Original paper

Predictors of poor cosmesis in breast cancer patients treated with adjuvant whole breast radiation therapy plus high-dose-rate interstitial brachytherapy boost after breast conservation surgery

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Abstract

Purpose: To identify patient, tumor, and treatment-related factors, which predict cosmesis in breast cancer survivors treated with adjuvant whole breast irradiation (WBI) plus high-dose-rate (HDR) multicatheter interstitial brachytherapy (MIBT) boost after breast conservation surgery.

Material and methods: At least 12 months after completion of radiotherapy, cosmetic outcomes were measured both objectively with BCCT.core software (using a front view digital photograph), and subjectively according to Harvard's criteria. MIBT dose fractionation regimen was 13.6 Gy/4 fractions (bid). To evaluate the correlation between cosmetic scores and dose-volume histogram (DVH) parameters, WBI and MIBT plans were retrospectively analyzed, and ipsilateral skin and breast biologically equivalent dosimetric indices were recorded (α/β = 3 Gy). A multivariate ordinal logistic regression model was used for statistical analysis.

Results: Twenty-eight consecutive patients were enrolled into this study. The median time from completion of radiation therapy to cosmesis scoring was 18 months. In evaluation with BCCT.core software, no patient was scored as excellent. Cosmesis was good in 18%, fair in 50%, and poor in 32% of patients. According to Harvard's scale, 10.5% of patients had excellent cosmesis, and 43%, 28.5%, and 18% of patients had good, fair, and poor scores, respectively. In univariate analysis, patients with higher absolute MIBT V_{29Gy} (cc), those treated with irradiation of regional lymphatics (odds ratio ≈ 5), and patients with larger breast volumes had statistically significant lower Harvard's scores. In the multivariate model, none of the mentioned factors remained statistically significant, except for a trend for poorer cosmesis in patients with higher absolute MIBT V_{29Gy} (p-value = 0.066).

Conclusions: Based on the results of this study, MIBT breast V_{29Gy}, regional nodal irradiation, and larger breast volumes are the potential factors, which could predict cosmesis.

J Contemp Brachytherapy 2022; 14, 5: 429–437
DOI: https://doi.org/10.5114/jcb.2022.121403

Key words: radiation therapy, breast cancer, brachytherapy, boost, cosmetic outcome.

Purpose

With recent advances in breast cancer loco-regional and systemic therapies, which resulted in high survival rates, cosmetic outcomes became more important [1, 2]. In addition, better recognition of risk factors contributing to poor cosmetic results may improve the quality of life of these patients [2].

Breast conservation surgery (BCS) plus whole breast irradiation (WBI) is the standard of care in early-stage breast cancer [3]. Also, there is evidence that a tumor bed boost enhances local control, especially in young patients, and in the presence of lympho-vascular space invasion or positive or close surgical margins [4, 5].

Low-energy electrons (range, 9-12 MeV) are widely used for delivering the boost dose. However, considering their limited therapeutic range, only superficial regions of the breast can be effectively irradiated. Using higher energy electrons to treat deeper areas of the breast results

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Received: 10.09.2022
Accepted: 29.10.2022
Published: 21.11.2022

in overdosing of skin, normal breast, lungs, and heart, and also may have a negative impact on breast cosmesis. In this context, the EORTC boost trial showed that high energy electrons were linked to a higher 10-year risk of severe breast fibrosis.

Other techniques for tumor bed boosting, especially deep-seated tumor beds, are external beam radiation therapy (EBRT) and multicatheter interstitial brachytherapy (MIBT). Data regarding the pros and cons of these boost techniques in terms of effectiveness, toxicity, and cosmetic results are limited, and the most published data on MIBT boost comes from time before the widespread availability of high-dose-rate (HDR) sources, computerized remote after loaders, stepping source technology, cross-sectional image-based treatment planning, and inverse optimization algorithms. The advantage of each boost modality depends on breast anatomy and lumpectomy cavity location. For a shallow target, if the breast contour is roughly flat and beam obliquity can be avoided, en-face low energy electron beam is the preferred technique, as electron beam obliquity reduces its' therapeutic range and increases the skin absorbed dose [6]. In deep-seated tumor beds (depth ≥ 4 cm), modern image-guided multicatheter interstitial brachytherapy boost in comparison with other boost modalities, such as high energy electron beams or advanced external beam photon techniques (e.g., intensity modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT]), can better protect nearby healthy organs from high doses of radiation, and therefore are an excellent modality for dose escalation [6-8].

