



Comparison of brachytherapy and external beam radiotherapy boost in breast-conserving therapy: Patient-reported outcome measures and aesthetic outcome

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Abstract

Objective This study aimed to estimate the probability of an unfavourable aesthetic outcome (AO) 2 years after breast-conserving therapy (BCT) and evaluate the possible influence of brachytherapy (BT) and external beam radiotherapy (EBRT) boost on patient-reported outcomes (PROs) and AO.

Patients and methods Patients treated with BCT starting April 2015 were prospectively included. Selection of the boost technique followed an in-house flowchart based on the depth of the tumour bed. An electron boost was performed for a superficial clinical target volume (maximum 28 mm under the epidermis), a BT boost was proposed in all other cases. Patients were followed-up for 2 years. AO was scored by the BCCT.core software and the patient. Further PROs were measured with the EORTC QLQ-C30, QOL-BR23 and the BIBCQ questionnaires.

Results The analysis included 175 patients, 80 received a BT boost and 95 an EBRT boost. BT patients were significantly older; had a higher breast cup and band size, body mass index and surgical specimen weight of the wide excision; more seroma at baseline and less positive surgical section margins than patients in the EBRT group, and more patients drank alcohol. Cancer- and breast cancer-specific quality of life (QOL) and body image did not differ between the boost techniques over time. Although mean scores for breast symptoms and sexual enjoyment did differ significantly over time ($p=0.05$ and <0.01 , respectively), the effect was due to differences before boost administration. Measured with BCCT.core, AO was unfavourable in 28% of patients 2 years after treatment (31% scored by the patient) and results were similar in the BT and EBRT groups.

Conclusion Using the presented flowchart (See Verhoeven et al. [16]), AO and PROs on QOL or body image up to 2 years after BCT are not influenced by the boost technique.

Keywords Breast neoplasms · Questionnaires · Patient reported outcome measures · Toxicity · Quality of life

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Vergleich von Brachytherapie und perkutaner Boost-Strahlentherapie nach brusterhaltender Therapie: Patientenbewertung und ästhetisches Ergebnis

Zusammenfassung

Zielsetzung Ziel war es, die Wahrscheinlichkeit eines ungünstigen ästhetischen Ergebnisses (AE) 2 Jahre nach brusterhaltender Therapie (BCT) abzuschätzen sowie den möglichen Einfluss von Brachytherapie (BT) und perkutaner Strahlentherapie (ERBT)-Boost auf patientenberichtete Ergebnisse (PBE) und AE zu beurteilen.

Patienten und Methoden Prospektiv inkludiert wurden Patientinnen, die ab April 2015 mit BCT behandelt wurden. Die Auswahl der Boost-Technik erfolgte über einen hauseigenen Ablaufplan abhängig von der Tiefe des Tumorbetts. Ein Elektronenboost wurde durchgeführt bei einem oberflächlichen klinischen Zielvolumen (weniger als 29 mm unter der Epidermis), ein BT-Boost bei allen anderen Fällen. Die Patientinnen wurden bis zu 2 Jahre nachbeobachtet. Das AE wurde durch die Patientinnen und die BCCT.core-Software bewertet. Weitere PBE wurden mit dem EORTC QLQ-C30, QOL-BR23 und dem BIBCQ-Fragenbogen gemessen.

Ergebnisse Die Studie beinhaltete 175 Patientinnen: 80 bekamen einen BT- und 95 einen ERBT-Boost. Patientinnen der BT-Gruppe waren signifikant älter, hatten eine größere Brustgröße, einen größeren Brustumfang, einen größeren Body-Mass-Index, höheres chirurgisches Probengewicht der breiten Exzision, mehr Serum zu Beginn der Analyse, weniger positive Resektionsränder und mehr Alkoholkonsum als die der ERBT-Gruppe. Krebs- oder brustkrebspezifische Lebensqualität (QOL) und Körperbild unterschieden sich zwischen beiden Boost-Techniken im Zeitverlauf nicht signifikant. Durchschnittswerte für Symptome der Brust und sexuellen Genuss waren im Zeitverlauf zwar signifikant unterschiedlich zwischen beiden Gruppen, waren aber Unterschieden vor Verabreichung des Boosts geschuldet (jeweils $p=0,05$ und $<0,01$). Gemessen mit BCCT.core war das AE bei 28 % der Patientinnen 2 Jahre nach Behandlung ungünstig (31 % bewertet durch die Patientinnen); die Ergebnisse beider Gruppen waren vergleichbar.

Schlussfolgerung Unter Verwendung des vorgestellten Ablaufs hat die benutzte Boost-Technik bis zu 2 Jahre nach BCT keinen Einfluss auf AE und PBE im QOL oder Körperbild.

