Original Article

Eur J Breast Health 2023; 19(4): 287-296
DOI: 10.4274/ejbh.galenos.2023.2023-5-4

Impact of Radiotherapy Volumes on Late-Term Cosmetic Outcomes and Quality of Life in Patients With Unifocal and Multifocal/Multicentric Breast Cancer After Breast-Conserving Surgery

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ABSTRACT

Objective: Breast-conserving surgery (BCS) followed by radiotherapy (RT) is the standard treatment for early-stage breast cancer. The use of an additional RT dose (boost) to the tumour bed improves local control but may worsen quality of life (QOL) and cosmetic results. Multifocal/multicentric tumours (MMTs) pose a challenge as they require larger boost volumes. This study investigated the impact of RT volumes on late-term cosmetic outcomes and QOL in patients with unifocal and MMTs who underwent adjuvant RT after BCS.

Materials and Methods: Retrospective data of 367 patients who underwent BCS between 2012 and 2014 were reviewed. A cohort of 121 patients with at least six months of completed RT were prospectively included in the study. Cosmetic results were evaluated using a modified scoring system, and QOL was assessed using The European Cancer Treatment and Organization Committee tools.

Results: The results showed that the inclusion of regional lymphatics in the RT treatment field significantly affected QOL, particularly in terms of role functioning and social functioning. Higher boost volume ratios were associated with increased pain-related symptoms. However, the presence of MMTs did not significantly affect cosmetic outcomes compared to unifocal tumours.

Conclusion: The size of the boost and inclusion of regional lymphatics in RT significantly impact QOL in patients undergoing BCS. Tumour foci number does not affect cosmetic outcomes. These findings emphasize the need for careful consideration of RT volumes to minimize long-term adverse effects on QOL. Future prospective studies should evaluate early side effects and baseline QOL scores to provide a comprehensive assessment.

Keywords: Breast conserving surgery; cosmetic outcome; quality-of-life; radiotherapy

Cite this article as: Altınok P, Tekçe E, Kızıltan HŞ, Gücin Z, Mayadağlı A. Impact of Radiotherapy Volumes on Late-Term Cosmetic Outcomes and Quality of Life in Patients With Unifocal and Multifocal/Multicentric Breast Cancer After Breast-Conserving Surgery. Eur J Breast Health 2023; 19(4): 287-296

Key Points

- Breast-conserving surgery followed by whole-breast radiotherapy ± boost is the current standard treatment for early-stage breast cancer.
- Regardless of the focality of the tumor, the expansion of the boost area and the addition of lymphatic areas to the treatment fields negatively affect the quality of life.
- The presence of multicentric/multifocal tumors does not affect cosmetic results.
- Using standard dosimetric parameters in treatment planning and recommending appropriate lifestyle changes after treatment will improve quality of life.

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Received: 23.05.2023
Accepted: 27.07.2023
Available Online Date: 01.10.2023

Introduction

The current standard treatment for early-stage breast cancer is breast-conserving surgery (BCS) followed by whole-breast radiotherapy (RT) (1-3). The general approach is to give an additional dose (boost) to the tumour bed in high-risk cases, based on individual clinical and pathological features. Studies show that the use of boost increases local control at the expense of worsening quality of life (QOL) and cosmetic results (4). The most important factor that increases the negative effects on cosmetic results is large boost volumes. However, enlargement of the boost field is inevitable in breasts with multicentric/multifocal tumours (MMTs) that have undergone BCS. Thirteen to sixty percent of newly diagnosed breast cancers are MMTs (5). Although mastectomy has been performed in MMTs for many years, Hartsell et al. (6) published the rules used today regarding BCS in multicentric tumours in 1994. Thus, it has been included in the basic guideline that BCS can be applied in multicentric tumours if all clinical and radiological abnormal findings are cleared, a clean surgical margin is provided, and there is no widespread intraductal component. The results of the Alliance Z11102 study revealed that BCS and RT are possible in the presence of more than one tumour focus in the same breast, and that increased boost volume does not adversely affect long-term cosmetic results (7).

Based on these results, the aim of the present study was to investigate the effect of RT volumes on late-term cosmetic outcomes in patients with unifocal and MMTs who underwent adjuvant RT after BCS in a single center. In addition, since they have not been discussed in the literature, the effect of RT volumes and cosmetic results on QOL was examined using the European Cancer Treatment and Organization Committee (EORTC) QOL assessment tools (8).

Materials and Methods

For the study, the data of 367 patients aged 18 years and older who underwent BCS and were treated in a single centre between 2012 and 2014 were retrospectively reviewed. In those years, oncoplastic surgery had not entered routine surgical practice, so conventional BCS was performed. Computed tomography of thorax, abdomen and pelvis, plus bone scan or fluorodeoxyglucose-positron emission tomography was done for staging purposes. All patients with suspicion of multicentricity/multifocality after mammography+breast ultrasound were evaluated with magnetic resonance imaging.

