Treatment Results of MammoSite Catheter in Combination with Whole-breast Irradiation

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Abstract. *Aim. To report the initial outcomes of patients treated with the MammoSite brachytherapy device (MSBT) as a boost followed by external whole-breast irradiation (WBI). Patients and Methods: From June 2011 to March 2014, 107 patients (typically with pT1-2, pN0-1, M0 disease) were treated with breast-conserving therapy and adjuvant radiotherapy with MSBT (15 Gy in 2.5-Gy fractions) followed by WBI (median=50.4 Gy). Toxicity was classified according to the Common Terminology Criteria for Adverse Events v3.0. The median follow-up was 21 months. Results: To date, no ipsilateral breast-tumor recurrences have been observed; 102 patients (95%) were alive at last follow-up. Two patients (2%) developed distant metastases. Five patients (5%) died during follow-up, only one as a result of breast cancer. The 2-year disease-free survival was 95±3%. The incidence of asymptomatic and symptomatic seroma in 90 days after MSBT was 28% and 10%, respectively. Infectious mastitis was observed in three patients (3%), who were treated successfully with antibiotics. Only three patients (3%) developed RT-induced dermatitis greater than grade 2 after WBI. Conclusion: The boost technique used in this study seems to provide excellent local control with acceptable toxicity, similar to the results observed with other forms of interstitial accelerated partial-breast irradiation as a boost. Long-term follow-up is necessary to refine the patient selection criteria and to assess efficacy and late toxicities.*

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Different techniques can be used to deliver adjuvant breast radiotherapy (RT), including accelerated partial-breast irradiation (APBI), which is an option to deliver RT after lumpectomy in carefully selected patients. Patients treated with APBI who fulfill consensus statement eligibility criteria have early-stage breast cancer treated with breast-conserving therapy (BCT) (1). The most frequently used and best studied RT technique is interstitial brachytherapy (2). However this is a difficult technique that uses multiple catheters, so that experienced experts are needed and initial patient acceptance has remained limited (3). For this reason, the MammoSite breast brachytherapy (MSBT) catheter (Hologic, Inc., Marlborough, MA, USA) was developed, which only uses one single catheter and thus is logistically simpler and easier to use (4). This device was clinically approved by the U.S. Food and Drug Administration in May 2002. Still many patients continue to receive whole-breast irradiation (WBI) with or without boost. Treatment techniques vary from institution to institution. The role of local dose escalation or boost RT has mainly been derived from a large collaborative trial (5). Several authors report on a benefit from administering an additional dose to the tumor bed, which leads to a reduction of the 5-year local recurrence rate of about 10% (6-8). The usual procedure for a boost is to apply an additional 10-16 Gy to the tumor bed after completing conventional fractionated WBI with approximately 50 Gy. The potential benefits of using MSBT as a boost are the exact adjustable allocation of the radiation dose, protection of the skin, shorter treatment time, and immediate application after surgery compared to external-beam RT as a boost. Herein we report the early outcomes of treatment efficacy and toxicity in patients treated with an early postoperative irradiation-boost delivered with MSBT followed by WBI at the Marien Hospital Herne, Ruhr University Bochum, Germany.

Patients and Methods

Patients' characteristics. We retrospectively reviewed the data of 107 patients who were treated with MSBT, followed by WBI with a total dose of 50.4 Gy in 28 fractions (3-D conformal tangent fields) between June 2011 and March 2014. Inclusion criteria were: age ≥40 years, small tumor (<3 cm), negative surgical margins, no evidence of multicentricity, maximum of three positive lymph nodes without extracapsular extension, and no distant metastases. The median age was 61 years (range=40-84 years) and the median follow-up duration was 21 months (range=4-38 months). Twenty-four patients (22%) had positive lymph nodes. Patient characteristics are presented in Table I.

Treatment. All patients underwent BCT with a recommended minimal clear margin of at least 2 mm, and 104 patients (97%) underwent sentinel node biopsy with/without axillary lymph node dissection.

Placement of the device was performed directly after lumpectomy to avoid re-opening of the lumpectomy incision and reduce the rate of infection and seroma. All patients underwent diagnostic mammography and computer tomography (CT) or magnetic resonance imaging (MRI) to confirm the correct positioning of the MammoSite catheter (distance of the applicator to the skin ≥7 mm, symmetry of the catheter shaft and conformance of the applicator to the lumpectomy cavity). Acceptable diameters for the balloon ranged from 4-5 cm, corresponding to 35-70 cm^3 fill volumes. The mean inflated volume was 55 cm^3. The intent was to minimize air- and fluid-filled gaps between the tissue and the balloon surface. If the final pathology review was not consistent with the inclusion criteria, the MammoSite device was removed and standard adjuvant treatment (external beam RT with/without chemotherapy) was performed.