Schlüsselwörter Brustneoplasien · Fragebögen · Patientenberichtete Ergebnisse · Toxizität · Lebensqualität

Every year, 1.7 million women are diagnosed with breast cancer, making it the most common malignancy in women worldwide [1]. Breast-conserving therapy (BCT), including breast-conserving surgery followed by radiotherapy (RT), is the cornerstone of locoregional treatment, since randomized trials have shown survival rates equal to mastectomy [2, 3]. Standard adjuvant RT starts with whole-breast irradiation and is followed by a sequential boost to the tumour bed in high-risk patients [4]. The boost can be administered either by external beam radiotherapy (EBRT) or by brachytherapy (BT). The oncological outcome of breast cancer patients has improved during recent decades, resulting in a growing number of long-term survivors and 10-year survival rates exceeding 70% [5, 6]. This high number has imposed a new, growing demand to identify the long-term toxicity of treatment and its impact on quality of life (QOL; [7]).

Prior research on long-term toxicity due to breast cancer RT has created insight into cardiac and pulmonary toxicity and secondary malignancies [8, 9]. However, for other outcomes such as aesthetic outcome (AO), the available data remain unclear, mainly due to heterogeneity between studies. Different studies use a variety of methods to assess AO, such as scoring by the physician, scoring by the patient or automated scoring based on photographs. Moreover, AO is reported using a large set of outcome parameters such as

asymmetry, scar appearance or skin colour differences [10]. In 2012, Cardoso et al. published guidelines to homogenize future research on AO [10]. Recently, knowledge on long-term toxicity and the treatment itself has gained attention regarding the effect on QOL. Health-related QOL represents the patient's physical, psychological and social response to the disease and its treatment. The term "patient-reported outcome measures" (PROMs) was introduced, comprising health-related QOL and also broader concepts such as patient satisfaction with care [11]. In clinical practice, insight into patient-reported outcomes (PROs) could help generate a roadmap of recovery for the patients which predicts functioning in specific areas over time, to help answer the patients' questions and set appropriate expectations, and which could even be incorporated into the process of shared decision-making [12, 13].

With similar local control between different boost techniques, it seems interesting to further assess the influence on AO and PROs. Firstly, PROs might analyse the burden of the different RT techniques in the short-term. An EBRT and a BT boost have some intrinsic differences, such as the longer treatment duration with EBRT (5–8 daily fractions for EBRT versus 1 fraction for BT), the outpatient procedure with EBRT compared to day-clinic hospitalization with BT, the invasive procedure and anaesthesia in case of

BT, and the anxiety related to the BT procedure itself [14]. Secondly, long-term PROs on AO, QOL and body image are of interest. The boost techniques namely also differ from a radiobiological point of view, with a theoretical advantage of BT on AO due to higher doses to small volumes and a skin-sparing effect, and 2–3-times larger irradiated volumes with a sequential EBRT boost [14, 15].

The purpose of the present study was to prospectively follow a group of patients treated with BCT for 2 years and to estimate the probability of an unfavourable AO 2 years after RT. In this study, the influence of the RT boost technique on short- and long-term outcomes was evaluated in the BCT setting. We have therefore investigated the relationship of boost techniques to PROs on QOL and body image as well as AO.

Patients and methods

Patient cohort

All consecutive patients treated for breast cancer with BCT with curative intent who consulted the RT department at the University Hospitals Leuven, Belgium, between April 2015 and April 2016 were invited to participate in this prospective cohort study. Informed consent was obtained from all individual participants. Patient-, tumour- and treatment-related characteristics were prospectively collected. The study was approved by the Clinical Trial Centre and the Ethical Committee of our institution.

BCT included whole-breast irradiation followed by a boost to the tumour bed. Two fractionation schedules were applied for whole-breast irradiation: normofractionation (50 Gy in 25 fractions) and hypofractionation (42.56 Gy in 16 fractions). For the boost, either 16 Gy in 8 fractions (20 Gy in case of positive margins) or 13.3 Gy in 5 fractions (e.g., 18.62 Gy in case of positive surgical section margins) were applied with EBRT. High dose-rate BT doses were 8.5 Gy in 1 fraction (10 Gy in case of positive margins). For selection of the boost technique, an in-house developed flowchart based on the depth of the tumour bed was used. For a clinical target volume lying more than 28 mm beneath the epidermis, BT was chosen over an electron boost because of skin doses. If the patients refused a BT boost or it was technically impossible, a photon boost was suggested [16]. Patients were informed on the proposed boost technique within the first or second week of RT. Treatment regimens were discussed at the multidisciplinary tumour board. Regional nodal irradiation was allowed. Hormonal therapy included tamoxifen and aromatase inhibitors in different regimens and was prescribed in hormone receptor-positive breast cancer patients. Chemotherapy was given

according to standard protocol and included epirubicin, cyclophosphamide and taxanes.

