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Cosmetic Analysis Following Breast-Conserving Surgery and Adjuvant High-Dose-Rate Interstitial Brachytherapy for Early-Stage Breast Cancer: A Prospective Clinical Study

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Abstract

Purpose—To prospectively evaluate cosmetic outcomes in women treated with accelerated partial breast irradiation (APBI) using high-dose-rate (HDR) interstitial brachytherapy for early-stage breast cancer.

Methods and Materials—Between 2004 and 2008, 151 patients with early-stage breast cancer were enrolled in a phase II prospective clinical trial. Eligible patients had Tis-T2 tumors ≤ 3 cm, excised with negative margins, and with no nodal involvement. Patients received 3.4 Gy BID to a total dose of 34 Gy. Both patients and the treating radiation oncologist qualitatively rated cosmesis as excellent, good, fair, or poor over time and ascribed a cause for changes in cosmesis. Cosmetic outcome was evaluated quantitatively by the percentage breast retraction assessment (pBRA). Patients also reported their satisfaction with treatment over time.

Results—Median follow-up was 55 months. The rate of excellent/good cosmesis reported by patients and the treating radiation oncologist was as follows: 92% and 97% pretreatment, 91% and 97% at 3–4 months follow-up, 87% and 94% at 2 years, and 92% and 94% at 3 years. Breast infection and adjuvant chemotherapy were independent predictors of a fair/poor cosmetic outcome at 3 years. Compared to the pretreatment pBRA (7.35), there was no significant change in pBRA

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over time. V150 was the only significant predictor of pBRA. The vast majority of patients (86.6%) were completely satisfied with their treatment.

Conclusions—Patients and the treating physician reported a high rate of excellent/good cosmetic outcomes at all follow-up time points. Acute breast infection and chemotherapy were associated with worse cosmetic outcomes. Multicatheter interstitial brachytherapy does not significantly change breast size as measured by pBRA.

Keywords

Breast cancer; brachytherapy; partial breast; cosmesis

Introduction

Breast-conserving therapy (BCT) is a standard treatment for early-stage breast cancer. The use of whole-breast irradiation (WBI) after breast-conserving surgery has been shown to reduce the risk of ipsilateral breast tumor recurrence (IBTR) compared to breast conserving surgery alone (1). The majority of local recurrences after breast-conserving surgery are at or near the lumpectomy site (2). This observation 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. Early studies have reported low ipsilateral breast tumor recurrence (IBTR) rates after APBI (3).

Cosmesis following BCT is an important outcome of treatment. Qualitative cosmetic outcomes after APBI have been reported in several large series (4–6). Unfortunately, qualitative cosmetic evaluations suffer from substantial interobserver variability, and patient and physician evaluations can differ considerably (7, 8). The breast retraction assessment (BRA) and percentage breast retraction assessment (pBRA) are objective measurements of the amount of breast retraction, determined by comparing nipple positions relative to the sternal notch between the treated and contralateral breast (8, 9). The pBRA has been shown to have a low intra- and interobserver variability. Lower values of pBRA have been shown to correlate with improved cosmetic outcomes, making pBRA a reliable, objective measure of cosmesis (8).

To our knowledge no prospective, objective, quantitative measurement of cosmetic outcome has been reported in patients who have received APBI. The current prospective study reports the qualitative and quantitative cosmetic outcomes of a large cohort of patients with early-stage breast cancer treated with APBI using high-dose-rate (HDR) multicatheter interstitial brachytherapy. We examined clinical and treatment-related factors that could predict poorer cosmesis.

METHODS AND MATERIALS

Between March 2004 and December 2008, 151 patients with early-stage breast cancer were enrolled in a prospective study evaluating APBI using HDR multicatheter interstitial brachytherapy at XXXX. Whole breast external beam radiation therapy 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. All but one of the 123 patients with invasive disease had a sentinel lymph node biopsy. Patients were ineligible if they had: 1) lobular carcinoma *in-situ* (LCIS), 2) multicentric carcinoma, 3) diffuse suspicious microcalcifications, 4) suspicious microcalcifications remaining on the post-lumpectomy mammogram, or 5) systemic lupus erythematosus, scleroderma, or dermatomyositis with a CPK level above normal or with an

active skin rash. The XXXX Human Research Protection Office approved this study, and all patients provided written informed consent.

