	0.80 (0.06)
IRAK	
Mean (SD)	0.34 (0.08)

Abbreviations: V100 = volume encompassed by the prescription isodose; V150 = volume encompassed by the 150% isodose; V200 = volume encompassed by the 200% isodose; DHI = dose homogeneity index = $1 - (V150/V100)$; IRAK = integrated reference air kerma

Table 3

Logistic regression analysis of variables associated with fat necrosis

Variable	Univariate		Multivariate	
	Odds Ratio (95% CI)	<i>p</i>	Odds Ratio (95% CI)	<i>p</i>
Age	1.015 (0.982–1.049)	0.374		
Hypertension	1.937 (0.989–3.788)	0.054		
Diabetes mellitus	2.475 (0.989–6.211)	0.052		
Smoking history				
Current vs. nonsmoker	1.802 (0.720–4.505)	0.208		
Former vs. nonsmoker	0.937 (0.406–2.165)	0.880		
Prior radiation therapy				
Yes vs. no	0.573 (0.069–4.717)	0.605		
Chemotherapy				
Yes vs. no	2.105 (0.949–4.673)	0.067		
Anthracycline-based chemotherapy				
Yes vs. no	2.353 (1.022–5.405)	0.043	2.053 (0.853–4.926)	0.108
Acute infection				
Yes vs. no	4.016 (1.032–15.63)	0.045	2.985 (0.708–12.50)	0.136
Hormonal therapy				
Yes vs. no	0.917 (0.405–2.075)	0.834		
Date of implant	0.997 (0.993–1.002)	0.237		
Number of catheters	1.080 (1.009–1.156)	0.026		
V100	1.004 (1.001–1.007)	0.012		
V150	1.024 (1.009–1.039)	0.002	1.021 (1.007–1.035)	0.004
V200	1.080 (1.029–1.133)	0.002		
DHI	0.027 (0.001–6.541)	0.197		
IRAK	1.047 (1.009–1.088)	0.016		

Abbreviations: V100 = volume encompassed by the prescription isodose; V150 = volume encompassed by the 150% isodose; V200 = volume encompassed by the 200% isodose; DHI = dose homogeneity index = $1 - (V150/V100)$; IRAK = integrated reference air kerma

Table 4

Fat necrosis in selected interstitial accelerated partial breast irradiation series

Author	Year	N	Total fat necrosis	Symptomatic fat necrosis	Median time to fat necrosis	Predictors of fat necrosis	Negative impact of fat necrosis on cosmesis
Lovey <i>et al.</i> (9)	2007	258	36.8%	11.5%	15.5 mo	Bra cup size	Yes (symptomatic)
Ott <i>et al.</i> (10)	2005	33	15.2%	NR	25.6 mo	NR	NR
Wazer <i>et al.</i> (11)	2006	75	13.3%	NR	NR	V150, V200	NR
Yeo <i>et al.</i> (12)	2010	48	10.4%	0%	NR	No	NR
Chen <i>et al.</i> (19)	2006	199	20.6%	4.5%	66 mo	NR	NR
Current Series	2011	236	17.6%	10.1%	21 mo	V150	Yes

Abbreviations: NR = not reported; V100 = volume encompassed by the prescription isodose; V150 = volume encompassed by the 150% isodose; V200 = volume encompassed by the 200% isodose