Patient-reported outcome measures

Several tools have been used to measure PROs in patients with a history of breast cancer [17]. In 2017, the International Consortium for Health Outcomes Measurement developed a standard set of value-based measures for breast cancer [18]. The working group recommended use of at least a cancer-specific and a breast cancer-specific questionnaire and, optionally, an extra questionnaire to capture extra outcomes. Based on this guideline and the review by Kanatas et al., the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 were used for cancer-related QOL and the Body Image After Breast Cancer Questionnaire (BIBCQ) for body image [18, 19].

The QLQ-C30 was developed as a cancer-specific QOL questionnaire. It has 30 items that form five functional scales (physical, role, emotional, cognitive and social), a global QOL scale, three symptom scales (fatigue, pain and nausea/vomiting), five single-item symptom measures (dyspnoea, insomnia, appetite loss, constipation and diarrhoea), and one financial impact question. These are coded with the same response categories (scored 1 to 4): “not at all”, “a little”, “quite a bit” and “very much”; except for the global QOL scale, which is scored as a visual analogue scale ranging from 1 (very bad) to 7 (excellent). All the scales and single-item scores are transformed to range from 0 to 100. A high score for a functional scale or global QOL indicates better levels of functioning and/or global QOL, with a score above 80 considered to be satisfactory. A high score for a symptom scale or item represents a high level of symptoms or problems, with a score below 20 considered to be satisfactory [20]. Clinical significance between groups is interpreted according to Osaba et al.: the mean differences from 5 to 10 points can be considered minimal, from 10 to 20 points intermediate and mean differences of more than 20 points are considered large [21].

The QLQ-BR23 module consist of 23 items assessing disease symptoms, side effects related to different treatment modalities (surgery, chemotherapy, radiotherapy and hormonal therapy), body image, sexual functioning and future perspective. It incorporates five domains: body image, systemic therapy side effects, breast symptoms, arm symptoms and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective. The scoring approach is identical to that for the functioning and symptom scales and for the single items in QLQ-C30 [22].

The BIBCQ was specifically designed to measure the long-term impact of breast cancer on body image in a multidimensional fashion. It is a measure with a 53-item ques-

tionnaire comprising six optional items specific to women with two breasts [23]. The BIBCQ is suggested to evaluate various treatment forms for breast cancer [19].

Besides the three questionnaires, PROs were also assessed for AO: patients were asked to score their AO according to Harris et al. as “excellent”, “good”, “fair” or “poor” at baseline and 2 years after RT [24].

Objective aesthetic outcome analysis

An anterior view picture of the patient was taken with the patients’ hands on the hips. The BCCT.core software was used to evaluate AO [10, 25]. Based on the semi-automatic localization of fiducial points (nipple complex, breast contour, sternal jugular notch, mark 25 cm beneath the jugular notch), the software first measures asymmetry, skin colour changes and surgical scar appearance. Secondly, the set of measures is automatically converted into an overall objective AO: excellent, good, fair or poor [25].

Follow-up

Patients were evaluated at pre-set timepoints: at baseline; after surgery and before the start of RT; before the start of the boost; at the end of RT; between 3 and 6 months after RT; 1 year after RT and 2 years after RT. No photographs were taken at the end of RT because of the acute breast changes immediately after the removal of interstitial needles in case of a brachytherapy boost.

Statistical analysis

AO was dichotomized into excellent/good (“favourable”) versus fair/poor (“unfavourable”). The sample size was calculated to independently estimate AO for the BT and the EBRT group assuming a 25% unfavourable AO measured with BCCT.core after 2 years. Calculations were performed for estimating with 80% power the 95% confidence interval (CI) with a halfwidth of 10%. For each group—EBRT (i.e. electrons or photons) and BT—76 patients were needed [26].

Proportions of 2-year AO classifications were estimated with the Wilson 95% CI, excluding patients with unfavourable AO at baseline. Differences in proportions between the BT and the EBRT group were tested using Fisher’s exact test. The Mann–Whitney U test was used to compare the groups in terms of continuous or ordinal variables. Linear models were used for the analysis of continuous or ordinal scale scores. A random intercept for patients was modelled to account for the longitudinal structure of the data. Logistic regression was used for analysis of the binary AO score, with estimations based on generalized estimating equations to deal with longitudinal

data. To assess whether the difference in mean outcomes between the BT and EBRT groups differed over time, we tested the interaction between the boost technique and time. A significant interaction would imply that the differences between patients with a BT and an EBRT boost would vary over time. Multivariable models were used to correct for variables that significantly differed between treatment groups.

