

CLINICAL INVESTIGATION

Breast

FAT NECROSIS AFTER PARTIAL-BREAST IRRADIATION WITH BRACHYTHERAPY OR ELECTRON IRRADIATION VERSUS STANDARD WHOLE-BREAST RADIOTHERAPY—4-YEAR RESULTS OF A RANDOMIZED TRIAL

KATALIN LÖVEY, M.D.,* JÁNOS FODOR, M.D., PH.D., D.Sc.,* TIBOR MAJOR, M.Sc., PH.D.,* ÉVA SZABÓ, M.D.,† ZSOLT OROSZ, M.D., PH.D.,‡ ZOLTÁN SÜLYÖK, M.D.,§ LEVENTE JÁNVÁRY, M.D.,* GEORGINA FRÖHLICH,* MIKLÓS KÁSLER, M.D., PH.D.,* AND CSABA POLGÁR, M.D., PH.D.*

Departments of *Radiotherapy, †Diagnostic Radiology, ‡Human and Experimental Tumor Pathology, and §General and Thoracic Surgery, National Institute of Oncology, Budapest, Hungary

Purpose: To examine the incidence and clinical relevance of fat necrosis after accelerated partial-breast irradiation (PBI) using interstitial high-dose-rate brachytherapy (HDR-BT) in comparison with partial-breast electron irradiation (ELE) and whole-breast irradiation (WBI).

Methods and Materials: Between 1998 and 2004, 258 early-stage breast cancer patients were randomized to receive 50 Gy WBI ($n = 130$) or PBI ($n = 128$). The latter consisted of either 7×5.2 Gy HDR-BT ($n = 88$) or 50 Gy ELE ($n = 40$). The incidence of fat necrosis, its impact on cosmetic outcome, accompanying radiologic features, and clinical symptoms were evaluated.

Results: The 4-year actuarial rate of fat necrosis was 31.1% for all patients, and 31.9%, 36.5%, and 17.7% after WBI, HDR-BT and ELE, respectively ($p_{WBI/HDR-BT} = 0.26$; $p_{WBI/ELE} = 0.11$; $p_{ELE/HDR-BT} = 0.025$). The respective rate of asymptomatic fat necrosis was 20.2%, 25.3%, and 10% of patients. The incidence of symptomatic fat necrosis was not significantly different after WBI (8.5%), HDR-BT (11.4%), and ELE (7.5%). Symptomatic fat necrosis was significantly associated with a worse cosmetic outcome, whereas asymptomatic fat necrosis was not. Fat necrosis was detectable with mammography and/or ultrasound in each case. Additional imaging examinations were required in 21% of cases and aspiration cytology in 42%.

Conclusions: Asymptomatic fat necrosis is a common adverse event of breast-conserving therapy, having no significant clinical relevance in the majority of the cases. The incidence of both symptomatic and asymptomatic fat necrosis is similar after conventional WBI and accelerated partial-breast HDR-BT. © 2007 Elsevier Inc.

Fat necrosis, Side effects, High-dose-rate brachytherapy, Accelerated partial-breast irradiation, Breast-conserving therapy.

INTRODUCTION

Fat necrosis of the breast is a benign inflammatory process that mostly occurs after any trauma of the breast; however the exact etiology of this condition is still unclear (1, 2). Retrospective studies suggest that, in addition to the trauma caused by the operation, irradiation after breast surgery has a significant role in the pathogenesis of fat necrosis (3–9). In the majority of cases, asymptomatic fat necrosis is described by follow-up mammograms and ultrasound (US) examinations, as “post-therapeutic findings” or “postirradiation changes” of the treated breast. Usually these findings have no clinical consequences. On the other hand, symptomatic (or clinically evident) fat necrosis includes cases accompanied by a palpable mass with or without pain, which some-

times requires medication or even surgical intervention (10–15).

The cautionary article from investigators at Tufts University (15) about the high rate of clinically evident fat necrosis after accelerated partial-breast irradiation (APBI) using interstitial high-dose-rate (HDR) implants prompted us to review and evaluate the incidence, clinical significance, and possible risk factors of fat necrosis in our patients who were treated within a randomized study with partial-breast irradiation (PBI) or standard whole-breast irradiation (WBI).

METHODS AND MATERIALS

A total of 258 selected early-stage breast cancer patients with pT1 pN0–1mi, nonlobular breast cancer without the presence of

Reprint requests to: Katalin Lövey, M.D., Department of Radiotherapy, National Institute of Oncology, Ráth György u. 7-9, Budapest, H-1122, Hungary. Tel: (+36) 1-224-8600; Fax: (+36) 1-224-8680 E-mail: klovey@oncol.hu

Conflicts of interest: none.
 Received Nov 22, 2006, and in revised form March 26, 2007.
 Accepted for publication March 28, 2007.

extensive intraductal component, and resected with negative margins were randomized at the National Institute of Oncology, Budapest between July 1998 and May 2004 to treatment with either conventional WBI ($n = 130$) or PBI ($n = 128$). In the PBI arm, 88 patients were assigned to treatment with 7×5.2 Gy b.i.d. use of HDR interstitial multi-catheter brachytherapy (BT) alone and the protocol allowed 50-Gy limited-field electron irradiation (ELE) for patients who were technically unsuitable for interstitial implantation ($n = 40$). Patient selection criteria, and details of treatment technique were described elsewhere (14, 16).