In electron and external beam photon boosts, even if accompanied by modern treatment verification techniques, a larger volume (compared to brachytherapy) need to be irradiated to account for inter- and intra-fractional organ motions, and accelerator and patient's setup uncertainties (planning target volume concept). These problems are irrelevant for MIBT. Multicatheter interstitial brachytherapy, as a minimally invasive procedure, has its' limitations, including relative patient discomfort and the necessity of significant learning curve [6].

Several patient, tumor, and treatment-related factors have been connected to sub-optimal cosmetic outcomes after breast conservation therapy, but the results are not consistent across studies (many of them lack objective assessment of breast cosmesis). These factors include high body mass index (BMI), age (both younger and older patients), breast volume, inner quadrant tumor location, tumor size, extent of breast surgery (volume of tissue removed from the breast at lumpectomy), type of surgical incision, complete axillary dissection (versus sentinel node biopsy), receiving chemotherapy, regional nodal irradiation, higher total radiation doses (to the breast's skin and tissue), conventionally fractionated regimens (versus hypofractionated schedules), receiving a boost, boost technique, and higher boost volumes [2, 9-13]. Additionally, in patients treated with an interstitial brachytherapy boost, the number of implanted catheters and automatic optimization technique (vs. manual optimization) have been reported to be inversely correlated with breast cosmesis [10].

This study was designed to measure breast cosmesis in breast cancer patients treated with adjuvant WBI plus high-dose-rate MIBT boost after BCS, both objectively by BCCT.core software (using front view digital photographs) and subjectively with Harvard's score. Also, to identify patient, tumor, and treatment factors, including dosimetric parameters of external beam and brachytherapy plans, which predict poor cosmetic scores.

Material and methods

Study design

In this retrospective research, cosmetic outcomes of 28 consecutive breast cancer patients treated with adjuvant WBI plus HDR-MIBT boost after BCS (± adjuvant chemotherapy and/or hormone therapy) at Radiation Oncology Department of Ahvaz Golestan Hospital (Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran) between 2017-2018 were objectively measured with BCCT.core software using a front view digital photograph, and subjectively evaluated according to Harvard's scale. Informed consent for taking photographs and reviewing medical records was obtained from every participant included in the study. In our center, HDR interstitial brachytherapy boost are offered to patients at higher risk for local recurrence (e.g., young age, LVSI, and close or positive surgical margins) or with deep-seated tumor beds unsuitable for low energy electron boosts. Single cross-sectional cosmetic scoring was performed at least 12 months after completion of radiation therapy treatments. Moreover, to evaluate the correlation between cosmetic outcomes and dose-volume histogram (DVH) parameters, external beam and brachytherapy treatment plans were retrospectively analyzed, and ipsilateral skin and breast tissue dosimetric indices were recorded.

Whole breast irradiation

All patients received a total dose of either 50 Gy in 25 fractions, 50.4 Gy in 28 fractions, or 42.5 Gy in 16 fractions using opposed tangential photon beams (± irradiation of regional lymphatics at the discretion of treating physician). A collapsed cone super-position algorithm was applied for EBRT dose calculations (Isogray v. 4.2.265L, Dosisoft, Cachan, France).

HDR interstitial brachytherapy boost

Boost dose (13.6 Gy in 4 bid fractions) was delivered at 1 to 2 weeks either before or after WBI using a ^{60}Co source. In all patients, catheter implantation, contouring, and dose calculations (based on TG-43 formalism) (HDR Plus v. 3.0.7.0, Eckert & Ziegler BEBIG GmbH, Germany) were performed with adherence to GEC-ESTRO guidelines [14].

Cosmesis evaluation

BCCT.core software: For this purpose, front view digital photographs were obtained from enrolled patients (in arm down position) and imported to the software. All photographs were captured in the same room under the same light conditions, and also with the same cam-

era and photographer. After marking the nipples, breasts contours, and sternal notch on the patient's photograph and adjusting the image scale, the software automatically classified the patient's aesthetics into four categories, including excellent, good, fair, and poor based on asymmetry, color, and scar measures [15].

Harvard's scale: Aesthetic results were subjectively classified by a physician (NF) into four groups, such as excellent (if the treated breast was nearly identical to the untreated one), good (if the treated breast was slightly different from the untreated breast), fair (if the treated breast was clearly different from the untreated breast, but not seriously distorted), and poor (if the treated breast was seriously distorted) [16].