Patients who received neoadjuvant systemic therapy, patients with another malignancy other than basal cell skin cancer, and patients who had undergone hypofractionated RT were excluded, in order to homogenize the group as much as possible. A final cohort of 121 patients who had completed RT and were followed up for at least six months (the minimum time required for late side effects of RT to appear) and met the study criteria were prospectively included in the study. When these patients came to routine outpatient clinic controls, they were asked to sign the study consent form, cosmetic result evaluations were made, and they were asked to fill in the questionnaire forms.

Clinical characteristics of patients (age, menopausal status), type of approach to the axilla during BCS (sentinel lymph node sampling, axillary dissection), pathological features of the disease (type, number and diameter of foci, stage, grade, receptor and human epidermal growth factor receptor two status, presence of lymphatic space invasion), adjuvant systemic treatments (chemotherapy, hormone therapy), RT fields (breast, breast+regional lymphatics), breast RT volumes (breast and additional dose volumes, in cc) were noted. The presence of tumours located less than 5 cm in the same quadrant was considered multifocal, and the presence of tumours located more than 5 cm in different quadrants was considered multicentric.

Radiotherapy: In all patients, breast (±lymphatic fields) irradiation was applied as 50 Gy in 25 fractions and 10 Gy in 5 fractions as an additional dose (boost) to the tumour bed. To use the standard tangential field-in-field technique and to ensure dose homogeneity, 6 and 18 MV photon beams were used. The Radiation Therapy Oncology Group breast contouring atlas was used as a guide for contouring RT volumes (9). Treatments were recorded according to reports 50 and 62 of the International Commission on Radiotherapy Units (10, 11).

Each patient with positive nodes on histopathological examination was evaluated for regional nodal irradiation. Isolated tumour cells, sub-micrometastases and micrometastases were not included in the regional irradiation field. pN2, pN3 disease and extra nodal involvement were certain indications for irradiation of supraclavicular nodes and level 1-2-3 axilla (supra+axilla). For internal quadrant tumours over 3 cm, the mammary interna was also included in the field (full regional lymphatics=RL). Supraclavicular region plus level 3 only irradiation was not performed in any patient.

Cosmetic Evaluation and Quality of Life Analysis: The patients were evaluated for cosmetic results at their first admission following the start of the study, and they were asked to complete breast cancer QOL questionnaires. For cosmetic scoring, the 4-point scoring system described by Winchester and Cox (12) in 1998 was modified and used. Accordingly, cosmetic results were recorded as "good" with little or no change in the treated breast compared to the untreated breast, recorded as "moderate" with clear difference between the treated and untreated breasts, and recorded as "poor" with significant functional and aesthetic sequelae in the treated breast.

The EORTC's 30-item general QOL scale (EORTC QLQ-C30) and the 23-item breast cancer-specific QOL scale (EORTC QOL-BR23) were used to evaluate and score QOL. EORTC-30 scoring includes global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) were evaluated. Functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss) were evaluated in the EORTC-23 module, which was prepared specifically for breast cancer. In scoring out of 100, higher scores for the functional scales indicates better results, and higher scores for the symptom scales indicates worse results.

This study was approved by the Bezmialem Vakif University Non-Invasive Clinical Research Ethics Committee (date: 04.04.2017, no: 7/63).

Statistical Analysis

While evaluating the findings of the study, the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed was analysed using descriptive, graphical, and statistical methods. Kolmogorov-

Smirnov test was used to assess the normality of the scores obtained from a continuous variable with the statistical method. The reliability of the measurement tool in this study was tested with Cronbach's alpha coefficient used in internal consistency control. While evaluating the study data, comparisons between the two groups in quantitative data were made with the Mann-Whitney U test, as well as descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.). Fisher's exact test was used for qualitative comparisons between groups. Survival calculations were made using the Kaplan-Meier analysis method. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$.

Results

The median time for enrollment in the study was 48 (12–75) months after the completion of RT. Patient and pathological tumour characteristics are summarized in Table 1.

In 24 patients with MMTs, the number of foci varied between 2-11 and tumour sizes between 3–40 mm. In 97 patients with unifocal tumours, the mean tumour size was 22.21 mm. While the median boost/breast volume ratios were 3.25% (0.24–29.11) in unifocal patients, this mean ratio was 5.52% (0.75–14.61) in multifocal/multicentric patients.

The surgical, systemic treatment and details of RT applied to the patients and the follow-up results are summarized in Table 2.