This analysis was limited to those patients who received at least one fraction of the assigned treatment. Two patients were excluded. One patient in PBI arm refused her assigned therapy (HDR-BT) and underwent mastectomy without radiotherapy (RT). Another patient in WBI arm developed distant metastasis before RT and did not receive the assigned treatment. Thus, the analysis included 256 patients.

Brachytherapy implants were performed 4 to 6 weeks after surgery under local anesthesia. Patients were treated with an HDR remote after loading equipment using a ^{192}Ir stepping source. Geometry of the implant was planned according to the Paris system guidelines. The entrance and exit points of the guide needles were determined with the help of preimplant radiograph simulation using a template with holes in triangular geometrical arrangement. The spacing between the needles was 13 or 15 mm. The guide needles were implanted according to the preimplant simulation and planning. Then the rigid needles were replaced with flexible plastic catheters, which were fixed with buttons. The treatment planning was based on a three-dimensional reconstruction of the surgical clips, skin points, and the implanted flexible catheters. The coordinates were digitized from two postimplant radiographs using the variable-angle reconstruction technique. All HDR-BT patients received antibiotics during the treatment period, plus 2 days thereafter.

The WBI (median dose, 50 Gy) was delivered with telecobalt ($n = 29$) or 6-MV to 9-MV photon beams ($n = 100$) using wedged tangential fields with 2-Gy daily fractions prescribed to the 95% isodose line. During treatment planning, the aim was to achieve a dose distribution with less than 10% of dose inhomogeneity in the central plane.

None of the patients received regional nodal irradiation, and only 1 patient received 16-Gy electron boost to the tumor bed.

We performed ELE irradiation (median dose, 50 Gy) using a 6- to 15-MeV *en face* electron field to the tumor bed extended with a margin of 1.5 to 2 cm. Electron fields were shaped using available conical or square applicators. The 2-Gy daily fractions were prescribed to the 80% isodose line.

Adjuvant systemic treatments were given according to the actual institutional treatment protocol. Hormone therapy consisted of tamoxifen (132 patients) or aromatase inhibitors (47 patients), with or without goserelin acetate, according to the menopausal status and hormone receptor levels. Only 7 patients received adjuvant chemotherapy before RT. Four of these patients were treated with an anthracycline containing regimen, and the others with cyclophosphamide, methotrexate, and fluorouracil. Details of patient and treatment characteristics are listed in Table 1.

Follow-up

Patients were seen every 3 months in the first 2 years and every 6 months thereafter. Mammography and breast US examinations were done at 6 and 12 months postirradiation and then once a year. In the case of uncertain or controversial mammography or US findings, breast MRI, was performed with or without aspiration cytology

Table 1. Patient and treatment characteristics by radiotherapy technique

Characteristic	WBI ($n = 129$)	HDR-BT ($n = 87$)	ELE ($n = 40$)
Mean age (y)	58	59	58
Range	31–80	30–79	30–84
Median follow-up (months)	48	50	49.5
Premenopausal (n)	27 (21%)	16 (17%)	11 (27.5%)
Median excised tissue volume (ml)	225	252	208
Range	40–825	70–576	48–600
Bra cup size (n)*			
A–B	75 (58%)	41 (47%)	29 (72.5%)
C–D	54 (42%)	46 (53%)	11 (27.5%)
Adjuvant systemic treatment			
None	35 (27%)	28 (32%)	10 (25%)
AHT	89 (69%)	58 (67%)	29 (72.5%)
CHT	2 (2%)	1 (1%)	1 (2.5%)
AHT and CHT	3 (2%)	0	0
Implant parameters			
Median no. of catheters (range)	–	9 (4–13)	–
No. of planes			
1	–	1 (1%)	–
2	–	47 (54%)	–
3	–	38 (44%)	–
4	–	1 (1%)	–
Mean V100 cm ³ (range)	–	63 (27–120)	–
Mean V150 cm ³ (range)	–	24 (7–56)	–
Mean DHI (range)	–	0.62 (0.37–0.79)	–

Abbreviations: AHT = antihormonal therapy; CHT = chemotherapy; DHI = dose homogeneity index = $(V100 - V150)/V100$; ELE = partial-breast electron irradiation; HDR-BT = high-dose-rate brachytherapy; V100 = volume encompassed by the surface of the prescription isodose; V150 = volume encompassed by the surface of the 150% isodose; WBI = whole-breast irradiation.

* $P_{\text{HDR-BT/ELE}} = 0.006$; $P_{\text{HDR-BT/WBI}} = 0.073$; $P_{\text{WBI/ELE}} = 0.073$.

or core biopsy. Abdominal US, chest X-ray, and blood tests were performed at least annually.