All patients were treated with HDR multicatheter interstitial brachytherapy using a high activity Iridium-192 source. The interstitial implants 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. In general, an intraplane catheter spacing of 1.2 cm and an interplane spacing of 1.5 to 2.0 cm were used. All implants were multiplanar, and the use of more than two planes was common. Interstitial implants were placed intraoperatively with a reopened surgical cavity in thirteen patients, including the first eight patients in the trial. This was done as a separate operative procedure from the breast conserving surgery after the final pathology was known. Real-time ultrasound guidance with an unopened, surgical cavity was predominantly used after the first eight cases. Real-time ultrasound guided implantation was performed using a strict sterile technique and under a combination of narcotic and anxiolytic sedation with local anesthesia.

All patients underwent computed tomography (CT) simulation and three-dimensional treatment planning. The Plato Brachytherapy planning system (Nucletron BV, Veenendaall, 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 planning target volume (PTV) 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 PTV.

Patients received 3400 cGy delivered in 10 twice-daily fractions. Treatment was given over 5–7 days, with a minimum of 6 hours separation between fractions. Dosimetric goals were: 95% of the PTV receiving the prescribed dose, V150 $\leq$ 50 cm^3, V200 $\leq$ 20 cm^3, and dose homogeneity index, defined as 1-(V150/V100), $\geq$ 0.7, where Vx is the volume receiving x% of the prescription dose (10). If all dosimetric goals could not be achieved in a particular case, then coverage was optimized at the expense of exposure.

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. Hormonal therapy was allowed during brachytherapy, but in practice was rarely started prior to APBI.

Cosmetic Assessment

Cosmesis was evaluated pretreatment, 6–8 weeks post-treatment, 3–4 months post-treatment, 6–8 months post-treatment, then every 6 months for the next 4.5 years, and yearly thereafter. Late skin toxicity was graded according to the Common Terminology for Adverse Events version 3.0. Cosmesis was qualitatively evaluated by the treating radiation oncologist by comparing the treated breast with the untreated breast using the rating system described by Aaronson *et al*. (11). The global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin color, location of the areola and nipple, and shape of the areola and nipple were scored on a 4-point scale: "0" excellent result (no difference), "1" good result (small difference), "2" fair result (moderate difference), "3" poor result (large difference). Patients evaluated the global cosmetic result qualitatively using the same 4-point scale at each time point. The BRA was calculated according to the method of Pezner *et al*., which yields the difference in distance from the sternal notch to nipple between the treated and untreated breasts (9). The percentage BRA (pBRA) is defined as (BRA/reference length) x 100, where reference length is the distance between the sternal notch and the untreated nipple (Fig. 1). Physical measurements to calculate BRA and pBRA were taken directly on each patient in a seated position with both arms alongside the body. Both BRA

and pBRA were determined pretreatment and at each follow-up. The pBRA was used for analysis, because it reports retraction as a percentage rather than a distance, and is therefore less dependent on breast size. At each time point both the patients and treating physician reported the perceived cause of cosmesis changes as mostly due to radiation, mostly due to surgery, unknown, or no significant change. Patients also reported their level of satisfaction with treatment. The cosmetic questionnaire was presented to the patient by a trained radiation oncology nurse. The patient and physician questionnaires used in this study are presented in Appendices eI and eII.

Statistical Analysis

The pretreatment assessment was made after surgery and prior to brachytherapy. All time intervals were calculated from the date of completion of brachytherapy. For this analysis, cosmetic outcomes were analyzed up to three years after completion of therapy. Due to poor intraobserver and interobserver correlation reported with the four category qualitative cosmesis scale, the results were dichotomized into excellent/good and fair/poor for analysis (7). Agreement between patient and physician cosmetic evaluation was measured by the normalized kappa statistic (12). A kappa of less than 0.20 indicated poor agreement; 0.21–0.40 slight agreement; 0.41–0.60 fair agreement; 0.61–0.80 good agreement; 0.81–1.00 very good agreement. Logistic regression was used to examine clinical and treatment-related factors that could contribute to developing a fair/poor cosmetic outcome at the 3-year time point. The pBRA values were log-transformed to obtain a Gaussian distribution for statistical analysis. The effect of time on pBRA was assessed with a mixed repeated measures model using a heterogeneous autoregressive covariance structure. Student's t-test was used to analyze the effect of symptomatic fat necrosis on pBRA. To describe the association between pBRA and qualitative cosmetic evaluations, Spearman correlation coefficients were calculated. The following interpretation of the correlation coefficient was used: 0.20–0.40 indicated slight correlation, 0.41–0.60 moderate correlation, 0.61–0.80 substantial correlation, and a coefficient above 0.80 indicated very strong correlation. 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-related factors are summarized in Table 1. The median time from surgery to ISI placement was 5 weeks (range, 1–12 weeks). Dosimetric goals for V150 and/or V200 were not met for 28% of patients. The median follow-up was 55 months (range, 1–81 months). Eighty-two patients (54%) had cosmetic outcome data through 3 years of follow-up. Six patients experienced a breast infection after ISI and 19 developed symptomatic fat necrosis. The incidence of late skin toxicity was: grade 0 (76%), grade 1 (21%), grade 2 (1%), grade 3 (1%). There was no grade 4 or 5 late skin toxicity. Seven patients developed less than 1.0 cm^2 regions of telangectasias. The global cosmetic results as graded by the patient and physician are presented in Figure 2.