The median follow-up period was 99 (32–127) months. In the analyses performed, no statistically significant correlation was found between the presence of local/regional and systemic recurrence and the RT field, RT volume ratio, axillary surgery type and tumour focal status ($p>0.05$). Since the number of patients was not sufficient for survival analysis, the results were given as proportional difference, according to cut-off quarters. There was no difference in survival rates (Table 3).

Mean EORTC QLQ-C30 Scores of the Patients

The mean EORTC QLQ-C30 global health status score of the patients was 67.77. For functional scales, physical functioning average was 73.22, role functioning average was 88.84, emotional functioning average was 76.17, cognitive functioning average was 80.72, and social functioning average was 86.64 points. In terms of symptoms scales the average score for fatigue was 34.16, for nausea-vomiting was 9.37, for pain was 23.42, for dyspnoea was 15.43, for insomnia was 30.85, appetite loss was 11.02, constipation was 19.56, diarrhoea was 5.51, financial difficulties were 20.66. Cronbach's alpha (α) coefficients of the EORTC QLQ-C30 global health status, physical functioning scales and symptom scales were 0.96, 0.76 and 0.79, respectively. With these findings, the scale reliability level was found to be at an acceptable level (Table 4).

Mean EORTC QLQ-BR23 Scores of the Patients

The QLQ-BR23 functional scales of the patients, the mean body image, sexual functioning, sexual enjoyment, and future perspective averaged 84.16, 12.81, 40.83 and 58.95 points, respectively. The mean scores of the symptom scales were 27.94 for systemic therapy side effects, 21.14 for breast symptoms, 23.05 for arm symptoms and 22.04 for upset by hair loss. Cronbach's alpha (α) coefficients of the EORTC QLQ-BR23 functional scales and symptom scales were 0.60 and 0.76, respectively. With these findings, the scale reliability level was found to be at an acceptable level (Table 4).

Mean EORTC QLQ-C30 Scores of Patients Based on Tumour and RT Characteristics

There was no significant difference in EORTC QLQ-C30 scores according to tumour focus status, RT volume ratio and cosmetic results ($p>0.05$). When associated with the RT field, there was a significant difference in role functioning ($p = 0.017$), social functioning ($p = 0.002$) and financial difficulties ($p = 0.028$) scales. Patients irradiated to the breast+regional lymphatics (RL) field had lower role functioning

Table 1. Patient and pathological tumour characteristics (n = 121)

Variables	Categories	n (%)
Age, median (range)	All	52 (35–78)
Age group	≤50	55 (45.5)
	>50	66 (54.5)
Menopausal status	Premenopausal	50 (41.3)
	Postmenopausal	71 (58.7)
Tumour type	Ductal	94 (77.7)
	Other	27 (22.3)
Tumour focal status	Unifocal	97 (80.2)
	Multifocal/multicentric	24 (19.8)
pT Stage	pT1	56 (46.3)
	$pT2_{(n=63)}$-$3_{(n=2)}$	65 (53.7)
pN Stage	pN0	75 (62.0)
	pN1	30 (24.8)
	$pN2_{(n=12)}$-$3_{(n=4)}$	16 (13.2)
p Stage	p Stage-1	48 (39.7)
	p Stage-2	56 (46.3)
	p Stage-3	17 (14.0)
Tumour diameter (mm), median (range)	All	22 (1-80)
Grade	$I_{(n=20)}$-$II_{(n=51)}$	71 (58.7)
	III	50 (41.3)
LVI	Positive	32 (26.4)
	Negative	89 (73.6)
DCIS	Positive	97 (80.2)
	Negative	24 (19.8)
ER	Positive	103 (85.1)
	Negative	18 (14.9)
PR	Positive	94 (77.7)
	Negative	27 (22.3)
HER2	Positive	10 (8.3)
	Negative	111 (91.7)
Molecular subtype	Luminal	104 (86.0)
	Non-luminal	17 (14.0)

LVI: lymphovascular invasion; DCIS: ductal carcinoma *in situ*; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor two

Table 2. The treatment information applied to the patients and the follow-up results (n = 121)

Variables	Categories	n (%)
Axillary surgery	SLNB	71 (58.7)
	Axillary dissection	50 (41.3)
Adjuvant chemotherapy	Yes	81 (66.9)
	No	40 (33.1)
Hormone therapy	Yes	104 (86.0)
	No	17 (14.0)
Radiotherapy field	Breast	82 (67.8)
	Breast+supra+axilla+MI	7 (5.8)
	Breast+supra+axilla	32 (26.4)
RT breast volume, median (IQR)	All	786 (511–1127)
RT boost volume, median (IQR)	All	25.9 (12.8–44.8)
RT volume ratio median (IQR)	All	3.3 (1.9–5.6)
Breast cosmetic outcome	Good	81 (66.9)
	Moderate	36 (29.8)
	Poor	4 (3.3)
Local regional recurrence	Yes	4 (3.3)
	No	117 (96.7)
Systemic recurrence	Yes	6 (5.0)
	No	115 (95.0)
Follow-up period (month), median (range)	All	99 (32–127)

RT: radiotherapy; IQR: interquartile range; SLNB: sentinel lymph node biopsy; MI: mammaria interna

and social functioning QOL, and more financial problems compared to patients irradiated to the breast only (Table 5).