Evaluation of toxicity and cosmetic results

Mammograms were evaluated in the regular morning audit of the diagnostic radiology department and all follow-up mammograms were also reviewed retrospectively by one expert searching for visible signs of fat necrosis. Incidence, time to occurrence, clinical symptoms, and radiologic features of fat necrosis, type, and number of additional differential diagnostic procedures (*e.g.*, radiologic examinations, fine needle aspiration cytology or core biopsy) were documented. Because of the lack of clinically useful grading systems, an institutional scoring scheme was developed and used to grade fat necroses (Table 2).

The possible relation between the radiologic appearance and clinical symptoms of fat necrosis was examined. The cosmetic results were scored using the Harvard criteria (17). The possible effect of fat necrosis on the final cosmetic outcome was assessed.

Table 2. Scoring system for fat necrosis

Grade	Definition
Grade 0	No fat necrosis
Grade 1	Asymptomatic fat necrosis (only radiologic and/or cytologic findings)
Grade 2	Symptomatic fat necrosis not requiring medication (palpable mass with or without mild pain)
Grade 3	Symptomatic fat necrosis requiring medication (palpable mass with significant pain)
Grade 4	Symptomatic fat necrosis requiring surgical intervention

Possible patient- and treatment-related risk factors for developing fat necrosis were examined. Treatment related factors included tissue volume excised during surgery, RT technique (WBI vs. HDR-BT vs. ELE), implant parameters (number of implant catheters and planes, V100%, V150%, dose-homogeneity index) for HDR-BT patients, beam energy of WBI (telecobalt vs. 6–9 MV photons), and adjuvant systemic treatments. Incidence of fat necrosis was also evaluated by patient age, menopausal status, and breast size (using bra cup classification).

Statistical analysis

Time to fat necrosis was calculated from the date of surgery. Fat necrosis-free survival, and actuarial rate of fat necrosis was calculated using the Kaplan-Meier method. The log-rank test was used to compare time distributions. Relative risk (RR) and associated confidence intervals (95% CI) were calculated from the proportional regression coefficients. Relations between fat necrosis and continuous variables were studied using Pearson's and Spearman's correlation tests. Discrete variables were analyzed using chi-square and Fisher's exact tests. A probability level of 0.05 was considered to be statistically significant. Cox's regression analysis was used to determine predictors of fat necrosis. The SOLO software (Department of Biometrics, University of California, Los Angeles, CA) was used for statistical analyses.

RESULTS

With a median follow-up time of 48 months (range, 3–85), overall 76 patients (29.7%) developed fat necrosis. The crude rate of fat necrosis was 28.7% ($n = 37$) in the WBI, 36.8% ($n = 32$) in the HDR-BT, and 17.5% ($n = 7$) in the ELE arms, respectively. The 4-year actuarial rate of fat necrosis was 31.1% for all of the patients; 31.9%, 36.5%, and 17.7% after WBI, HDR-BT, and ELE, respectively (Fig. 1). The difference in the 4-year actuarial rates of fat necrosis was not statistically significant among patients treated with WBI and HDR-BT ($p = 0.26$; RR = 0.76; 95% CI = 0.48–1.23). However, the actuarial rate and relative risk of fat necrosis after ELE was significantly lower than in the HDR-BT group ($p = 0.025$; RR = 0.42; 95% CI = 0.18–0.94).

Incidence and grading of fat necrosis by RT technique are presented in Table 3. The crude rate of asymptomatic (Grade 1) fat necrosis was 20.2% ($n = 26$), 25.3% ($n = 22$), and 10.0% ($n = 4$) in patients treated with WBI, HDR-BT, and ELE, respectively. The respective rate of symptomatic (Grade 2–4) fat necrosis was 8.5% ($n = 11$), 11.5% ($n = 10$), and 7.5% ($n = 3$), in the WBI, HDR-BT, and ELE groups

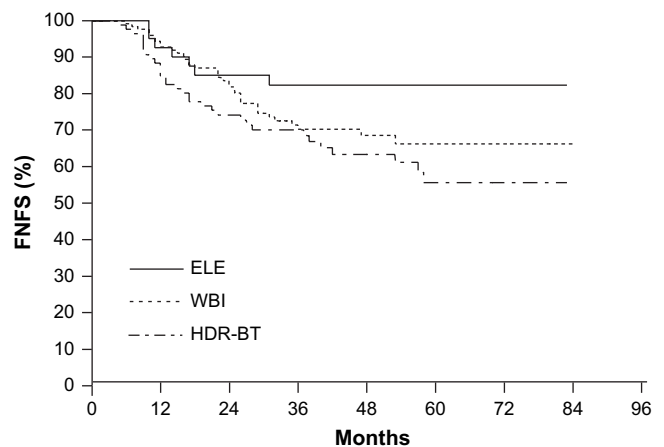


Fig. 1. Probability of fat necrosis-free survival (FNFS) after whole-breast irradiation (WBI), high-dose-rate brachytherapy (HDR-BT), and partial-breast electron irradiation (ELE). Four-year actuarial rate of fat necrosis: WBI: 31.9%, HDR-BT: 36.5%, ELE: 17.7%. Relative risk (RR) of fat necrosis after WBI vs. HDR-BT = 0.76 (95% CI = 0.48–1.23, $p = 0.26$); RR after WBI vs. ELE = 1.88 (95% CI = 0.84–4.22, $p = 0.11$); RR after ELE vs. HDR-BT = 0.42 (95% CI = 0.18–0.94, $p = 0.025$).