Dichotomizing the global cosmetic results into excellent/good or fair/poor, the percentage of patients reporting excellent/good cosmetic outcomes is as follows: 92% pretreatment, 91% 3–4 months after treatment, 87% at 2 years, and 92% at 3 years. The percentage of patients with excellent/good outcomes based on physician evaluation is as follows: 97% pretreatment, 97% 3–4 months after treatment, 94% at 2 years, and 94% at 3 years. The normalized kappa ranged from 0.72–0.84 for patient and physician agreement on qualitative cosmetic evaluation, indicating good to very good agreement.

Patient impressions of the cause of cosmesis changes over time are shown in Figure 3. At 3 years, 16.5% of patients reported that cosmetic changes were mostly due to radiation, 57% reported that cosmetic changes were mostly due to surgery, 19% were unsure, and 7.5% of patients reported no cosmetic changes. Three years after treatment, 86.6% of patients were completely satisfied with the treatment and results. If they had to do it again, 98.8% of patients self reported that they would choose breast conserving surgery with APBI as received over mastectomy without radiation therapy.

Logistic regression was performed to determine whether there was an association between the clinical and treatment-related factors listed in Table 1 and a fair/poor global cosmetic outcome based on physician evaluation at 3 years. Univariate results indicated that breast infection was a significant predictor of a fair/poor cosmetic outcome (odds ratio (OR), 30.4; $p=0.009$), as was open cavity catheter placement (OR, 8.88; $p=0.0125$). Chemotherapy showed a trend toward significance (OR, 5.025; $p=0.053$). Multivariate analysis including breast infection, method of catheter placement and chemotherapy as variables indicated that breast infection (OR, 66; 95% confidence interval (CI) 4.1–999; $p=0.003$) and chemotherapy (OR, 9.9; 95% CI 1.5–67; $p=0.019$) were independent predictors of a fair/poor cosmetic outcome. Logistic regression assessing the association of clinical and treatment-related factors with a fair/poor cosmetic outcome based on patient evaluation at 3 years indicated that none of the factors included in Table 1 was significant.

A graph of mean pBRA over time is shown in figure 4. The mean pretreatment pBRA was 7.35 (95% confidence interval (CI), 6.49–8.21). The mean pBRA 3 years after treatment was 7.64 (95% CI, 6.68–8.6). To assess the effect of time on pBRA, a mixed repeated measures model was utilized with pBRA measurements taken pretreatment, 3–4 months, 1 year, 2 years, and 3 years after treatment. There was no significant change in pBRA over the repeated measures taken from pretreatment up to 3 years after treatment. In addition, pBRA was not significantly different in the patients who developed symptomatic fat necrosis compared to those who did not. The relationship between the clinical and treatment-related factors listed in Table 1 and pBRA at 3 years was examined using linear regression. Results indicated that only V150 significantly correlated with pBRA (regression coefficient (β)=0.008; $p=0.044$).

The correlation between pBRA and physician reported qualitative cosmetic results at 3 years is listed in Table e1. There was a slight correlation between pBRA and the physician rated global cosmetic score at 3 years ($\rho=0.36$). There was slight to moderate correlation between pBRA and the physician rated specific cosmetic items ($\rho=0.37$–0.47). The correlation between the patient rated global cosmetic score and pBRA was minimal (ρ 0.18).