During the study, removal of the MammoSite device was necessary for three patients, in one case due to the pathology report and in two because of an air cavity around the balloon (>10% of the planning target volume).

The dose fractionation scheme for MSBT was 15 Gy delivered to a distance of 0.5 cm from the surface of the balloon in 2.5-Gy fractions twice daily with a minimum interfraction interval of 6 hours over 3 days (Figure 1). An Ir-192 remote afterloader was used for the brachytherapy. After the final MSBT fraction, the device was removed and 3 to 4 weeks later, additional WBI was given (median time from the last MSBT to WBI: 4 weeks). If systemic chemotherapy was indicated, this treatment was administered between MSBT and WBI. Eighty-two patients (77%) received an adjuvant hormonal therapy after RT. Detailed treatment characteristics are presented in Table II.

Assessment of the toxicity and follow-up. Patients were seen after MSBT, weekly during WBI, 6-8 weeks after WBI and then every 3 months for the first 2 years. However, for the present study, the results of the follow-up and toxicity assessment at three different examination time points are reported (Table III).

Toxicity was evaluated at each follow-up visit according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0 (9). The presence of seroma was assessed clinically or mammographically, and then sub-categorized into asymptomatic or symptomatic (associated with pain, intervention needed). Telangiectasia development was dichotomized into a mild degree of telangiectasia (not confluent telangiectasia) and a moderate/severe degree of telangiectasia development (confluent telangiectasia) to facilitate analysis.

Table I. *Patients' characteristics*.

Characteristic	N (%)
Age	
Median (range), years	61 (40-84)
Follow-up, median (range), months	21 (4-38)
UICC stage	
0	9 (8%)
I	49 (46%)
II	44 (41%)
III	5 (5%)
Histopathological grading	
G1	10 (9%)
G2	68 (64%)
G3	24 (22%)
Data not available	5 (5%)
Tumor stage	
pT0	7 (7%)
pT1	56 (52%)
pT2	41 (38%)
DCIS	3 (3%)
Tumor localization	
Upper outer quadrant	44 (41%)
Not upper outer quadrant	63 (59%)
Histological type	
Invasive ductal	84 (79%)
Invasive lobular	9 (8%)
Other type	14 (13%)
DCIS (pure, without invasive tumor) (n=3)	
Median size (range) (mm)	12 (5-20)
Tumor size (mm)	
Median (range)	18 (0-50)
Extensive intraductal component	
Yes	43 (40%)
No	64 (60%)
Component <25%	36 (34%)
Component ≥25%	7 (7%)
Nodal status	
pN0	80 (75%)
pN+	24 (22%)
pNx	3 (3%)
Progesterone receptor status	
Positive	78 (73%)
Negative	29 (27%)
Estrogen receptor status	
Positive	84 (79%)
Negative	23 (21%)
HER2/neu status	
Positive	67 (63%)
Negative	40 (37%)
Comorbidities	
Hypertension	57 (53%)
Current smoking	10 (9%)
COPD	2 (2%)
Diabetes mellitus	12 (11%)
Cardiac arrhythmia	11 (10%)

DCIS: Ductal carcinoma *in situ*; COPD: chronic obstructive pulmonary disease; HER2/neu: human epidermal growth factor receptor 2.

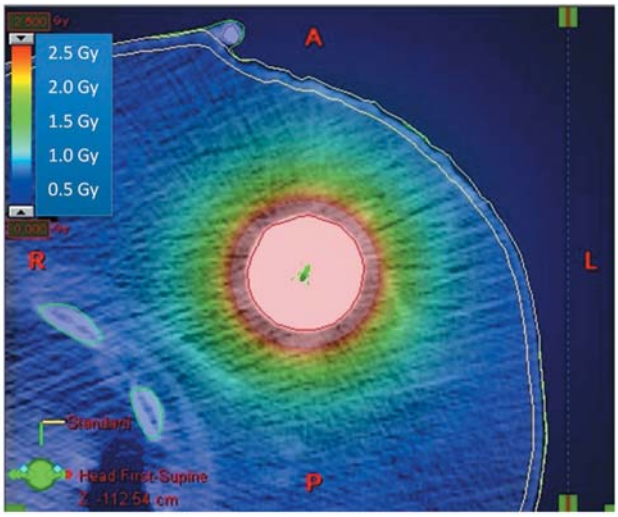

Figure 1. *Dose distribution for the application of the MammoSite brachytherapy device as a boost.*