($p = \text{NS}$). Among these patients, 8 (6.3%), 2 (2.3%), and 1 (2.5%) developed significant breast pain (Grade 3 fat necrosis) requiring medication ($p = \text{NS}$). Only 1 patient (1.1%) in HDR-BT group required surgical intervention because of a painful firm mass (Grade 4 fat necrosis). On the other hand, one patient (0.8%) in WBI group underwent mastectomy, because of severe breast pain and fibrosis (without evidence of fat necrosis).

The median time to diagnosis of fat necrosis was 17 months (range, 5–58), and it was not significantly different according to RT technique: 22, 15.5, and 14 months after WBI, HDR-BT, and ELE, respectively. The incidence of fat necrosis increased over time. However, more than two-thirds ($n = 51$; 67.1%) of all fat necroses were diagnosed during the first 2 years of follow-up.

Radiologic signs of fat necrosis were detectable with mammography and/or US in each case. Four main radiologic types of fat necrosis were identified (Fig. 2). The rates of different radiologic types of fat necrosis were similar after WBI, HDR-BT, or ELE. There was no association between the radiologic types and clinical signs of fat necrosis. The mean size of fat necrosis measured by mammography, US, or MRI was 14 mm (range, 3–42 mm). The size of fat necrosis did not change over time in 65 patients (85.5%), slightly increased (with 2–15 mm) in 5 cases (6.6%), and decreased in 6 patients (7.9%). Among the latter, 2 fat necroses (2.6%) disappeared completely within 24 months.

Of 76 fat necroses, 64 (84.2%) were located in the tumor bed or next to the surgical scar and 12 (15.8%) elsewhere in the breast or in the axillary tail. The latter localization was more often after PBI than in the WBI arm (20.5% vs. 10.8%, $p = 0.25$).

At the date of analysis, data on cosmetic outcome were available in 86% ($n = 220$) of patients. Cosmetic results

Table 3. Incidence and grading of fat necrosis by radiotherapy technique

Fat necrosis score	WBI (<i>n</i> = 129)	HDR-BT (<i>n</i> = 87)	ELE (<i>n</i> = 40)	All patients (<i>n</i> = 256)
Grade 0	92 (71.3%)	55 (63.2%)	33 (82.5%)	180 (70.3%)
Grade 1	26 (20.2%)	22 (25.3%)	4 (10%)	52 (20.3%)
Grade 2	3 (2.3%)	7 (8%)	2 (5%)	12 (4.7%)
Grade 3	8 (6.2%)	2 (2.3%)	1 (2.5%)	11 (4.3%)
Grade 4	0 (0%)	1 (1.1%)	0 (0%)	1 (0.4%)

Data presented as number of patients, with percentages in parentheses.

Abbreviations: ELE = partial-breast electron irradiation; HDR-BT = high-dose-rate brachytherapy; WBI = whole-breast irradiation.

Grade 1 represents asymptomatic fat necrosis. Grade 2 to 4 represent symptomatic fat necrosis.

according to fat necrosis and RT technique are presented in Table 4. Symptomatic fat necrosis was significantly associated with worse cosmetic outcome for all patients ($p=0.0014$). However, asymptomatic fat necrosis had no impact on cosmetic results. Only 1 patient, who was in the WBI group, underwent plastic surgery to improve cosmetic outcome.

To evaluate suspicious or uncertain findings, 16 of 76 patients (21%) with fat necrosis required additional mammography either with or without US. Additional breast MRI was necessary for differential diagnosis in 9 patients (12%). Aspiration cytology was performed in 32 patients (42%). Because of unrepresentative samples, a second aspiration was required in 2 patients. Among these 34 patients undergoing fine-needle aspiration, the diagnosis of fat necrosis was confirmed in 27 (79%); in the other 7 (21%), seroma formation and/or fibrosis was found. In only 3 cases (4%) were core biopsies performed after indefinite aspiration cytology. Taking all additional differential diagnostic procedures into account, 36 of 76 patients (47%) required at least one complementary examination.

Among the evaluated patient-, tumor-, and treatment-related variables, only bra cup size was significantly associated with the incidence of fat necrosis. In all, 36 of 145 patients (24.8%) having bra cup size A–B and 40 of 111 patients (36%) with larger breast size (cup size C–D) developed fat necrosis ($p = 0.036$). The crude rate of fat necrosis in the WBI group was similar in patients treated with telecobalt

or 6- to 9-MV photon beams (30.4% and 28.3%, $p = \text{NS}$). In the HDR-BT group, there was no correlation among specific implant parameters (V100, V150, DHI, number of catheters, and implant planes), and the actual rate of fat necrosis (Table 5).