Analyses were performed using SAS software (version 9.4 of the SAS System for Windows, SAS Institute, Heidelberg).

Results

Patient cohort

The analysis included 175 patients, 4 patients refused participation. A BT boost was received by 80 patients and 95 were treated with an EBRT boost (91 with electrons and 4 with photons). Patients in the BT group were significantly older; had higher breast cup, breast band size, body mass index (BMI) and surgical specimen weight of the wide excision; more seroma at baseline and less positive surgical section margins for the invasive and/or in situ component compared to patients in the EBRT group, and more patients drank alcohol (any vs. none; Table 1). Furthermore, patients in the EBRT group were more frequently treated with normofractionation compared to the BT group.

All patients filled in the QLQ-C30 and QLQ-BR23, scored their AO and had a photographic evaluation at baseline. Missing data during follow-up can be seen in Table 2.

No toxicity evaluation by means of photographs was available for 5 patients 2 years after RT (2 in the EBRT group and 3 in the BT group). One patient from the EBRT group underwent a contralateral mastectomy between 1 and 2 years after RT and was excluded from further follow-up. The baseline scores of the functional and symptom scales of the QLQ-C30, QLQ-BR23 and BIBCQ are reported in Table 3.

Short-term patient-reported outcomes

Mean scores for breast symptoms and sexual enjoyment differed significantly between the two patient groups in the short-term. Patients in the EBRT group showed an increase in breast symptoms (QLQ-BR23) in the short-term compared to the BT group, with a *p*-value of 0.050 for the interaction with time (Fig. 1). With mean difference −6.0 and *p*-value 0.060, the only minimally clinically relevant and trend towards a statistically significant difference was observed before the boost was administered [21]. The boost

Table 1 Patient, tumour and treatment characteristics

<i>Characteristic</i>		Brachytherapy boost (<i>n</i> = 80)		EBRT boost (<i>n</i> = 95)		<i>p</i> -value
		<i>Median</i>	<i>IQR</i>	<i>Median</i>	<i>IQR</i>	
Age (years)		61.0	53.5;65.5	57.0	50.0;64.0	0.02
Breast cup		C	B;D	B	B;C	<0.01
Breast band size (EU size)		85	75;90	80	75;85	<0.001
<i>Characteristic</i>		<i>n</i>	%	<i>n</i>	%	<i>p</i> -value
Menopausal status	Premenopause	11	13.75	22	23.16	0.27
	Perimenopause	4	5.00	3	3.16	–
	Postmenopause	65	81.25	70	73.68	–
BMI (kg/m ²)	<20	1	1.25	14	14.74	<0.001
	20–25	26	32.50	49	51.58	–
	25–30	39	48.75	24	25.26	–
	>30	14	17.50	8	8.42	–
Smoking	Never/stopped	67	83.75	76	80.00	0.56
	Current	13	16.25	19	20.00	–
Alcohol	Never/stopped	13	16.25	31	32.63	0.02
	Current	67	83.75	64	67.37	–
Diabetes	No	77	96.25	91	95.79	1.00
	Yes	3	3.75	4	4.21	–
Arterial hypertension	No	58	72.50	74	77.89	0.48
	Yes	22	27.50	21	22.11	–
Side	Left	41	51.25	47	49.47	0.82
	Right	39	48.75	48	50.53	–
Whole-breast irradiation	Normofractionation	26	32.50	44	46.32	0.06
	Hypofractionation	54	67.50	51	53.68	–
Tumour bed boost	Low dose	78	97.50	91	95.79	0.54
	High dose	2	2.50	4	4.21	–
Chemotherapy	No	63	78.75	64	67.37	0.13
	Yes	17	21.25	31	32.63	–
Hormonal therapy	No	10	12.50	13	13.68	1.00
	Yes	70	87.50	82	86.32	–
Trastuzumab	No	74	92.50	82	86.32	0.23
	Yes	6	7.50	13	13.68	–
Lymphadenectomy	None	9	11.25	14	14.74	0.47
	Sentinel	58	72.50	71	74.74	–
	ALND	13	16.25	10	10.53	–
Section margins	Negative	79	98.75	85	89.47	0.01
	Positive	1	1.25	10	10.53	–
Position of tumour	Upper inner	13	16.25	25	26.32	0.10
	Upper outer	49	61.25	49	51.58	–
	Lower inner	6	7.50	12	12.63	–
	Lower outer	12	15.00	7	7.37	–
	Retro-areolar	0	0.00	2	2.11	–
Re-resection	No	56	70.00	71	74.74	0.50
	Yes	24	30.00	24	25.26	–
Seroma	No	44	55.00	83	87.37	<0.001
	Yes	36	45.00	12	12.63	–
Target volume	Breast only	57	71.25	66	69.47	0.87
	Breast and regional nodes	23	28.75	29	30.53	–