Contouring

Ipsilateral breast: This organ was contoured according to the ESTRO guidelines [17]. It should be noted that in brachytherapy treatment plans, clinical target volume (CTV) was included in this volume.

Ipsilateral skin: This structure was defined as a 5 mm layer underneath the skin surface on the involved breast [14].

Biologically effective dose-volume histogram parameters (α/β = 3 Gy)

Table 1 presents ipsilateral skin and breast histogram parameters (from external beam whole breast and brachytherapy boost treatment plans) that we reported in this study. Due to our technical limitation, since separate software was used for external beam and brachytherapy treatment plannings, cumulative (WBI + MIBT) DVH parameters could not be calculated.

Statistical analysis

Jamovi software version 1.6.23.0 was applied for statistical analysis [18]. Medians (with 25-75th percentiles) were reported to describe the central tendency of data. The correlation between variables was assessed with Spearman's rank test. Univariate ordinal logistic regression analysis was conducted to screen for significant predictors of breast cosmesis scores. For each variable, *p*-value, odds ratio, and 95% confidence interval were calculated. Then, variables with a *p*-value < 0.1 obtained from univariate analysis were entered into a multivariate ordinal logistic regression model. *P*-value < 0.05 in the final model was considered statistically significant.

Results

Patient, tumor, and treatment characteristics are summarized in Table 2. The median time from completion of radiation therapy to cosmesis scoring was 18 months. In cosmesis evaluation with BCCT.core software, no patient was scored as excellent. Cosmesis was good in 5 (18%), fair in 14 (50%), and poor in 9 (32%) patients. According to the Harvard's scale, 3 (10.5%) patients had excellent cosmesis. Moreover, 12 (43%), 8 (28.5%), and 5 (18%) patients had good, fair, and poor Harvard's scores, respectively (Figure 1). There was a statistically significant strong direct correlation between BCCT.core and Harvard's scores (p = 0.002) (Spearman's coefficient = 0.54) (Figure 2).

Table 1. Histogram parameters reported and analyzed in this study

Whole breast irradiation (for ipsilateral skin and breast)	HDR brachytherapy boost	
	For ipsilateral skin and breast	For ipsilateral skin only
V_{86Gy}	V_{29Gy}	$D_{0.01cc}$
V_{90Gy}	V_{36Gy}	$D_{0.1cc}$
V_{94Gy}	V_{43Gy}	$D_{0.2cc}$
V_{98Gy}	V_{50Gy}	$D_{0.5cc}$
V_{102Gy}	V_{57Gy}	D_{1cc}
V_{106Gy}	V_{64Gy}	D_{2cc}
V_{110Gy}	V_{71Gy}	D_{5cc}
V_{114Gy}		
V_{118Gy}		
Maximum point dose (D_{max})		

V parameters: Volume of the organ that receives at least the mentioned biologic effective dose.
D parameters: Minimum biologic effective dose received by the most exposed mentioned volume of the organ.

Absolute values of ipsilateral breast and skin biologically effective V parameters in WBI and MIBT plans are summarized in Table 3. WBI and MIBT relative dose-volume histograms are shown in Figures 3 and 4. In WBI, the median breast and skin biologically effective maximum doses (BED_{max}) (25-75th percentile) were 114 Gy (range, 109-118 Gy) and 108 Gy (range, 104-113 Gy), respectively. Skin D parameters in MIBT plans are presented in Table 4.

In univariate analysis, no patient (age, follow-up time, breast volume, and breast tumor location), tumor (pT stage, pN status, and tumor size), and treatment characteristics (lumpectomy specimen volume, hormone therapy regimen, WBI dose-fractionation schedule, before or after EBRT brachytherapy boost timing, and regional nodal irradiation), or dosimetric parameters were predictive of BCCT.core scores. Only there was a trend for higher BCCT.core scores in pN-positive cases, and patients who received regional nodal irradiation. In contrast, receiving regional nodal irradiation (p = 0.039), larger breast volumes (p = 0.037), higher WBI absolute breast V_{86Gy} (p = 0.038), and higher MIBT absolute breast V_{29Gy} (p = 0.037) were significant predictors of poorer Harvard's scores. Also, there was a trend for higher Harvard's scores in pN-positive cases, patients with higher WBI absolute breast V_{90Gy}, and higher MIBT absolute breast V_{36Gy}, V_{43Gy}, V_{50Gy}, and V_{57Gy} (Table 5).