DISCUSSION

Fat necrosis of the breast is a benign inflammatory process that has certain histologic features, a spectrum of imaging features and a number of etiologies (1, 18, 19). Traumatic fat necrosis was first described by Lee and Adair (2) in 1920. In the majority of cases, fat necrosis is caused by trauma, which can be accidental or iatrogenic, related to breast surgery or biopsy. Radiation therapy and some medications (*e.g.*, calciphylaxis and anticoagulant therapy) have been documented as additional factors associated with the development of fat necrosis (19). It has been stated that benign calcifications caused by fat necrosis may develop in one third to one half of irradiated breasts (6–9). On the other hand, Boyages *et al.* (3) noted that fat necrosis has not been described in patients with breast cancer treated by radiation alone. One may argue that interstitial brachytherapy (given as a boost or sole radiation treatment) can increase the incidence of fat necrosis because of the additional trauma caused by the implant needles and/or the inhomogeneity of the dose delivered by brachytherapy. Hypofractionation used in

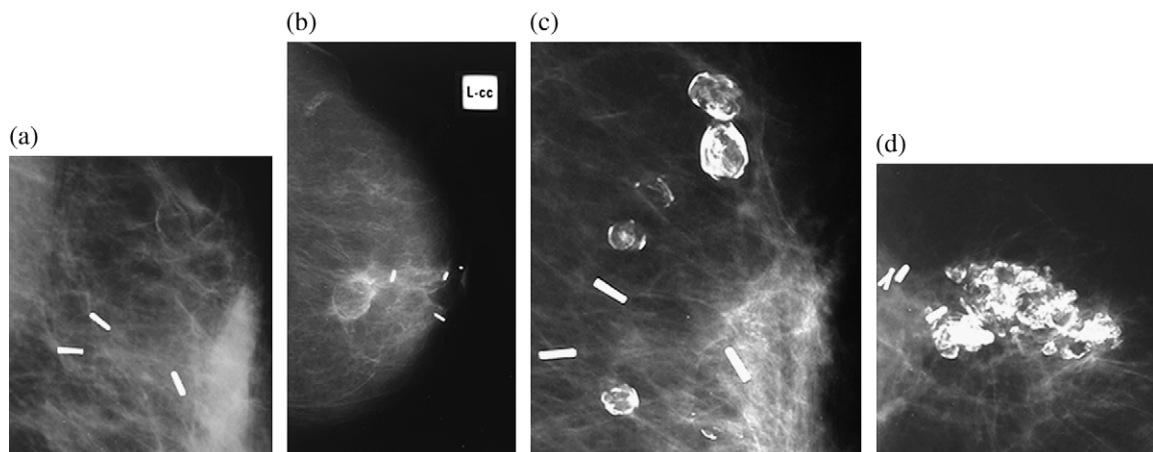


Fig. 2. Radiologic features of fat necrosis. (a) Oil cysts without calcification; (b) pseudocyst with benign-type macrocalcification; (c) pseudocysts with ring-like coarse calcification; (d) benign-type macrocalcification without cyst formation.

Table 4. Incidence of good/excellent cosmetic results according to grade of fat necrosis and radiotherapy technique

Fat necrosis	WBI (n = 102)	HDR-BT (n = 80)	ELE (n = 38)	All patients (n = 220)*
No fat necrosis (G0)	62% (44/71)	94% (47/50)	74% (23/31)	75% (114/152)
Asymptomatic fat necrosis (G1)	68% (15/22)	85% (17/20)	75% (3/4)	76% (35/46)
Symptomatic fat necrosis (G2–4)	22% (2/9)	60% (6/10)	33% (1/3)	41% (9/22)
All cases (G0–4)	60% (61/102)	87% (70/80)	71% (27/38)	72% (158/220)

Data are presented as percentage of patients with good/excellent cosmesis, with numbers in parentheses.

Abbreviations: ELE = partial-breast electron irradiation; HDR-BT = high-dose-rate brachytherapy; WBI = whole-breast irradiation.

* Data on cosmetic results were available for 220 of 256 patients (86%).

accelerated partial-breast HDR-BT protocols may also contribute to a higher incidence of late subcutaneous toxicity.

To explore these hypotheses, we have reviewed the clinical records and imaging findings of 256 patients treated in a randomized trial with PBI using multi-catheter HDR-BT or ELE versus conventional WBI. At a median follow-up of 48 months, there was no significant difference in the 4-year actuarial rates of fat necrosis between patients treated with HDR-BT and those given WBI (36.5% vs. 31.9%). The possible explanation for the lower incidence of fat necrosis (17.7%) observed in the ELE group is that significantly more patients with smaller breast cup sizes (*e.g.*, cup size A–B) and superficial excision cavity were preferably selected for ELE in the PBI arm. It is also supported by our finding that among the evaluated patient-, tumor-, treatment-related variables, only bra cup size (C–D vs. A–B) was significantly associated with the incidence of fat necrosis. It is assumed that less surgical trauma might contribute to the lower rate of fat necrosis among patients with smaller breasts. Theoretically, dose inhomogeneity associated with larger bra cup size might also influence the incidence of fat necrosis in patients treated with WBI. In the majority of our patients treated with WBI, the dose distribution was determined in one CT slice in the central plane of the breast. Thus, we could not analyze the possible relationship between three-dimensional dose distribution and location of fat necroses.