When the RT volume ratio (RTVR) was classified according to the 75% quartile, the RTVR was 5% or less in 90 patients (74.4%) and above 5% in 31 patients (25.6%). Among breast+RL irradiated patients (n = 39), those with RTVR above 5% (n = 13) had significantly lower QOL scores related to role functioning (p = 0.12) and emotional functioning (p = 0.048) and significantly higher pain-related symptoms (p = 0.019). There was no significant difference in the QOL of the patients according to RTVR classification in multifocal tumours (p>0.05). However, in unifocal tumours, patients with RTVR above 5% (n = 22) had significantly higher pain-related symptoms (p = 0.018) (Table 6).

Mean QLQ-BR23 Scores of Patients According to Tumour and RT Characteristics

There was no significant difference in QLQ-BR23 scores according to RT treatment fields and RTVR (p>0.05). Compared to unifocal tumours, patients with MMTs had lower body image-related QOL (p = 0.021) and patients with moderate/poor cosmetic results had worse arm-related symptoms (p = 0.029) compared to patients with good breast cosmetic results after RT (Table 5).

Among breast+RL irradiated patients (n = 39), those with RTVR above 5% (n = 13) had significantly higher breast (p = 0.019) and arm (p = 0.028) related symptoms. In MMTs, no significant difference was found in the QLQ-BR23 scores of patients according to RTVR classification (p>0.05). However, in unifocal tumours, patients with RTVR above 5% had significantly worse scores for arm-related symptoms (p = 0.041) (Table 6).

Discussion and Conclusion

It is now generally accepted that BCS and RT can be performed in multifocal tumours, just as in unifocal tumours (13, 14). However, there is concern that increased boost volumes, especially in multifocal tumours, may worsen cosmetic results and have a negative impact

Table 3. Relapse outcomes in relation to study parameters

	All	Local regional recurrence (n = 4, 3.3%)		Systemic recurrence (n = 6, 5%)	
Variables	**n**	**n (%)**	***p****	**n (%)**	***p****
Radiotherapy field			0.999		0.084
Breast	82	3 (3.7)		2 (2.4)	
Breast+RL	39	1 (2.6)		4 (10.3)	
RT volume ratio			0.271		0.646
≤5%	90	2 (2.2)		4 (4.4)	
>5%	31	2 (6.5)		2 (6.5)	
Axillary surgery			0.642		0.690
SLNB	71	3 (4.2)		3 (4.2)	
Axillary dissection	50	1 (2.0)		3 (6.0)	
Tumour focal status			0.176		0.340
Unifocal	97	2 (2.1)		4 (4.1)	
Multifocal/multicentric	24	2 (8.3)		2 (8.3)	

p>0.05; ***:** Fisher's exact test; RT: radiotherapy; SLNB: sentinel lymph node biopsy; RL: regional lymphatics

Table 4. EORTC QLQ-C30 and EORTC QLQ-BR23 quality of life scores

QLQ-C30	No. of items	Mean ± SD	95% CI	α
Global health status/QOL	2	67.77±24.88	63.29–72.25	0.96
Functional scales				0.76
Physical functioning	5	73.22±20.20	69.59–76.86	
Role functioning	2	88.84±21.45	84.98–92.70	
Emotional functioning	4	76.17±24.42	71.78–80.57	
Cognitive functioning	2	80.72±20.86	76.96–84.47	
Social functioning	2	86.64±20.60	82.93–90.35	
Symptom scales				0.79
Fatigue	3	34.16±24.93	29.67–38.65	
Nausea & vomiting	2	9.37±20.29	5.72–13.02	
Pain	2	23.42±24.40	19.02–27.81	
Dyspnoea	1	15.43±25.11	10.91–19.95	
Insomnia	1	30.85±35.00	24.55–37.15	
Appetite loss	1	11.02±21.68	7.12–14.92	
Constipation	1	19.56±29.08	14.32–24.79	
Diarrhoea	1	5.51±15.72	2.68–8.34	
Financial problems	1	20.66±27.64	15.69–25.64	
QLQ-BR23	**No. of items**	**Mean ± SD**	**95% CI**	
Functional scales				0.60
Body image functioning	4	84.16±20.96	80.39–87.93	
Sexual functioning	2	12.81±18.73	9.44–16.18	
Sexual enjoyment	1	40.83±23.25	33.40–48.27	
Future health function	1	58.95±32.99	53.02–64.89	
Symptom scales				0.76
Systemic therapy side effects	7	27.94±20.04	24.33–31.55	
Breast symptoms	4	21.14±20.10	17.53–24.76	
Arm symptoms	3	23.05±22.69	18.97–27.13	
Hair loss	1	22.04±34.31	15.86–28.21	