Statistical methods. This trial was reviewed and approved by the Ethics Committee of the Ruhr University Bochum (approval number: 15-5382; date of approval: 15.08.2015). All time intervals were calculated from the date of MammoSite placement. Overall survival (OS) was defined as death from any cause; disease-free survival (DFS) was defined as the time to the first relapse, progression, or death from any cause. The definition of a local recurrence was the confirmed diagnosis of malignant cells in the irradiated breast after a cancer-free interval. Any axillary, supraclavicular, or internal mammary node recurrence was defined as "regional failure". OS and DFS were estimated using the Kaplan–Meier product-limit method. Associations between clinical, pathological, and treatment-related variables and clinical events were analyzed using Cox regression. Associations between different variables were analyzed using Pearson's chi-square or Fisher's exact test (two-tailed) and logistic/linear regression. Statistical significance between actuarial outcome curves was calculated with the log-rank test. All test results were regarded as statistically significant if $p \leq 0.05$. SPSS (v22.0; SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

No ipsilateral breast-tumor recurrences were observed up to the last follow-up date; 102 (95%) patients were alive at the last follow-up. Two patients (2%) developed distant metastasis, one to the liver, one to the lung. Five patients (5%) died during follow-up (all older than 74 years at the start of treatment), but only the patient with liver metastasis died as a result of breast cancer. The incidence of asymptomatic seroma was 28% and that for symptomatic seroma was 10%. The 2-year OS and DFS were 98±2% and 95±3%, respectively. Outcome data are displayed in Table IV.

Table II. *Treatment-related characteristics.*

Characteristic	Findings
Margins, n (%)	
Close (0.1-1.9 mm)	14 (13%)
Negative (≥2 mm)	93 (87%)
Systemic treatment, n (%)	
Hormonal therapy	82 (77%)
No hormonal therapy	25 (23%)
Chemotherapy	52 (49%)
No chemotherapy	55 (51%)
Neoadjuvant chemotherapy	8 (7%)
Type of placement, n (%)	
Closed cavity	107 (100%)
Open cavity	0 (0%)
Balloon size	
Small (4-5 cm), n (%)	107 (100%)
Median (range), cm^3	55 (35-70)
Skin spacing	
>7 mm, n (%)	88 (86%)
≤7 mm, n (%)	14 (14%)
>9 mm, n (%)	80 (78%)
≤9 mm, n (%)	22 (22%)
Median, mm	14.9
Mean, mm	16.8
Lymphadenectomy, n (%)	
Yes	104 (97%)
No	3 (3%)
Sentinel lymph node only, n (%)	81 (75%)
+ Axilla level 1	6 (6%)
+ Axilla level 2	13 (12%)
+ Axilla level 3	4 (4%)
Time from BCS to first day of MammoSite, n (%)	
≤7 Days	40 (37%)
>7 Days	67 (63%)
Median, days	8
Time from last day of MammoSite to WBI	
≤12 Weeks, n (%)	56 (52%)
>12 Weeks, n (%)	51 (48%)
Median, weeks	4

BCS: Breast-conserving surgery; WBI: whole-breast irradiation.

Treatment sequelae. To better analyze the side-effects of the treatment, we defined three time periods: T1: After the placement of the MSBT balloon until the start of the external beam RT or chemotherapy (median time=4 weeks); T2: the time period between the start of the WBI (T2a, no chemotherapy after MSBT), or chemotherapy followed by WBI (T2b), until the last fraction of WB; and t3: at the last follow-up.

Pain in the breast of grade 1 and grade 2 was reported at T1 by 38 (36%) and four patients (4%), respectively. Device-related breast hematomas were found in 27 (25%) patients. Symptomatic seroma was observed in five patients (5%).

Table III. *Toxicities at different time points: T1: after MSBT, T2: after WBI (median 2 months after MSBT for patients without chemotherapy =>T2a, 7 months for patients with chemotherapy =>T2b), T3: last follow-up (median 21 months after MSBT for patients without chemotherapy =>T3a, 20 months for patients with chemotherapy =>T3b).*