Interestingly, the rate of fat necrosis located outside the tumor bed and the surgical scar (*e.g.*, elsewhere in the breast or in the axillary tail) was higher in the PBI arm (20% vs. 11%, $p = \text{NS}$). Wazer *et al.* (15) also found that only in 4 of 8 cases, mammographic macrocalcifications consistent with fat necrosis have developed within the implant volume after interstitial brachytherapy. These observations point to the possible role of non-RT-related factors (*e.g.*, the trauma caused by the implant needles themselves) in the development of this adverse event.

Unfortunately, the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme is not suitable to make distinction between symptomatic and asymptomatic fat necrosis, as using its definitions all fat necroses should be scored as Grade 4 (20). The LENT-SOMA scoring scheme also has limitations to grade fat necrosis because of its complexity (21). Furthermore, using the LENT-SOMA criteria, asymptomatic fat necrosis (without pain and palpable density or firmness) should not be classified as a side effect. Because of the lack of clinically useful grading systems, an institutional scoring scheme was developed and used to grade fat necrosis (Table 2). Using this classification, we could objectively assess the clinical relevance of fat necrosis according to different RT techniques. More than two thirds ($n = 51$; 67.1%) of all fat necroses were asymptomatic (Grade 1) without any palpable firmness or breast pain. The rate of symptomatic (Grades 2–4) fat necrosis was similar independent of the RT technique used. Only one patient (1.1%) in HDR-BT group required surgical intervention because of a Grade 4 fat necrosis. These findings obtained from a randomized clinical trial give further evidence to the observation of others that APBI using multi-catheter implants does not increase the risk of fat necrosis compared with conventional WBI (22, 23).

The overall rate of fat necrosis in other interstitial APBI series was reported in the range of 2% to 52% (10–13, 22–30) (Table 6). It is to be noted that in earlier studies, only symptomatic or so called “clinically evident” fat necroses were reported, excluding cases that can only be detected by a systematic review of imaging findings (10, 12, 15, 25, 26, 29). The cautionary publication of Wazer *et al.* (15) about a relatively high rate (27%) of clinically definable fat necrosis after HDR-BT alone prompted some investigators to explore the true incidence and clinical relevance of fat necrosis associated with partial-breast brachytherapy (11, 13, 22, 31). The

Table 5. Implant parameters by presence of fat necrosis (high-dose-rate brachytherapy group, $n = 87$)

Implant parameter	Fat necrosis (n = 32)	No fat necrosis (n = 55)
Median no. of catheters	9	9
Range	5–13	4–13
Median no. of planes	2	2
Range	2–3	1–4
Mean V100 (cm ³)	63	63
Range (cm ³)	28–120	27–107
Mean V150 (cm ³)	25	24
Range (cm ³)	8–56	7–46
Mean DHI	0.61	0.62
Range	0.37–0.78	0.45–0.79

Abbreviations: DHI = dose homogeneity index = (V100–V150)/V100. V100 = volume of tissue encompassed by the prescription isodose surface; V150 = volume of tissue encompassed by the 150% isodose surface.

Table 6. Reported incidence and grading of fat necrosis in different interstitial accelerated partial-breast irradiation series

Institution (Reference)	Patients (n)	Median follow-up (mo)	Total dose and technique	Crude rate of fat necrosis			
				Grade 1	Grade 2–3	Grade 4	Overall
William Beaumont Hospital (23)	89	≥36	50 Gy LDR/32–34 Gy HDR	4%*		0	4%
William Beaumont Hospital (11)	199	77	50 Gy LDR/32–34 Gy HDR	16%	3.0%	1.5%	21%
Tufts/Brown/Virginia Universities (24)	75	73	34 Gy HDR	NR	NR	NR	13%
Ochsner Clinic (12, 25)	51	75	45 Gy LDR/32 Gy HDR	NR	20%	4%	24%
Massachusetts General Hospital (26)	48	23	50–60 Gy LDR	NR	0	6%	6%
National Institute of Oncology (13)	45	81	30.3–36.4 Gy HDR	20.0%*		2%	22%
Virginia Commonwealth University (10)	44	42	45 Gy LDR/34 Gy HDR	NR	2%	0	2%
London Regional Cancer Center (27, 28)	39	91	37.2 Gy HDR	5%	8%	0	13%
University Hospital Erlangen (22)	33	35	32 Gy HDR/49.8 Gy LDR	12%	3.0	0	15%
Tufts/Brown University (29)	33	33	34 Gy HDR	NR	24%	0	24%
Tufts/Brown University (30)	33	83	34 Gy HDR	NR	NR	NR	52%
Present study (HDR-BT group)	87	48	36.4 Gy HDR	25%	10%	1%	36%

Abbreviations: HDR = high-dose-rate; HDR-BT = high-dose-rate brachytherapy; LDR = low-dose-rate; NR = not reported.

* Grade 1–2 fat necroses were reported together, Grade 3 fat necrosis did not occur.

observed rate of asymptomatic fat necrosis ranging from 12% to 20% in the latter studies is fairly comparable to our findings of 25%. In our previous retrospective comparative study, 7 years after HDR-BT and WBI the corresponding rates of asymptomatic fat necrosis were 20% and 21% (13). Nevertheless, all investigators reported a consequently low rate (0–6%) of Grade 4 fat necrosis requiring surgical intervention (Table 6).