SD: standard deviation; CI: confidence interval; α: Cronbach alpha coefficient; EORTC: European Cancer Treatment and Organization Committee

on QOL (15). In the recently published analysis of the ACOSOG Z11102 (Alliance) study, it was stated that RT after BCS did not adversely affect long-term cosmetic results in multifocal tumours, and poor cosmetic results were observed in 3.6% of patients (7). In the present study, the rate of poor cosmetic result was 3.3%.

In the ACOSOG Z11102 study, it was observed that absolute and relative boost volume did not significantly affect the overall cosmetic appearance, but worsening of breast QOL scores was observed with the expansion of absolute boost volume. In the Dutch cohort, larger tumour size, axillary lymph node dissection, locoregional RT, and boost to the tumour bed were associated with breast oedema (16). Breast oedema was independently associated with more breast pain and worse QOL, physical functioning and body image. Our study revealed that the number of foci and boost/breast volume ratio were not significant in terms of cosmetic outcomes in patients who underwent only breast RT after BCS. Pain and arm-related symptoms were more common in unifocal tumours with a relative boost volume above 5%. The main factor that negatively affected QOL was irradiation of regional lymphatics. Breast and arm symptoms were particularly adversely affected.

In the present study, we did not include patients who underwent different fractionation regimens to avoid bias in the evaluation of the results. However, there are studies in the literature that examined this issue. Jacobs et al. (17) examined the effects of different RT schemes on QOL in 1512 patients in five prospective cohorts and found no difference between RT schemes, with the exception of breast symptoms. Those who underwent intraoperative RT and external accelerated partial breast irradiation had fewer breast symptoms than those who underwent whole breast irradiation. In the 5-year QOL review of the START A and B trials using hypofractionated regimens, arm and shoulder pain affected one-third of patients. But this was related to previous surgery rather than RT (18). These results suggest that the extent of surgery (e.g., addition of lymphatic dissection) and the increase in irradiated volume (partial vs whole breast vs breast+boost)

Table 5. Mean EORTC QLQ-C30 and QLQ-BR23 scores according to tumour focus status, RT volume ratio and cosmetic results

	Tumour focal status				RT volume ratio			
	Unifocal	Multifocal			≤5%	>5%		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	68.4±25.0	65.3±24.9	-0.54	0.587	68.8±25.3	64.8±23.6	-0.96	0.339
Functional scales								
Physical functioning	74.4±20.1	68.3±20.4	-1.65	0.099	73.7±20.9	71.8±18.3	-0.83	0.404
Role functioning	90.2±19.2	83.3±28.7	-0.86	0.392	90.2±20.7	84.9±23.3	-1.19	0.233
Emotional functioning	77.0±24.3	72.9±25.3	-0.88	0.381	76.3±25.0	75.8±23.2	-0.26	0.797
Cognitive functioning	79.4±21.6	86.1±16.8	-1.42	0.155	80.7±21.2	80.6±20.2	-0.05	0.960
Social functioning	87.6±19.3	82.6±25.3	-0.50	0.618	86.9±21.3	86.0±18.8	-0.47	0.636
Symptom scales								
Fatigue	33.6±24.3	36.6±27.7	-0.31	0.753	33.8±24.5	35.1±26.5	-0.17	0.866
Nausea & vomiting	10.5±22.0	4.9±10.4	-0.72	0.471	8.7±19.4	11.3±22.9	-0.34	0.733
Pain	23.4±24.5	23.6±24.5	-0.17	0.863	20.0±20.0	33.3±32.5	-1.82	0.068
Dyspnoea	17.2±26.8	8.3±14.7	-1.22	0.222	14.8±25.0	17.2±25.6	-0.64	0.520
Insomnia	29.9±35.5	34.7±33.3	-0.90	0.367	30.7±34.7	31.2±36.4	-0.03	0.980
Appetite loss	11.0±22.4	11.1±18.8	-0.48	0.635	10.0±20.9	14.0±24.0	-0.84	0.399
Constipation	18.9±27.6	22.2±35.0	-0.03	0.979	18.9±29.2	21.5±29.2	-0.63	0.526
Diarrhoea	6.2±16.9	2.8±9.4	-0.82	0.413	5.6±16.8	5.4±12.5	-0.48	0.635
Financial problems	19.6±27.1	25.0±29.9	-0.86	0.391	19.3±26.0	24.7±32.2	-0.63	0.526
QLQ-BR23								
Functional scales								
Body image functioning	86.2±19.8	76.0±23.9	-2.30	0.021*	85.5±19.9	80.4±23.7	-0.88	0.379
Sexual functioning	12.7±19.5	13.2±15.5	-0.59	0.556	13.0±18.2	12.4±20.6	-0.51	0.610
Sexual enjoyment	40.6±25.0	41.7±15.4	-0.08	0.940	38.9±23.3	46.7±23.3	-1.10	0.273
Future health function	59.8±31.5	55.6±38.9	-0.31	0.754	59.3±33.4	58.1±32.2	-0.24	0.811
Symptom scales								
Systemic therapy side effects	26.4±20.1	34.3±19.1	-1.96	0.050	26.9±19.1	31.0±22.6	-0.75	0.454
Breast symptoms	20.4±19.8	24.3±21.3	-0.86	0.389	19.7±19.4	25.3±21.9	-1.19	0.233
Arm symptoms	22.6±22.8	25.0±22.8	-0.75	0.452	20.4±19.7	30.8±28.6	-1.65	0.098
Hair loss	19.6±32.2	31.9±41.1	-1.34	0.181	21.9±33.9	22.6±35.9	-0.02	0.981