On multivariate analysis, none of the demographic factors, tumor, and treatment characteristics, or dose-volume histogram parameters remained statistically significant for predicting Harvard's score. Only there was a trend for higher Harvard's score in patients with higher MIBT absolute breast V_{29Gy} (p = 0.066) (Table 5).

Discussion

In recent two decades, the widespread availability of electron beams combined with their relative comfort of use,

Table 2. Patient, tumor, and treatment characteristics

Parameter	Results, mean (range) or *n* (%)
Age (years)	48 (43-53.5)[a]
pT stage	
I	14 (50)
II	14 (50)
pN stage	
N0	10 (36)
N1	10 (36)
N2	5 (18)
N3	3 (10)
Maximum tumor diameter (cm)	2.1 (1.5-3)[a]
Positive lymph node number	2 (0-4)[a]
Total resected specimen volume (cc)[b]	117 (110-255)[a]
Time from surgery to cosmesis evaluation (months)	26 (24-28)[a]
Time from end of radiation therapy to cosmesis evaluation (months)	18 (16-19.5)[a]
Breast volume (cc)	1,019 (858-1,373)[a]
Tumor location in breast	
Upper outer quadrant	20 (71)
Upper inner quadrant	1 (4)
Lower outer quadrant	3 (11)
Lower inner quadrant	2 (7)
Central	2 (7)
Chemotherapy	
Yes	26 (93)
No	2 (7)
Adjuvant	23 (88)
Neoadjuvant	3 (12)
Chemotherapy regimen	
AC[c] × 4-T[d] × 4	23 (88)
AC[c] × 8	1 (4)
EC[e] × 8	1 (4)
TCH[f] × 6	1 (4)
Hormonal therapy	
Tamoxifen	11 (48)
Letrozole	4 (17)
Tamoxifen + GnRH agonist	7 (30)
Exemestane + GnRH agonist	1 (5)
No	5 (18)
WBI fractionation	
50.4 Gy/28 fractions	1 (3)
50 Gy/25 fractions	22 (79)
42.5 Gy/16 fractions	5 (18)
Regional nodal irradiation	
Yes	17 (61)
No	11 (39)
Brachytherapy boost timing	
Before EBRT	16 (57)
After EBRT	12 (43)
Locoregional recurrence[g]	
No	28 (100)
Yes	0 (0)

[a]Median (25-75th percentile); [b]final lumpectomy specimen volume + excisional biopsy specimen volume; [c]AC: doxorubicin + cyclophosphamide; [d]T: paclitaxel; [e]EC: epirubicin + cyclophosphamide; [f]TCH: docetaxel + carboplatin + trastuzumab; [g]at the time of cosmesis evaluation; WBI – whole breast irradiation; MIBT – multicatheter interstitial brachytherapy; GnRH – gonadotropin-releasing hormone

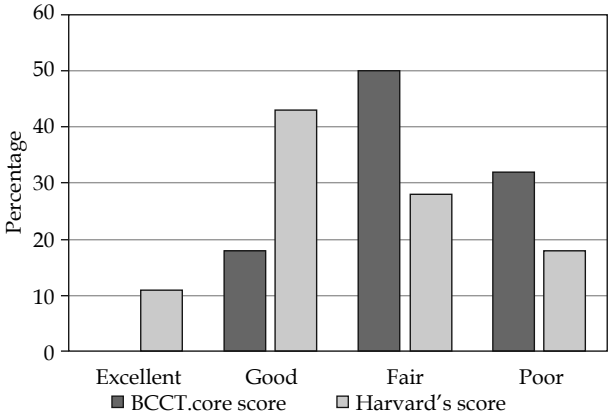

Fig. 1. BCCT.core and Harvard's scores bar plot

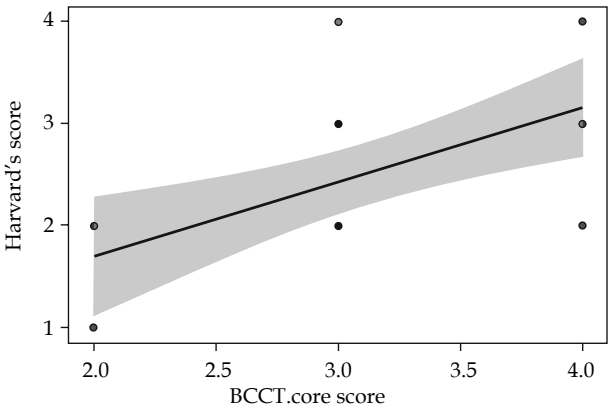

Fig. 2. This scatter plot illustrates the strong positive correlation between BCCT.core and Harvard's scores