The possible association between fat necrosis and final cosmetic outcome was also assessed. Asymptomatic fat necrosis did not have any influence on cosmetic results. However, symptomatic fat necrosis was significantly associated with worse cosmetic outcome, and this negative effect was independent of the RT technique used (Table 4).

The median time to diagnosis of fat necrosis was 17 months in our series. Incidence of fat necrosis increased over time with a plateau at 2 years, but no further fat necrosis was diagnosed after 5 years. On the contrary, the median time to occurrence was 66 months (range, 3–98 months) in the Beaumont series, and 30 months (range, 10–37 months) in the German–Austrian APBI trial (11, 22). The difference in the time pattern of fat necrosis among the three series is significant. In our study, each follow-up mammogram has been reviewed retrospectively by 1 expert in diagnostic radiology. In some patients, early imaging signs of fat necrosis (*e.g.*, small oil cysts without calcification) were less apparent, and imaging features became obvious only a few years after treatment as ring-like or coarse calcification deposited in the wall of the pseudo-cysts. In earlier mammography studies, others reported that fat necroses usually develop up to 5 years

after treatment and may or may not be associated with a change on the mammogram (3, 4, 6–9).

Approximately half (47%) of the 76 patients with fat necrosis underwent at least one post-treatment differential diagnostic procedure, including mammography/US in 21% patients, breast MRI in 12%, aspiration cytology in 42%, and core biopsy in 4%. However, the rate of patients needing additional diagnostic examination(s) was similar for groups treated with HDR-BT, ELE, or conventional WBI. Only 1 of 75 patients (1.3%) underwent open surgery.

In the study of Wazer *et al.* (15), core needle biopsy was performed in 5 of 8 patients with clinically evident fat necrosis, and no patient underwent open biopsy.

In the William Beaumont series, 45 of 199 patients (23%) treated with interstitial PBI underwent a post-treatment diagnostic procedure on the breast (31). Among the 41 patients developing fat necrosis, 6 (15%) required a biopsy to establish the diagnosis, and only 3 (7%) underwent surgical excision (11, 31). Benitez *et al.* (31) stated that with the advent of minimally invasive biopsy techniques differential diagnosis is potentially possible in patients who present with a tender and/or suspicious mass for fat necrosis. Our results also reinforce that routine follow-up examinations (*e.g.*, mammography, US, aspiration cytology) are sufficient for the differential diagnosis of fat necrosis in the vast majority of cases. To avoid needless open surgical biopsies, additional core biopsy and breast MRI are useful for differentiating fat necrosis from recurrent tumor.

In the combined Tufts/Brown/Virginia Commonwealth University study of multi-catheter HDR-BT alone, the use

of adriamycin-based chemotherapy was associated with an increased risk of clinically evident fat necrosis (24). In the present study, only 7 patients received chemotherapy, 4 of them (and only 1 in HDR-BT group) with anthracycline-containing regimens. Because of the small sample size, we cannot draw any conclusion on the possible interactive effect between chemotherapy and different RT techniques. However, it is to be noted that only 1 (14.2%) of our patients receiving chemotherapy developed asymptomatic fat necrosis.

Neither beam quality (telecobalt vs. 6- to 9-MV photons) in WBI group, nor parameters of implant quality in HDR-BT group had any impact on the incidence of fat necrosis (Table 5). In two consecutive analyses of Wazer *et al.* (24, 29) the volume of the implant and dose “hotspots” as defined by V100, V150, and V200 were significantly correlated with the incidence of fat necrosis, but DHI did not. It seems that in the range of our smaller volume implants (up to 120 cm³), neither implant volume (V100), nor volume of

high-dose region (V150), nor DHI was associated with an increased risk of fat necrosis.

CONCLUSION

Asymptomatic fat necrosis is a common adverse event in breast-conserving therapy, having no significant clinical relevance in the majority of cases. The incidence of both symptomatic and asymptomatic fat necroses is similar after conventional WBI and accelerated partial-breast HDR-BT. Routine follow-up examinations (*e.g.*, mammography, US, aspiration cytology) are sufficient for the differential diagnosis of fat necrosis in the vast majority of cases. Open surgical biopsy should be avoided when possible, because additional core biopsy and breast MRI are useful for differentiating fat necrosis from recurrent tumor. Because of the lack of clinically useful grading systems, a new scoring scheme is recommended for grading fat necrosis after breast-conserving therapy.