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

	Cosmetic outcome				RT field			
	Good	Moderate/ Poor			Breast	Breast/RL		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	69.4±25.0	64.4±24.5	-1.14	0.254	69.7±24.7	63.7±25.1	-1.31	0.191
Functional scales								
Physical functioning	73.5±21.3	72.7±18.1	-0.75	0.456	74.6±20.2	70.4±20.2	-1.10	0.270
Role functioning	89.3±22.9	87.9±18.5	-1.02	0.306	91.7±18.9	82.9±25.2	-2.39	0.017*
Emotional functioning	77.8±23.8	72.9±25.7	-0.93	0.355	75.1±25.8	78.4±21.4	-0.33	0.746
Cognitive functioning	80.5±20.5	81.3±21.7	-0.37	0.711	79.9±21.6	82.5±19.5	-0.72	0.471
Social functioning	85.8±21.7	88.3±18.2	-0.53	0.596	90.4±17.6	78.6±24.2	-3.04	0.002*
Symptom scales								
Fatigue	33.3±26.1	35.8±22.6	-1.00	0.317	33.7±23.8	35.0±27.5	-0.06	0.955
Nausea & vomiting	9.7±21.9	8.8±16.9	-0.35	0.727	8.9±19.8	10.3±21.5	-0.24	0.812
Pain	21.4±23.0	27.5±26.8	-1.18	0.239	23.0±21.9	24.4±29.3	-0.48	0.633
Dyspnoea	13.6±24.0	19.2±27.1	-1.21	0.228	15.9±26.3	14.5±22.7	-0.03	0.979
Insomnia	28.0±33.9	36.7±36.8	-1.32	0.186	30.5±35.2	31.6±35.0	-0.25	0.806
Appetite loss	10.7±21.6	11.7±22.1	-0.23	0.819	10.2±21.4	12.8±22.4	-0.75	0.453
Constipation	17.7±28.4	23.3±30.4	-1.20	0.231	17.9±26.8	23.1±33.5	-0.65	0.514
Diarrhoea	4.9±14.1	6.7±18.8	-0.40	0.687	4.5±12.6	7.7±20.9	-0.55	0.581
Financial problems	18.1±25.3	25.8±31.6	-1.24	0.215	16.7±24.7	29.1±31.7	-2.20	0.028*
QLQ-BR23								
Functional scales								
Body image functioning	85.7±17.7	81.0±26.3	-0.13	0.898	85.6±19.2	81.2±24.2	-1.01	0.312
Sexual functioning	13.6±19.0	11.3±18.3	-0.74	0.457	13.0±18.9	12.4±18.6	-0.11	0.911
Sexual enjoyment	36.9±21.0	50.0±26.6	-1.55	0.122	39.3±20.4	44.4±29.6	-0.54	0.587
Future health function	60.5±33.0	55.8±33.2	-0.71	0.481	57.3±33.2	62.4±32.6	-0.83	0.407
Symptom scales								
Systemic therapy side effects	26.3±19.2	31.2±21.5	-1.14	0.256	27.1±19.7	29.7±20.9	-0.50	0.618
Breast symptoms	19.1±19.1	25.2±21.6	-1.59	0.111	20.5±19.9	22.4±20.8	-0.41	0.681
Arm symptoms	19.3±19.3	30.6±27.1	-2.19	0.029*	20.1±20.6	29.3±25.7	-1.94	0.053
Hair loss	19.8±32.0	26.7±38.6	-0.80	0.425	17.9±29.7	30.8±41.5	-1.31	0.191