Table 3. Absolute ipsilateral breast and skin biologically effective V parameters

WBI			MIBT		
V_X (cc)	Median (25-75th percentile)		V_X (cc)	Median (25-75th percentile)	
	Breast	Skin		Breast	Skin
V_{86Gy}	827 (470-1,125)	36 (19-53)	V_{29Gy}	100 (66-119)	3 (0-5)
V_{90Gy}	595.5 (302-822)	21 (8-35)	V_{36Gy}	80 (53-95)	1 (0-3)
V_{94Gy}	353 (116-570)	12 (3-23)	V_{43Gy}	66 (39-74)	1 (0-2)
V_{98Gy}	195 (49-321)	5 (1-14)	V_{50Gy}	51 (30-57)	0 (0-1.5)
V_{102Gy}	111 (12-171)	2 (0-7)	V_{57Gy}	41 (23.5-44)	0 (0-1)
V_{106Gy}	44 (1-74)	0 (0-2.5)	V_{64Gy}	32 (29-36)	0 (0-1)
V_{110Gy}	5 (0-28)	0 (0-1)	V_{71Gy}	26 (17-30)	0 (0-1)
V_{114Gy}	0 (0-8)	0 (0-0)			
V_{118Gy}	0 (0-0)	0 (0-0)			

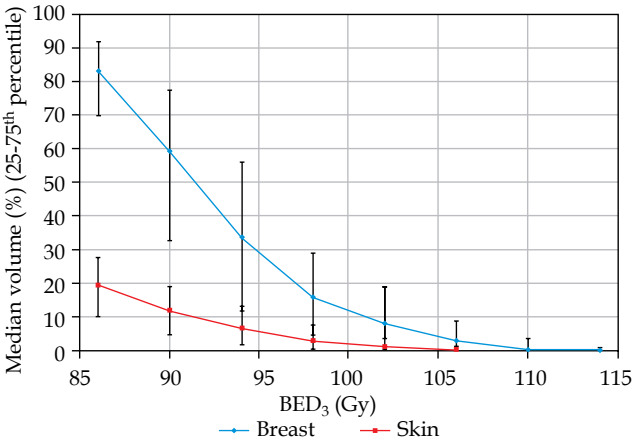

Fig. 3. Whole breast irradiation relative ipsilateral breast and skin biologically effective dose-volume histogram

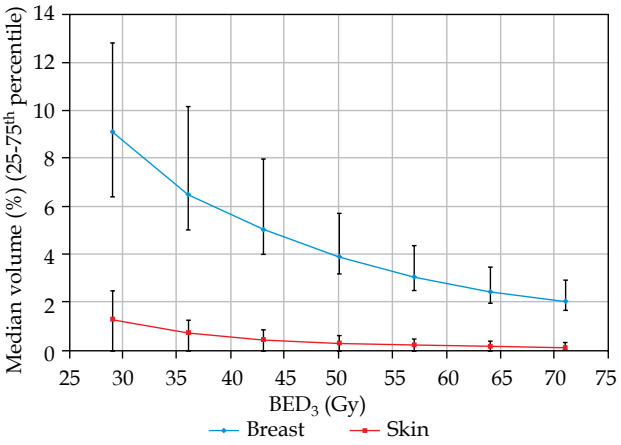

Fig. 4. Multicatheter interstitial brachytherapy relative ipsilateral breast and skin biologically effective dose-volume histogram

has led to decreased use of interstitial brachytherapy for delivering boost dose. In fact, in superficial lumpectomy beds, if the breast contour is roughly flat and beam obliquity could be avoided, the preferred modality for breast boost is low energy electrons. However, in women with large breasts and centrally located deep-seated tumor bed, MIBT boost could be a great tool in radiation oncology armamentarium, since it can better protect nearby tissues from high doses of radiation in comparison with high energy electrons (> 12 MeV) due to increased skin dose, or sophisticated photon EBRT techniques. Additionally, with a MIBT boost, safer dose escalation is achievable in patients with a higher risk for local recurrence [6].

Recently, following the availability of highly effective systemic treatments for breast cancer, and as a consequence of longer survivals in these patients, long-term treatment toxicity and cosmetic outcomes have become more important. Therefore, the present study assessed the potential patient, tumor, and treatment-related factors, which could predict poor cosmesis in patients treated with WBI + MIBT boost [1,2].