Table 1 (Continued)

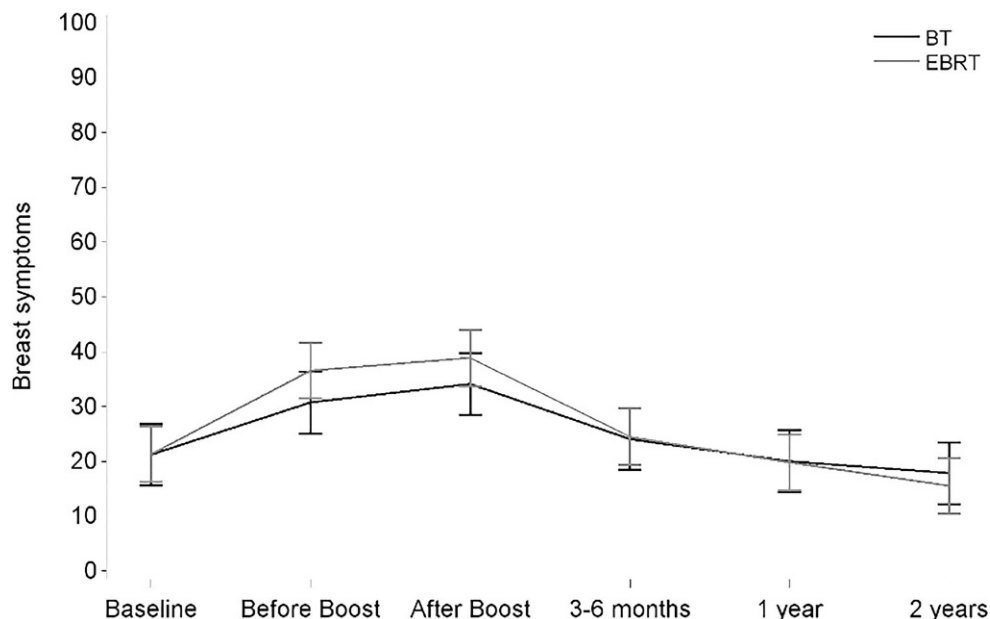
Characteristic	Brachytherapy boost (<i>n</i> = 80)		EBRT boost (<i>n</i> = 95)		<i>p</i> -value
	Mean	Range	Mean	Range	<i>p</i> -value
Surgical specimen weight wide excision (g)	37.5	9.0;101.0	25.7	1.0;80.0	<0.001
Surgical specimen weight axillary lymph node dissection (g)	87.0	51.0;155.0	102.8	29.0;181.0	0.18
Pathological tumour size invasive+ in situ (mm)	18.2	0.0;40.0	17.9	0.0;55.0	0.79

ALND axillary lymph node dissection, EBRT external beam radiotherapy, BMI body mass index

Table 2 Outcome measures during follow-up

	Number of patients					
	Baseline	Before boost	After boost	3–6 months	1 year	2 years
AO scored with BCCT.core	175	173	/	170	165	170
AO scored by the patient	175	/	/	/	/	170
QLQ-C30	175	173	172	169	175	172
QLQ-BR23	175	173	172	169	175	172
BIBCQ	174	173	170	170	167	169

AO aesthetic outcome, QLQ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, BIBCQ Body Image after Breast Cancer Questionnaire

Fig. 1 Breast symptoms over time in the brachytherapy (BT) and external beam radiotherapy (EBRT) groups

can thus not explain the difference between the groups. Sexual enjoyment (QLQ-BR23) significantly decreased in the EBRT group compared to the BT group ($p < 0.01$ for interaction). Similar to the breast symptoms, the only marginally significant difference was observed before the boost was administered; thus, the boost cannot explain the difference ($p = 0.053$). However, mean differences also seemed minimally clinically relevant after the boost and 2 years after RT (mean differences -9.5 and 8.1 , respectively; [21]). Given this ambiguous result, the analysis was repeated with sexual enjoyment as a binary score (“no”, score 1 versus “yes”, scores 2–4). No difference could be observed between the two treatment groups over time ($p = 0.56$ for interaction).