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

Table 6. Mean EORTC QLQ-C30 and QLQ-BR23 scores in tumour focus status and RT field groups classified according to RT volume

	Unifocal				Multifocal			
	RTVR ≤5% (n = 75)	RTVR >5% (n = 22)			RTVR ≤5% (n = 15)	RTVR >5% (n = 9)		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	70.1±25.3	62.5±23.5	-1.45	0.147	62.2±25.6	70.4±24.3	-0.63	0.526
Functional scales								
Physical functioning	74.6±21.3	73.9±15.8	-0.67	0.505	69.3±19.0	66.7±23.6	0.00	1.000
Role functioning	90.7±19.6	88.6±18.1	-0.76	0.445	87.8±26.3	75.9±32.4	-0.76	0.449
Emotional functioning	77.6±25.0	75.0±21.8	-0.75	0.456	70.0±24.4	77.8±27.6	-0.94	0.347
Cognitive functioning	80.2±22.0	76.5±20.4	-1.01	0.312	83.3±16.7	90.7±16.9	-1.23	0.221
Social functioning	87.8±20.4	87.1±15.4	-0.64	0.524	82.2±25.6	83.3±26.4	-0.21	0.837
Symptom scales								
Fatigue	32.7±24.2	36.4±25.2	-0.57	0.569	39.3±26.5	32.1±30.7	-0.67	0.502
Nausea & vomiting	8.9±20.6	15.9±26.0	-1.40	0.161	7.8±12.4	0.0±0.0	-1.89	0.058
Pain	19.3±20.1	37.1±32.5	-2.37	0.018*	23.3±19.7	24.1±32.4	-0.50	0.617
Dyspnoea	16.4±26.5	19.7±28.5	-0.58	0.561	6.7±13.8	11.1±16.7	-0.72	0.475
Insomnia	28.4±34.1	34.8±40.5	-0.59	0.559	42.2±36.7	22.2±23.6	-1.30	0.195
Appetite loss	10.2±21.9	13.6±24.5	-0.63	0.529	8.9±15.3	14.8±24.2	-0.49	0.625
Constipation	17.8±26.5	22.7±31.5	-0.62	0.534	24.4±40.8	18.5±24.2	-0.17	0.863
Diarrhoea	6.2±17.9	6.1±13.2	-0.48	0.631	2.2±8.6	3.7±11.1	-0.37	0.709
Financial problems	17.3±25.9	27.3±30.2	-1.54	0.124	28.9±24.8	18.5±37.7	-1.39	0.164
QLQ-BR23								
Functional scales								
Body image functioning	87.8±19.0	80.7±21.7	-1.39	0.165	73.9±20.6	79.6±29.5	-1.09	0.275
Sexual functioning	12.2±18.7	14.4±22.6	-0.20	0.844	16.7±15.4	7.4±14.7	-1.50	0.134
Sexual enjoyment	38.9±25.4	45.8±24.8	-0.83	0.406	38.9±13.6	50.0±23.6	-0.88	0.378
Future health function	61.3±31.5	54.5±31.8	-0.92	0.357	48.9±41.5	66.7±33.3	-0.99	0.320
Symptom scales								
Systemic therapy side effects	24.8±18.9	31.8±23.3	-1.22	0.224	37.5±17.3	29.1±21.9	-1.05	0.294
Breast symptoms	18.4±19.3	26.9±20.7	-1.85	0.064	26.1±19.1	21.3±25.4	-0.94	0.349
Arm symptoms	19.9±20.8	31.8±27.1	-2.05	0.041*	23.0±13.6	28.4±33.8	-0.43	0.669
Hair loss	19.1±31.1	21.2±36.4	-0.06	0.955	35.6±44.5	25.9±36.4	-0.39	0.694