DISCUSSION

We report the results of the first prospective study of cosmesis after APBI using both qualitative and quantitative evaluations. In previous reports, several methods of cosmetic evaluation have been used. The Harvard criteria (13) categorized the overall cosmetic outcome as excellent, good, fair or poor. Pezner *et al.* (7) reported low interobserver consensus with this 4-point scoring system, and found that substantial consensus was only achieved if the scoring system was reduced to two categories: excellent/good or fair/poor. Aaronson *et al.* (11) expanded the Harvard criteria to include appearance of the surgical scar, breast size, breast shape, skin color, location of the areola and nipple, and shape of the areola and nipple. Our study incorporated the Aaronson modification of the Harvard criteria for the physician cosmetic evaluation.

Through 3 years of follow-up, the percentage of patients with excellent/good cosmetic outcomes remained high for both physician and patient assessment (94% and 92%, respectively). Patients reported that changes in cosmesis were mostly due to surgery, and the vast majority were very satisfied with the overall treatment and results.

Other series evaluating cosmetic outcomes after APBI using interstitial brachytherapy have reported excellent/good cosmetic outcomes in 75–99% of patients, based on physician evaluation (4, 14, 15). Patient reported cosmetic evaluation has been limited. In the German-Austrian multicatheter brachytherapy trial, the rate of excellent/good cosmetic outcomes was similar for physician evaluation (90.1%) and patient evaluation (89.9%) (5).

Our results indicate that breast infection and adjuvant chemotherapy are independent predictors of a fair/poor cosmetic outcome at 3 years, based on physician evaluation. Of note, the vast majority (86.7%) of patients who received chemotherapy received Anthracycline-based chemotherapy. Due to the small number of patients with a fair/poor cosmetic result who also experienced a breast infection or underwent chemotherapy, the odds ratios of these significant predictors have a large confidence interval. There was no significant relationship between clinical and treatment-related variables and patient reported fair/poor cosmetic outcomes at 3 years. The lack of an association may be due to the limited number of patients (seven) who reported a fair/poor outcome.

Other investigators have found similar predictors of poor cosmesis. Chen *et al.* (4) and Wazer *et al.* (14) reported that chemotherapy was associated with worse cosmetic outcomes in their series of patients treated with APBI via ISI. Analysis of the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial showed that breast infection was predictive of a worse cosmetic outcome at 3 years, but this association was no longer significant at 5 years (6). Symptomatic fat necrosis was not associated with fair/poor cosmesis in our study, in contrast Lovey *et al.* (16) reported a significant association in their series. Possible reasons for this difference include the subjectivity of qualitative cosmetic grading, a difference in length of follow-up, and differences in treatment dose and fractionation.

The pBRA is an objective measure of cosmetic outcome that quantitate the retraction of the treated breast compared to the untreated breast. In a group of healthy controls, Fabry *et al.* (17) reported a median pBRA of 6.1. Vrieling *et al.* (8) evaluated the pBRA in 731 patients treated in EORTC trial 22881/10822, in which patients with early-stage breast cancer received WBI and were randomized to receive a boost dose or no-boost dose. The mean pBRA was 8.3 in the boost group, significantly higher than the pBRA of 7.6 in the no-boost group. The mean pBRA in the present study is of similar magnitude to the results reported after WBI.

To our knowledge, this is the first report of the breast retraction assessment in patients treated with breast-conserving surgery and APBI. There was no significant change in pBRA from pretreatment through 3 years of follow-up. This indicates that HDR multicatheter interstitial brachytherapy did not cause significant changes in breast size or retraction. V150 was found to be significantly correlated with pBRA, such that each increase of V150 by 1 cm^3 leads to an estimated 0.8% increase in pBRA. Symptomatic fat necrosis, a potential complication of treatment, did not cause significant breast retraction.

There was a slight to moderate correlation between physician cosmetic evaluation scores and the pBRA at 3 years. The strongest correlation was with position of the areola and nipple, which is unsurprising since the pBRA reflects the difference in nipple positions. There was minimal correlation between the patient reported cosmetic outcome and pBRA.

The pBRA does not account for disturbing scars or skin changes. This limitation of the pBRA may explain the low correlation with global cosmetic assessment in our study.