In our study, 18% and 53.5% of patients had an excellent or good cosmesis according to BCCT.core and Harvard's scores, respectively. Since baseline (pre-RT) cosmesis scoring was not performed, relative effects of surgery, chemotherapy, and radiation on cosmesis could not be distinguished. The Harvard score results are compatible with Polgár *et al*. [19] retrospective study showing 56% of excellent or good cosmesis, and contradictory to Rulli *et al*. [20] and Dolezel *et al*. [21] prospective studies, with 97% and 82.6% of excellent or good cosmesis, respectively. In our literature review, no study that used the BCCT.core objective scoring system for cosmesis evaluation was found (Table 6).

Table 4. Numerical values of skin D parameters for brachytherapy boost (ipsilateral side)

Parameter[a]	Median (25-75th percentile) (Gy)
$D_{0.01cc}$	302 (21-838)
$D_{0.1cc}$	120 (19-234)
$D_{0.2cc}$	79 (18-140)
$D_{0.5cc}$	48 (17-87)
D_{1cc}	39 (16-62)
D_{2cc}	33 (13-44)
D_{5cc}	22 (9-29)

[a]*Minimum biologic effective dose received by the most exposed mentioned volume of the organ*

Table 5. Ordinal logistic regression analysis

Scoring system	Parameter	Univariate[a]				Multivariate[b]			
		Odds ratio	95% CI		*p*-value	Odds ratio	95% CI		*p*-value
			Lower	Upper			Lower	Upper	
BCCT.core	Regional nodal irradiation (Yes vs. No)	4.87	1.04	28.4	0.055	Multivariate analysis was not performed due to strong collinearity between 'Regional nodal irradiation' and 'pN status' variables[c]			
	pN status (N+ vs. N0)	4.89	1.002	29.59	0.061				
Harvard's score	Regional nodal irradiation (Yes vs. No)	5.42	1.18	31.2	0.039	3.71	0.753	22.17	0.121
	pN status (N+ vs. N0)	4.73	1.006	27.7	0.061	Not included in multivariate model due to strong collinearity with variable 'pN status'[c]			
	Breast volume (cc)	1.002	1.0003	1.004	0.037	1.00	1.00	1.00	0.112
	WBI breast V_{86Gy} (cc)	1.002	1.0003	1.005	0.038	Not included in multivariate model due to strong collinearity with variable 'Breast volume'[c]			
	WBI breast V_{90Gy} (cc)	1.002	0.99	1.004	0.096				
	MIBT breast V_{29Gy} (cc)	1.02	1.002	1.03	0.037	1.01	1.00	1.03	0.066
	MIBT breast V_{36Gy} (cc)	1.02	0.99	1.04	0.064	Not included in multivariate model due to strong collinearity with variable 'MIBT breast V_{29Gy}'[c]			
	MIBT breast V_{43Gy} (cc)	1.02	0.99	1.05	0.065				
	MIBT breast V_{50Gy} (cc)	1.03	0.99	1.07	0.063				
	MIBT breast V_{57Gy} (cc)	1.04	0.99	1.09	0.09				

[a]Only parameters with a p-value < 0.1 were reported; [b]variables with a p-value < 0.1 obtained from the univariate analysis were entered into the multivariate model; [c]Spearman's coefficient > 0.7 (p < 0.001); CI – confidence interval

In the multivariate model, we did not find any statistically significant patient, tumor, or treatment-related factor for cosmesis prediction. There was a trend for poorer cosmesis in patients with higher absolute, but not relative, MIBT V_{29Gy} (volume of the breast tissue that received 100% of the prescribed dose in brachytherapy boost, if α/β = 3 Gy was assumed for normal breast late effects), with odds ratio = 1.01, meaning that every centimeter cube increase in MIBT breast $V_{100\%}$ (treated volume) increases the risk of poorer Harvard's score by 1%. This finding is in line with Kulik *et al*. [10], Cambeiro *et al*. [22], Quéro *et al*. [23], and Morales *et al*. [24] studies (Table 6). In univariate analysis, patients treated with irradiation of regional lymphatics (odds ratio ≈ 5), and patients with larger breast volumes presented statistically significant poorer cosmesis scores. Wang *et al*. [2], in a prospective longitudinal study, found that larger breast volumes and supra-clavicular regional nodal irradiation are associated with worse breast asymmetry one year after EBRT. Larger breast volumes or using a supra-clavicular field is often accompanied by a heterogeneous dose distribution (more hot spots) in EBRT planning. Other proposed mechanisms are higher susceptibility of breast adipose tissue to radiation-induced atrophy and radiation damage to regional lymphatics [2].