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

	Breast				Breast/RL			
	RTVR ≤5% (n = 64)	RTVR >5% (n = 18)			RTVR ≤5% (n = 26)	RTVR >5% (n = 13)		
	Mean ± SD	Mean ± SD	Z	*p*	Mean ± SD	Mean ± SD	Z	*p*
EORTC QLQ-C30								
Global health status/QOL	70.6±25.4	66.7±22.5	-0.77	0.445	64.4±25.2	62.2±25.8	-0.36	0.718
Functional scales								
Physical functioning	74.0±21.8	76.7±13.0	-0.18	0.856	73.1±18.8	65.1±22.6	-1.04	0.298
Role functioning	90.4±20.7	96.3±9.1	-0.99	0.322	89.7±21.1	69.2±27.9	-2.51	0.012*
Emotional functioning	73.6±26.5	80.6±23.2	-1.14	0.256	83.0±19.6	69.2±22.4	-1.98	0.048*
Cognitive functioning	79.2±22.2	82.4±19.4	-0.53	0.599	84.6±18.2	78.2±21.9	-0.82	0.411
Social functioning	89.3±18.9	94.4±11.4	-0.97	0.334	80.8±25.7	74.4±21.1	-1.15	0.250
Symptom scales								
Fatigue	35.8±24.6	26.5±19.5	-1.25	0.210	29.1±24.2	47.0±30.8	-1.81	0.070
Nausea & vomiting	9.6±21.4	6.5±13.0	-0.26	0.794	6.4±13.4	17.9±31.5	-0.86	0.393
Pain	22.1±20.6	25.9±26.3	-0.45	0.650	14.7±17.8	43.6±38.2	-2.35	0.019*
Dyspnoea	14.6±25.8	20.4±28.3	-1.05	0.295	15.4±23.5	12.8±21.7	-0.29	0.774
Insomnia	30.2±35.0	31.5±37.0	-0.14	0.885	32.1±34.6	30.8±37.2	-0.19	0.849
Appetite loss	10.4±22.1	9.3±19.2	-0.02	0.981	9.0±17.8	20.5±29.0	-1.23	0.220
Constipation	16.1±25.9	24.1±29.8	-1.20	0.232	25.6±35.7	17.9±29.2	-0.57	0.569
Diarrhoea	4.7±13.1	3.7±10.8	-0.18	0.859	7.7±23.7	7.7±14.6	-0.78	0.433
Financial problems	16.1±23.8	18.5±28.5	-0.21	0.834	26.9±29.8	33.3±36.0	-0.45	0.656
QLQ-BR23								
Functional scales								
Body image functioning	86.3±18.4	82.9±22.0	-0.32	0.750	83.3±23.3	76.9±26.4	-0.86	0.391
Sexual functioning	13.0±18.4	13.0±21.0	-0.24	0.811	12.8±17.8	11.5±20.8	-0.51	0.607
Sexual enjoyment	36.4±20.3	50.0±18.3	-1.45	0.146	45.8±30.5	41.7±31.9	-0.09	0.928
Future health function	55.7±33.1	63.0±34.1	-0.83	0.406	67.9±33.3	51.3±29.2	-1.72	0.085
Symptom scales								
Systemic therapy side effects	26.9±19.8	28.0±19.8	-0.34	0.731	26.9±17.6	35.2±26.3	-0.87	0.386
Breast symptoms	20.8±20.0	19.4±20.0	-0.38	0.707	17.0±17.9	33.3±22.6	-2.34	0.019*
Arm symptoms	19.8±20.1	21.0±22.8	-0.17	0.868	21.8±19.0	44.4±31.1	-2.19	0.028*
Hair loss	20.3±30.6	9.3±25.1	-1.71	0.087	25.6±41.4	41.0±41.2	-1.41	0.158

*****: $p<0.05$; Z: Mann-Whitney U test; SD: standard deviation; RT: radiotherapy; QOL; quality of life; RL: regional lymphatics; EORTC: European Cancer Treatment and Organization Committee

do not significantly change the cosmetic results, but negatively affect QOL scores. When combined with the data of the present study, we suggest that the factors that negatively affect QOL will be the same, regardless of which fractionation is used.

There are a few limitations of the present study. Since the main aim was to demonstrate the effects of RT, the negative cosmetic effect of surgery was not analysed separately. In any case, a study designed as post-surgery, pre-RT and post-RT would be the most accurate. Therefore, it is planned to add evaluation before RT in future patients. Second, the number of patients with MMTs was only 24 and statistical corrections were made to account for this. Nevertheless, as a result of our study, we believe that breast/boost ratios give an idea about how the tumour focal status may affect the cosmetic results. We hope that more effective and informative QOL studies will be performed with larger series. Another critical limitation is the retrospective nature of the treatment phase of the study. However, the fact that it was planned by the same team of physicians and physicists is an important factor that ensures standardisation in terms of patient treatment quality.

In summary, the major factors affecting QOL in patients receiving RT after BCS are the size of the boost fields and whether regional lymphatics are included in the treatment field. If the disease is multicentric it will not change the cosmetic effect of boost size. These factors inevitably affect long-term QOL. Therefore, standard dosimetry parameters should be determined in treatment planning and necessary lifestyle approaches should be recommended to improve QOL after treatment.

Ethics Committee Approval: This study was approved by the Bezmialem Vakif University Non-Invasive Clinical Research Ethics Committee (date: 04.04.2017, no: 7/63).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.A., Z.G., A.M.; Concept: P.A.; Design: P.A.; Data Collection or Processing: P.A., E.T., H.Ş.K., Z.G.; Analysis or Interpretation: P.A., E.T., H.Ş.K., Z.G., A.M.; Literature Search: P.A., E.T.; Writing: P.A., E.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial disclosure.

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