REFERENCES

1. Bilgen IG, Ustun EE, Memis A. Fat necrosis of the breast: Clinical, mammographic and sonographic features. *Eur J Radiol* 2001;39:92–99.
2. Lee BJ, Adair FE. Traumatic fat necrosis of the female breast and its differentiation from carcinoma. *Ann Surg* 1920;72:188–195.
3. Boyages J, Bilous M, Barraclough B, *et al.* Fat necrosis of the breast following lumpectomy and radiation therapy for early breast cancer. *Radiother Oncol* 1988;13:69–74.
4. Chaudary MM, Girling A, Girling S, *et al.* New lumps in the breast following conservation treatment for early breast cancer. *Breast Cancer Res Treat* 1988;11:51–58.
5. Clarke D, Curtis JL, Martinez A, *et al.* Fat necrosis of the breast simulating recurrent carcinoma after primary radiotherapy in the management of early stage breast carcinoma. *Cancer* 1983;52:442–445.
6. Dershaw DD, Shank B, Reisinger S. Mammographic findings after breast cancer treatment with local excision and definitive irradiation. *Radiology* 1987;164:455–461.
7. Dershaw DD. Evaluation of the breast undergoing lumpectomy and radiation therapy. *Radiol Clin North Am* 1995;33:1147–1160.
8. Dershaw DD. Mammography in patients with breast cancer treated by breast conservation (lumpectomy with or without radiation). *Am J Roentgenol* 1995;164:309–316.
9. Libshitz HI, Montague ED, Paulus DD. Calcifications and the therapeutically irradiated breast. *Am J Roentgenol* 1977;128:1021–1025.
10. Arthur DW, Koo D, Zwicker RD, *et al.* Partial breast brachytherapy after lumpectomy: Low-dose-rate and high-dose-rate experience. *Int J Radiat Oncol Biol Phys* 2003;56:681–689.
11. Chen PY, Vicini FA, Benitez P, *et al.* Long-term cosmetic results and toxicity after accelerated partial-breast irradiation: A method of radiation delivery by interstitial brachytherapy for the treatment of early-stage breast carcinoma. *Cancer* 2006;106:991–999.
12. Kuske RR, Bolton JS, McKinnon WMP, *et al.* 5-Year results of a prospective phase II trial of wide-volume brachytherapy as the sole method of breast irradiation in Tis, T1, T2, N0–1 breast cancer [Abstract]. *Int J Radiat Oncol Biol Phys* 1998;42(Suppl. 1):181.
13. Polgar C, Major T, Fodor J, *et al.* High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: Seven-year results of a comparative study. *Int J Radiat Oncol Biol Phys* 2004;60:1173–1181.
14. Polgar C, Sulyok Z, Fodor J, *et al.* Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-year results of a phase I–II study and initial findings of a randomized phase III trial. *J Surg Oncol* 2002;80:121–128.
15. Wazer DE, Lowther D, Boyle T, *et al.* Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2001;50:107–111.
16. Polgar C, Strnad V, Major T. Brachytherapy for partial breast irradiation: The European experience. *Semin Radiat Oncol* 2005;15:116–122.
17. Harris J, Levine M, Svensson G, *et al.* Analysis of cosmetic results following primary radiation therapy for stage I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979;5:257–261.
18. Hogge JP, Robinson RE, Magnant CM, *et al.* The mammographic spectrum of fat necrosis of the breast. *Radiographics* 1995;15:1347–1356.
19. Williams HJ, Hejmadi RK, England DW, *et al.* Imaging features of breast trauma: A pictorial review. *Breast* 2002;11:107–115.
20. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
21. LENT-SOMA tables. *Radiother Oncol* 1995;35:17–60.
22. Ott OJ, Schulz-Wendtland R, Uter W, *et al.* Fat necrosis after conserving surgery and interstitial brachytherapy and/or external-beam irradiation in women with breast cancer. *Strahlenther Onkol* 2005;181:638–644.
23. Vicini FA, Baglan KL, Kestin LL, *et al.* Accelerated treatment of breast cancer. *J Clin Oncol* 2001;19:1993–2001.
24. Wazer DE, Kaufman S, Cuttino L, *et al.* Accelerated partial breast irradiation: An analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2006;64:489–495.

25. King TA, Bolton JS, Kuske RR, *et al.* Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for Tis, 1, 2 breast cancer. *Am J Surg* 2000;180:299–304.
26. Lawenda BD, Taghian AG, Kachnic LA, *et al.* Dose–volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose-rate interstitial implant. *Int J Radiat Oncol Biol Phys* 2003;56: 671–680.
27. Perera F, Chisela F, Stitt L, *et al.* TLD skin dose measurements and acute and late effects after lumpectomy and high-dose-rate brachytherapy only for early breast cancer. *Int J Radiat Oncol Biol Phys* 2005;62:1283–1290.
28. Perera F, Yu E, Engel Y, *et al.* Patterns of breast recurrence in a pilot study of brachytherapy confined to the lumpectomy site for early breast cancer with six years' minimum follow-up. *Int J Radiat Oncol Biol Phys* 2003;57:1239–1246.
29. Wazer DE, Berle L, Graham R, *et al.* Preliminary results of a phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer. *Int J Radiat Oncol Biol Phys* 2002;53:889–897.
30. Kaufman SA, DiPetrillo TA, Midle JB, *et al.* Long-term outcome and toxicity in a Phase I/II trial using HDR multicatheter interstitial brachytherapy for T1–2 breast cancer [Abstract]. *Brachytherapy* 2006;5:86.
31. Benitez PR, Chen PY, Vicini FA, *et al.* Partial breast irradiation in breast conserving therapy by way of interstitial brachytherapy. *Am J Surg* 2004;188:355–364.