Other potential limitations of this study include cosmetic evaluation by the treating radiation oncologist and length of follow-up. Several studies assessing cosmetic outcomes after APBI or WBI have found that cosmetic outcomes stabilize after 2–3 years (4, 18, 19). However data from the MammoSite brachytherapy registry trial indicate that cosmetic outcomes may continue to change up to 5 years after treatment (6). Longer follow-up may be necessary to further characterize the long-term cosmetic outcomes.

Conclusions

In this prospective study, patients with early-stage breast cancer treated with APBI using HDR multicatheter interstitial brachytherapy had a high rate of excellent/good cosmetic outcomes based on patient and physician cosmetic evaluations. Chemotherapy and breast infection were associated with worse cosmetic outcomes. There was no significant difference in pBRA up to 3 years after treatment. Furthermore, the magnitude of pBRA in our study was comparable to that seen in whole breast irradiation studies. HDR multicatheter interstitial brachytherapy does not significantly change breast size or retraction as measured by pBRA over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SUMMARY

In a prospective study, cosmetic outcomes of 151 women treated with accelerated partial breast irradiation using high-dose-rate interstitial brachytherapy for early-stage breast cancer were analyzed through 3 years of follow-up. Both patients and the treating physician reported a high rate of excellent/good cosmetic outcomes. Breast infection and chemotherapy were associated with worse cosmetic outcomes. Multicatheter interstitial brachytherapy did not significantly change cosmesis as measured by percentage breast retraction assessment (pBRA) over time.
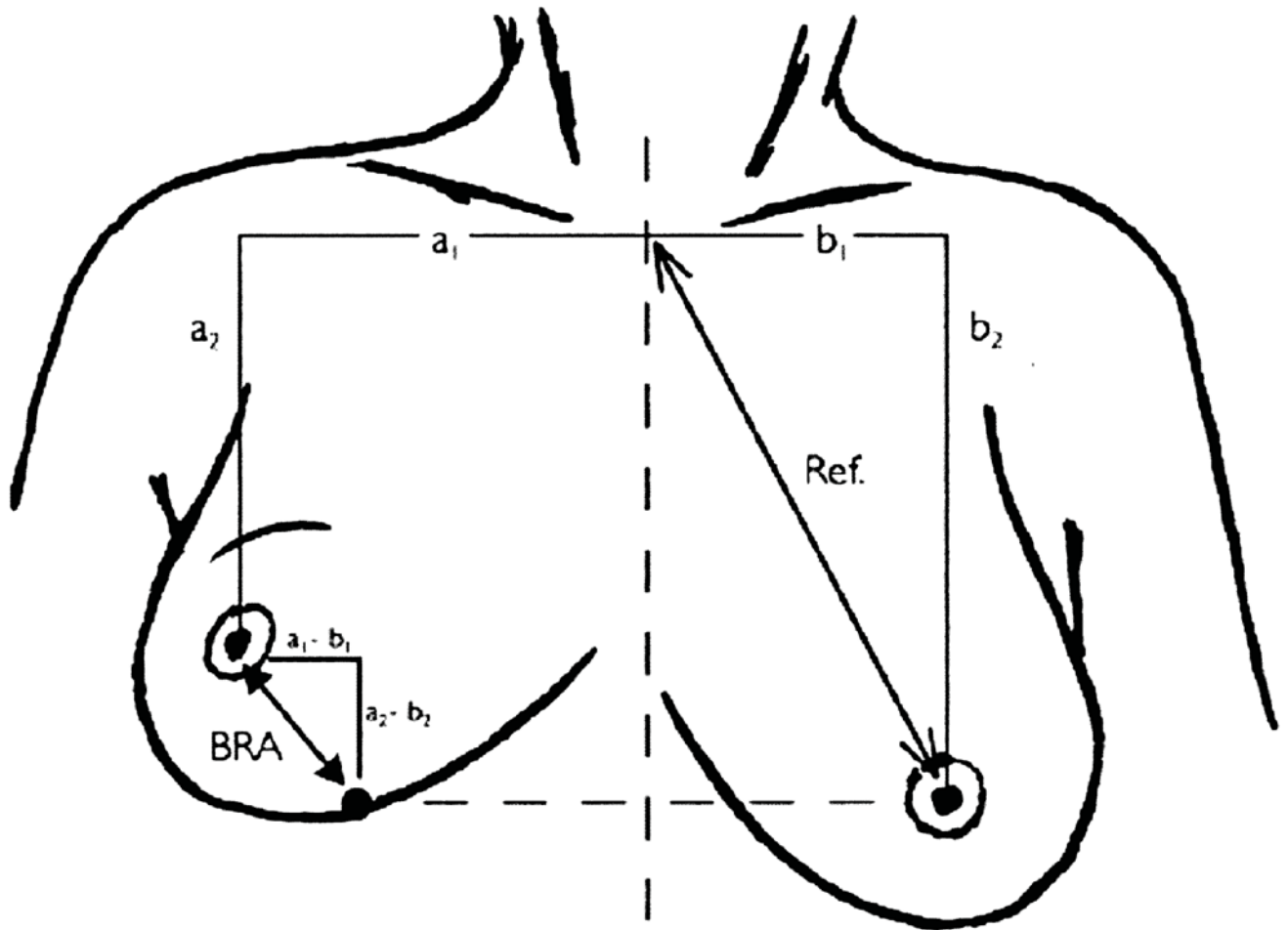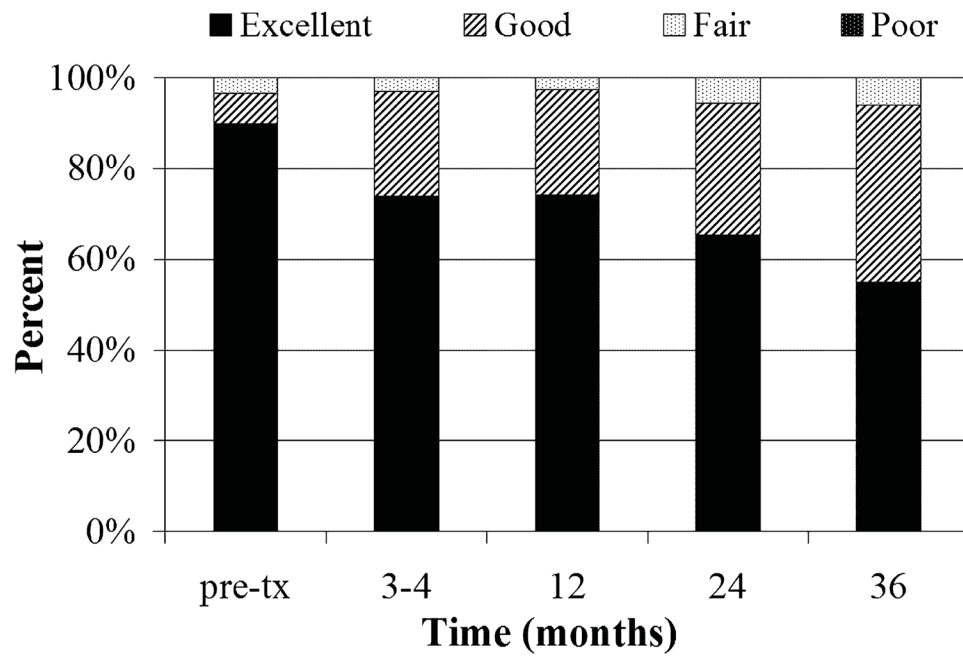
Fig 1.
Illustration of the BRA measurements.