Long-term patient-reported outcomes

There was no significant difference in mean scale PRO scores upon comparing the two boost techniques over time after correction for group differences (age, BMI, alcohol, breast cup and band size, surgical specimen weight, positive surgical margins and seroma) for any of the EORTC QLQ-C30 global health status, physical, role, emotional, cognitive or social functioning, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea or financial difficulties scores; nor for the EORTC QLQ-BR23 body image, sexual functioning, future perspec-

Table 3 Mean values and standard deviations of QLQ-C30, QLQ-BR23 and BIBCQ scores at baseline

Domain	Mean	SD
<i>QLQ-C30</i>		
Global QOL	67.0	18.38
Physical functioning	84.2	18.11
Role functioning	73.0	27.19
Emotional functioning	74.2	22.29
Cognitive functioning	83.9	21.95
Social functioning	82.0	23.40
Fatigue	31.6	24.74
Nausea and vomiting	2.5	7.38
Pain	22.5	23.83
Dyspnoea	12.4	22.44
Insomnia	31.0	29.38
Appetite loss	8.4	18.73
Constipation	9.0	20.0
Diarrhoea	5.5	15.62
Financial difficulties	7.6	19.15
<i>QLQ-BR23</i>		
Body Image	84.3	21.18
Sexual functioning	79.6	22.18
Sexual enjoyment	51.7	27.51
Future perspective	55.4	25.91
Systemic therapy side effects	16.2	15.35
Breast symptoms	22.2	20.08
Arm symptoms	17.7	20.20
Upset by hair loss	31.1	38.13
<i>BIBCQ</i>		
Vulnerability	31.1	8.28
Body stigma	33.6	9.08
Limitations	20.6	6.32
Body concerns	15.8	5.19
Transparency	9.1	3.53
Arm concerns	9.9	3.80

AO aesthetic outcome, *QLQ* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, *BIBCQ* Body Image after Breast Cancer Questionnaire, *QOL* quality of life, *SD* standard deviation

tive or arm symptoms or for the BIBCQ vulnerability, body stigma, limitations, transparency and arm concerns scale.

There was a trend towards increased body concerns (BIBCQ) in the BT group compared to the EBRT group from 1 year after RT onwards ($p=0.08$ for interaction; Fig. 2). The only marginally significant difference was observed 2 years after RT ($p=0.047$) and the mean difference then was 1.7.

The BCCT.core scores for AO were unfavourable for 3 patients (1.71%) at baseline, for 37 (21.39%) before the boost, for 33 (19.41%) 3 to 6 months after RT, for 43 (20.61%) 1 year after RT and for 47 (27.81%) patients 2 years after RT. In univariable analysis, the proportion

of patients with an unfavourable AO 2 years after treatment was greater in the BT group than in the EBRT group ($p=0.02$). This statistically significant difference disappeared after correction for baseline group differences (age, BMI, breast cup and band size, surgical specimen weight, seroma, positive surgical margins, use of alcohol and fractionation scheme of the whole-breast irradiation; $p=0.77$; Fig. 3).

At baseline, 6 patients (3.43%) scored their AO as unfavourable, whereas this rose to 53 patients (31.36%) 2 years after RT. The proportion of patients with an unfavourable AO 2 years after treatment was significantly higher in the BT group ($p<0.01$). However, after correcting for baseline group differences, the p -value was 0.19.

Discussion

Local control and survival are the key objectives in breast cancer treatment and long-term survival rates are high [6]. With different techniques and treatment schedules resulting in similar oncological outcomes, the current challenge is to define factors that could guide treatment decisions. The purpose of the present study was to assess the possible effect of boost technique on PROs and AO. Therefore, we prospectively evaluated a cohort of 175 patients treated with BCT over 2 years.

First of all, it is important to stress that in the present cohort, a flowchart was used basing the choice of the tumour bed boost technique on the depth of the clinical target volume [16]. Using this flowchart has proven to result in equal local control rates for the two techniques.

This study found that there is *no difference between EBRT and BT patient groups regarding short-term PROs on QOL and body image*. Differences between the boost techniques such as treatment duration, the in- or outpatient procedure, the invasiveness of the procedure or the anxiety associated with the treatment do not influence short-term PROs on QOL and body image. To the best of our knowledge, we are the first to examine PROs in terms of the boost technique.

However, two PROs did differ significantly over time when comparing the two boost technique groups: breast symptoms and sexual enjoyment. First of all, with mean scores under 80, both PROs indicated unsatisfactory levels at baseline. Secondly, the p -value for both outcomes only just trended towards significance before the administration of the boost, so the results are independent of the boost technique.