The small sample size and short follow-up times are the main limitations of the current study that preclude reaching a statistical significance. Moreover, due to the retrospective nature of this study, baseline (pre-RT) cosmetic scores were not available, therefore the impact of surgery or chemotherapy on cosmesis could not be distinguished from radiation therapy. Another problem was that since different software was used for EBRT and brachytherapy plannings, cumulative DVH parameters (WBI + MIBT) could not be calculated.

One strength of our study was that biological equivalent dose-volume parameters were used instead of physical ones to eliminate the impact of dose-fractionation regimens used for WBI and MIBT; thus, the study results can become more generalizable. Also, observer-independent objective measures (BCCT.core) for cosmesis scoring in addition to traditional subjective methods (Harvard's method) were applied.

Conclusions

Based on the findings of our study, higher absolute breast V_{29Gy} in multicatheter interstitial brachytherapy boost, regional nodal irradiation, and large breast volumes are the potential candidates that could have deleterious effects on cosmesis in breast cancer patients treated with whole breast radiotherapy plus HDR interstitial brachytherapy boost after breast conservation surgery. Larger-scale longitudinal prospective studies with longer follow-up durations are needed to confirm these results.

Ethical approval

The Ahvaz Jundishapur University of Medical Sciences ethics and scientific committees approved the study protocol according to the Helsinki Declaration (approval No.: ajums.REC. 1398.801).

Table 6. Summary of the cosmetic outcomes after high-dose-rate (HDR) brachytherapy boost from the available studies

Authors, publication year, [Ref.]	Study type	Patient accrual date	Patient No.	Median patient age (years)	Catheter implantation timing	Dose fractionation regimen		Median follow-up (months)	Cosmesis evaluation method	Cosmetic outcome			Predictors of cosmesis
						EBRT	BRT boost			Excellent	Good	Excellent + good	
Manning *et al.* (2000) [9]	Pros.	1994-1996	18	53	Post-op	50-50.4 Gy	15 Gy/6 fx.	50	N/R	22%	45%	67%	Excision volume
Berberich *et al.* (2001) [25]	Pros.	1986-1997	100	52 ±11[a]	Intra-op	42 Gy (range, 36-50)[b]	18 Gy	113	N/R[c]	28%	39%	67%	– Total dose to remaining glandular tissue – Boost dose
Polgar *et al.* (2002) [26]	Pros.	1995-1998	52	52	Post-op	50 Gy/25 fx.	12-14.25 Gy/ 3 fx.	64	Perez *et al.* scale	N/R	N/R	88.5%	–
Tortajada *et al.* (2005) [27][d]	Pros.	1999-2000	84	N/R	Post-op	46 Gy	7 Gy	43	N/R	N/R	N/R	95%	–
Budrukkar *et al.* (2007) [11]	Retro.	1980-2000	145	45	Post-op	45 Gy/25 fx.	10 Gy/1 fx.	36	JCRT scale	N/R	N/R	83.5%	Adjuvant chemotherapy
Guinot *et al.* (2007) [28]	Pros.	1996-2000	125	55	Post-op	50 Gy	13.2 Gy/3 fx.	84	N/R	N/R	N/R	77%	–
Kulik *et al.* (2009) [10]	Pros.	1996-1999	93	50.8[a]	Post-op	50 Gy/25 fx. 50 Gy/20 fx.	10 Gy/1 fx.	55.4	Modified EORTC scale	41%[e] (54%[f])	44%[e] (28%[f])	85%[e] (82%[f])	– Clinical and mammographic tumor estimation – Method of breast conserving surgery – Type of skin incision – Number of interstitial catheters – Irradiated reference volume (PTV) – Optimization method
Rulli *et al.* (2010) [20]	Pros.	2003-2007	5	65	Intra/ Post-op	N/R	9 Gy/1 fx. 12 Gy/3 fx.	32	Harvard's criteria	74%	23%	97%	–
Polgár *et al.* (2010) [19]	Retro.	1995-2007	79	56.7	Post-op	50 Gy (30-50)	10.35 Gy/1 fx. 12.8 Gy/2 fx. 14.25 Gy/3 fx.	90	Harvard's criteria	17%	39%	56%	– High boost dose (20 Gy LDR equivalent) – High DNR value
Perez *et al.* (2012) [29]	Pros.	1996-2005	63	N/R	Post-op	50 Gy/25 fx.	7 Gy	36	Fehlauer's scale[e] Five-level scale[f]	N/R	N/R	84.8[e] (96.5%[f])	– Extensive surgery – High T stage – Implant volume

Table 6. Cont.