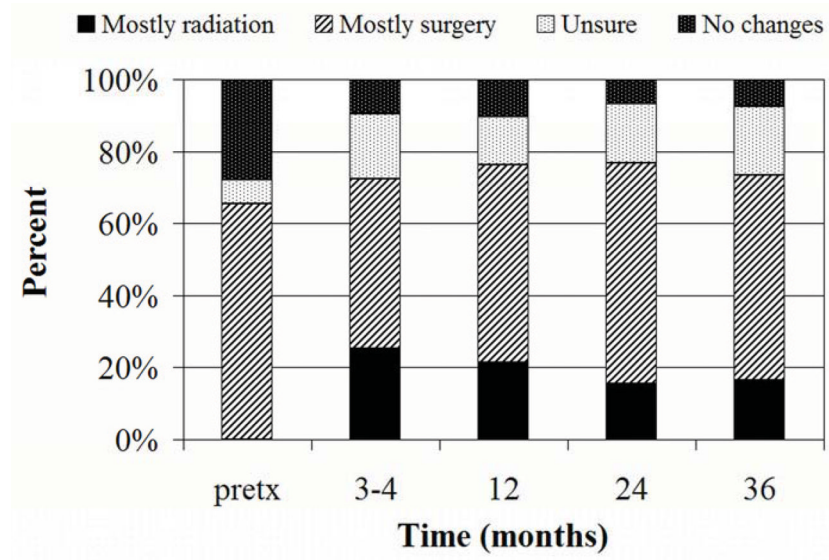$$\mathrm{BRA} = \sqrt{(a_1 - b_1)^2 + (a_2 - b_2)^2}$$
$$\mathrm{Reference\ length\ (ref.)} = \sqrt{b_1^2 + b_2^2}$$
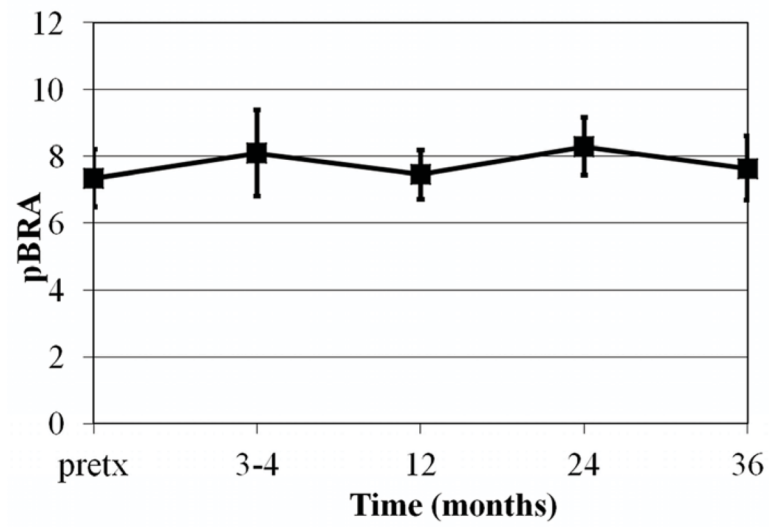$$\mathrm{pBRA} = (\mathrm{BRA/reference\ length}) \times 100$$