Interpretation of the mean differences for sexual enjoyment after administration of the boost and 2 years after RT according to Osaba et al. did, however, indicate minimal clinical relevance (values between 5 and 10), but the

Fig. 2 Body concern score over time in the brachytherapy (BT) and external beam radiotherapy (EBRT) groups

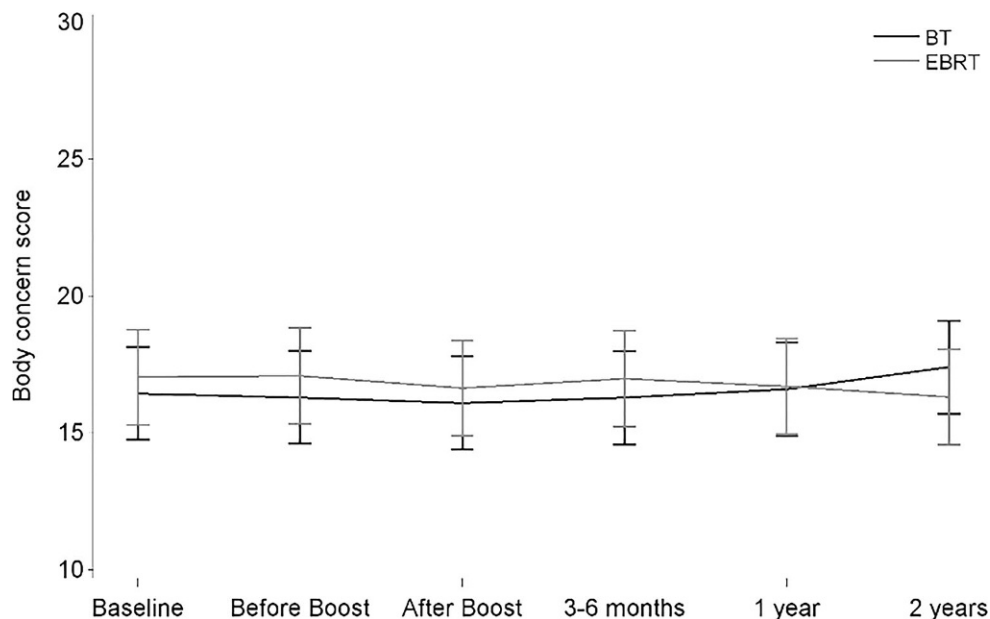
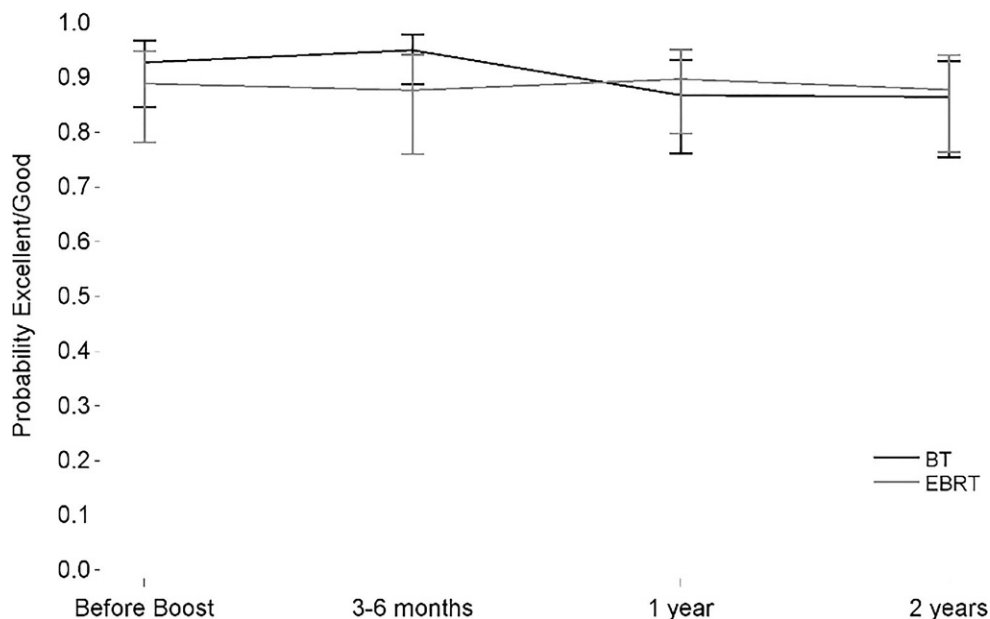


Fig. 3 Aesthetic outcome scored by BCCT.core [10, 25] over time in the brachytherapy (BT) and external beam radiotherapy (EBRT) groups (estimated figure for a specific patient profile with average value on continuous variables and most common value on categorical variables)



difference was not statistically significant [21]. Given this ambiguous result, the analysis was repeated with sexual enjoyment as a binary score, also resulting in no difference between the two treatment groups over time ($p=0.56$). Our data also show that factors which could potentially lead to impaired sexual enjoyment linked to the RT boost, such as an unfavourable AO or an impaired body image, were not observed in our study cohort. This also fits with literature data from population-based studies showing that breast cancer survivors report more frequent physical and menopausal symptoms than healthy women, yet report QOL and sexual functioning comparable to that of healthy age-matched women [27].