Authors, publication year, [Ref.]	Study type	Patient accrual date	Patient No.	Median patient age (years)	Catheter implantation timing	Dose fractionation regimen		Median follow-up (months)	Cosmesis evaluation method	Cosmetic outcome			Predictors of cosmesis
						EBRT	BRT boost			Excellent	Good	Excellent + good	
Dolezel *et al.* (2012) [21]	Pros.	N/R	23	46	Intra-op	48.6 Gy/27 fx.	12 Gy/4 fx.	43.3	Harvard's criteria	N/R	N/R	82.6%	– Starting irradiation immediately after or too soon after surgery – Using a single-large HDR dose – Method of planning (3D CT-based HDR-BRT with optimization) – Neoadjuvant chemotherapy
Roy *et al.* (2013) [30]	Pros.	2005-2007	20	N/R	Post-op	50 Gy/25 fx.	15 Gy/3 fx.	N/R	CTCAE (ver. 2)	50%	30%	80%	–
Sharma *et al.* (2013) [31][d]	Pros.	2005-2010	100	46	Peri-op	50 Gy	15 Gy/6 fx.	52	N/R	N/R	N/R	87%	–
Guinot *et al.* (2015) [32]	Pros.	1999-2007	167	41	Post-op	46-50 Gy	7 Gy	92	N/R	N/R	N/R	97%	–
Cambeiro *et al.* (2016) [22]	Pros.	2004-2014	34	62	Intra-op	39.9 Gy/15 fx.	13.6 Gy/4 fx.	8.7[h]	Wazer's criteria	11.7%	64.7%	76.4%	– Minimal breast implant[g] – Small CTV volume[g] – Exigent skin dose constraints[g]
Quéro *et al.* (2017) [23]	Retro.	1990-2002	264	56.7	Intra/ Post-op	44 Gy/20 fx.	10 Gy/2 fx.	124	RTOG/ EORTC LENT-SOMA	N/R	N/R	80%	– Small boost volume (mean V_{100}: 45.8cc)[g] – Implantation of 3 catheters in a single-plane[g]
Matuschek *et al.* (2019) [33]	Retro.	1991-1999	43	53	Post-op	50 Gy/25 fx.	≥ 10 Gy	17.7	Harvard's criteria, Cocquyt's score BRA score	80%	50%	30%	–
Morales *et al.* (2020) [24]	Pros.	2008-2016	12	52	Intra-op	39.9 Gy/15 fx.	13.6 Gy/4 fx.	89	Wazer's criteria	33.3%	33.3%	67%	– V_{100} > 10% – Higher BED
The current study results	Retro.	2017-2018	28	48	Post-op	50 Gy/25 fx. 50.4 Gy/28 fx. 42.5 Gy/16 fx.	13.6 Gy/4 fx.	18	BCCT.core, Harvard's criteria	0%[i], 10.5%[j]	18%[i], 43%[j]	18%[i], 53.5[j]	– Absolute breast V_{29Gy}[k,l] – Positive axillary lymph nodes and regional nodal irradiation[k] – Breast volume[k]

[a]Mean ± standard deviation; [b]2.4 Gy/fx.; [c]symmetry assessed; [d]only abstract reviewed; [e]evaluation by physicians; [f]evaluation by patients; [g]factors related to good cosmetics; [h]minimum; [i]BCCT.core; [j]Harvard's criteria; [k]based on trends (not statistically significant in multivariate analysis); [l]volume of the breast in centimeter cube that received 29 Gy biologic effective dose (α/β = 3 Gy for normal breast late effects)

BED – biologically effective dose; BRA – breast retraction assessment; BRT – brachytherapy; CTCAE – common terminology criteria for adverse events; CTV – clinical target volume; DNR – dose non-uniformity ratio; EBRT – external beam radiation therapy; EORTC – European Organization for Research and Treatment of Cancer; HDR – high-dose-rate; Intra-op – intra-operative; JCRT – Joint Centre for Radiation Therapy; LENT-SOMA – late effects normal tissue task force-subjective, objective, management, and analytic; LDR – low-dose-rate; N/R – not reported; Peri-op – perioperative; Post-op – post-operative; Pros – prospective; PTV – planning target volume; RTOG – Radiation Therapy Oncology Group

Disclosure

The authors report no conflict of interest.

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