Illustration from Vreiling *et al*. (8) (copyright 1999 Elsevier Inc.).

Fig 2.
Global cosmetic evaluation by (a) physician and (b) patient evaluation. Pretx=pretreatment

Fig 3.
Causes of cosmetic changes reported by patients. Pretx=pretreatment.

Fig 4.
Mean pBRA over time. Error bars indicate 95% confidence interval. Pretx=pretreatment.

Table 1

Patient, tumor and treatment-related characteristics

Characteristic	Findings
Age (y)	
Mean (range)	60 (40–85)
40–50	29 (19%)
50–60	50 (33%)
>60	72 (48%)
Tumor Location	
UOQ	54 (36%)
UIQ	46 (30%)
LOQ	30 (20%)
LIQ	21 (14%)
Pathologic tumor stage	
Tis	28 (19%)
T1mic	1 (1%)
T1a	19 (13%)
T1b	52 (34%)
T1c	38 (25%)
T2	13 (9%)
Sentinel lymph node biopsy (for patients with invasive cancer)	
Yes	122 (99%)
No	1 (1%)
Chemotherapy	
Yes	30 (20%)
Anthracycline based chemotherapy	26 (17%)
No	121 (80%)
Hormonal therapy	
Yes	116 (77%)
No	35 (23%)
Method of catheter placement	
Open cavity	13 (9%)
Closed cavity	138 (91%)
Number of catheters	
Mean (range)	21 (12–34)
V100 (cm^3)	
Mean (range)	246 (99.6–690)
V150 (cm^3)	
Mean	45.2 (19.1–129)
V200 (cm^3)	
Mean	16.1 (7–39.8)
DHI	

Characteristic	Findings
Mean	0.808 (0.680–0.880)
IRAK	
Mean	0.344 (0.199–0.659)
Toxicity	
Breast infection	6 (4%)
Symptomatic fat necrosis	19 (12.6%)

Abbreviations: UOQ = upper outer quadrant; UIQ = upper inner quadrant; LOQ = lower outer quadrant; LIQ = lower inner quadrant; DHI = dose homogeneity index; IRAK = integrated reference air kerma

Table 2

Agreement between patient and physician reported global cosmetic outcomes

	Percent agreement: dichotomized scoring	Normalized κ: dichotomized scoring
Pretreatment	92%	0.83
3–4 months	92%	0.84
2 years	90%	0.78
3 years	87%	0.72

Abbreviation: κ = kappa statistic