This study revealed *no difference between the patient groups in terms of long-term PROs on QOL, body image and AO*. There was no significant difference in cancer-specific or breast cancer-specific QOL and body image upon comparing EBRT and BT boost techniques over time.

Two years after treatment, AO was unfavourable in 28% of the patients as measured by BCCT.core and in 31% when scored by patients themselves. The BCCT.core has been shown to be a reliable instrument to measure cosmesis, and in contrast to what has been reported previously, patients in the present cohort judge their AO similarly to the BCCT.core software and not more positively [10, 28]. There

is no evidence for a difference between the boost techniques with respect to AO 2 years after RT in the present cohort.

RT mainly influences AO by causing fibrosis and asymmetry, differences in colour such as hyper- or hypopigmentation, and skin telangiectasia [29–33]. Increasing the administered RT dose, for example in case of positive surgical margins or in the case of a boost, has been shown to worsen AO [29, 34]. However, results are conflicting with regard to the influence of the boost technique on AO [35, 36]. The reason for the inconsistency in the literature might be found in the selection criteria for the boost technique. Women with inadequate breast tissue or tumours in inaccessible locations were, for example, preferably treated with electrons; however, these factors may in themselves be associated with unfavourable AO [36]. Patients in the present cohort were treated with an electron boost or a BT boost based on the depth of the clinical target volume. The practical convenience of the electron boost is chosen for clinical target volumes up to 28 mm below the epidermis. The risk for telangiectasia increases with high doses in the first 5 mm of the skin and doses increase with increasing electron energy [37]. A BT boost is then the first choice for a deeper lying clinical target volume, also because boost volumes are smaller with BT than with a sequential photon boost [38]. It is thereby known that to optimize cosmetic results after BCT, both the total dose and the irradiated volume should be kept as low as possible [15]. Kelemen et al. have shown that the risks of breast oedema and breast fibrosis increase by 21 and 12%, respectively, for every 10 cm³ increase in boost volume [39]. If a BT was refused or technically impossible, a photon boost was suggested [16]. More information on the possible influence of dose–volume metrics is needed, but beyond the scope of this article. Regardless of the boost, several other patient-, tumour- and treatment-related factors play an important role [30, 36, 40]. We have therefore conducted multivariable analyses taking into account the relevant factors that differed between the two treatment groups: age, breast cup and band size, BMI, surgical specimen weight, the presence of a seroma at baseline, surgical section margins, alcohol and whole-breast irradiation fractionation schedule.

Over the past years, efforts have been made to integrate the sequential boost simultaneously into the whole-breast irradiation. With this technique, the whole breast and the boost are irradiated with EBRT, regardless of the depth of the clinical target volume. These changes have led to shorter treatment times and smaller boost volumes compared to the sequential EBRT boost, without compromising effectiveness or safety. Firstly, concerning toxicity, a large amount of acute toxicity data and a smaller amount of long-term sequelae are reassuring, with some studies even concluding improved AO [41–44]. Furthermore, cosmetic results were mostly reported to be independent of the timing

of the boost. Secondly, to the best of our knowledge, a sequential BT boost and a simultaneous EBRT boost have not been evaluated with regard to PROs. We can assume that short-term PROs on QOL are comparable for a sequential or a simultaneous EBRT boost. Our study comparing PROs between EBRT and BT is thus not only of historical interest, but also currently pertinent in the evaluation of contemporary techniques such as a sequential BT boost or a simultaneous boost with EBRT.

Standard practice at our hospital was to treat all patients undergoing BCT with a sequential boost to the tumour bed. An important remark thereby is that according to current guidelines, the boost should be considered only in high-risk patients [4, 45]. The risk profile of a patient should, however, not alter the obtained results. A possible limitation of this study is that follow-up is currently at 2 years and it is therefore possible that not all patients will have expressed their final level of toxicity. The study is ongoing, and a re-analysis is planned at 5 years. However, there is evidence to suggest that the results at 2 years are predictive for late normal tissue outcomes 5 years after RT [46, 47]. Also, the effect of the boost on fibrosis presents in the first 3 years after RT [48]. A strength of this study is the very low number of losses to follow-up; only 5 patients lacked photographic evaluation at 2 years.

Conclusion

We have shown that PROs on QOL or body image and AO are not influenced by the boost technique if an EBRT boost is given for a clinical target volume lying in the upper 28 mm beneath the epidermis and if a BT boost is administered for deeper lying volumes. These data can be used when informing the patient on different boost techniques.

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Compliance with ethical guidelines

Conflict of interest I. Kindts, A. Laenen, M. Christiaens, H. Janssen, E. VanLimbergen and C. Weltens declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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