	Time point, n (%)						
Toxicity	T1 (n=107)	T2 all (n=106)	T2a (n=54)	T2b (n=52)	T3 all (n=102)	T3a (n=50)	T3b (n=52)
Seroma							
Asymptomatic	30 (28%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Symptomatic	5 (5%)	6 (6%)	6 (6%)	0 (0%)	5 (5%)	3 (3%)	2 (2%)
Radiation dermatitis							
Grade 1	1 (1%)	56 (53%)	27 (26%)	29 (27%)	0 (0%)	0 (0%)	0 (0%)
Grade 2	0 (0%)	38 (36%)	17 (16%)	21 (20%)	0 (0%)	0 (0%)	0 (0%)
Grade 3	0 (0%)	3 (3%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin hyperpigmentation							
Grade 1	0 (0%)	79 (75%)	38 (36%)	41 (39%)	16 (16%)	10 (10%)	6 (6%)
Grade 2	0 (0%)	3 (3%)	2 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Breast lymphedema							
Grade 1	0 (0%)	19 (18%)	10 (9%)	9 (8%)	0 (0%)	0 (0%)	0 (0%)
Fibrosis							
Grade 1	0 (0%)	1 (1%)	1 (1%)	0 (0%)	47 (46%)	23 (23%)	24 (24%)
Skin paresthesia of ipsilateral breast							
Grade 1	2 (2%)	15 (14%)	7 (7%)	8 (8%)	0 (0%)	0 (0%)	0 (0%)
Breast pain							
Grade 1	38 (36%)	24 (23%)	11 (10%)	13 (12%)	36 (35%)	23 (23%)	13 (13%)
Grade 2	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Breast hematoma							
Grade 1	27 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decrease in arm range of motion							
Grade 1	0 (0%)	9 (9%)	3 (3%)	6 (6%)	0 (0%)	0 (0%)	0 (0%)
Dyspnea							
Grade 1	0 (0%)	5 (5%)	3 (3%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)
Fatigue							
Grade 1	1 (1%)	38 (36%)	17 (16%)	21 (20%)	0 (0%)	0 (0%)	0 (0%)
Grade 2	1 (1%)	12 (11%)	6 (6%)	6 (6%)	0 (0%)	0 (0%)	0 (0%)
Grade 3	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Telangiectasia							
Grade 1 (not connected)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (7%)	2 (2%)	5 (5%)
Infectious mastitis	0 (0%)	3 (3%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Radiation dermatitis and skin hyperpigmentation grade 2 or more were observed at T2a in 20 (19%) and two (2%) patients, respectively. Three patients (3%) suffered from infectious mastitis. Symptomatic seroma was observed in six patients (6%).

Radiation dermatitis and skin hyperpigmentation grade 2 or more were observed at T2b in 21 (20%) and one (1%) patient, respectively. No patient had developed symptomatic seroma or infectious mastitis at this point.

No skin hyperpigmentation, breast fibrosis or telangiectasias grade 2 or more was observed at T3. In seven patients (7%), grade 1 telangiectasia was observed, that was significantly associated with a distance between the balloon surface and the skin of 9 mm or less ($p \leq 0.001$). Five patients (5%) suffered from temporary symptomatic seroma, that disappeared after 2-4 weeks without the need for clinical intervention.

Table IV. *Outcome of patients treated with MammoSite brachytherapy as a boost.*

Outcome measure	N (%)
Patient status	
Alive without IBTR	102 (95%)
Alive with IBTR	0 (0%)
Dead without IBTR	5 (5%)
Dead with IBTR	0 (0%)
Disease related death	
Metastasis related	1 (1%)
Failure pattern	
None	105 (98%)
In-breast	0 (0%)
Distant metastasis	2 (2%)
Both	0 (0%)

IBTR: Ipsilateral breast tumor recurrence.

Discussion

WBI with or without boost is a well-established component of BCT, typically associated with a low risk of serious side-effects, especially with modern 3-D planning and avoidance of dose hot-spots (10, 11). Different techniques and fractionation regimens have been studied. If a boost to the tumor bed is recommended, sequential administration after WBI is commonly chosen. However, simultaneous integrated boost and other techniques, including MSBT, and other intraoperative techniques are also feasible (12). Currently, no randomized head to head comparisons of all the different alternatives are available.

MSBT is an alternative that provides excellent target coverage (13). We used the combination of MSBT and WBI for several hypothetical advantages: i) early RT in the first week after lumpectomy can be guaranteed, ii) the lung, heart and skin doses are lower compared to external-beam boost (14), iii) the sole utilization of MSBT might be associated with higher risk of locoregional failures, while WBI minimizes that risk (15).

In order to be eligible for MSBT boost at our institution, a set of protocol-specified inclusion criteria had to be met. Typical patients were in their sixties and had invasive ductal carcinoma stage pT1 pN0 with positive receptor status, resected with clear margins and treated with adjuvant systemic therapy (Tables I and II). However, as shown in Table I, a few patients with tumors up to 50 mm in size and stage III disease also received this treatment. In the present study, initial results after a median follow-up of 21 months are presented. We used closed cavity placement and small brachytherapy balloons (4-5 cm) to reduce the incidence of seroma. Nevertheless, we observed symptomatic seroma in 10% of patients at the first two time points. The incidence of infectious mastitis (3%) in our study was lower compared to other series, that reported incidence up to 11% (14, 16). The lower incidence of infectious mastitis in our series might be the result of implantation of the MammoSite device directly after lumpectomy rather than during a further surgical intervention. We observed only 3% RT-induced dermatitis of more than grade 2, that is lower compared to 6-7% that is usually reported after using other techniques, such as interstitial brachytherapy with multiple catheters (6-7%) (17).

Several studies have reported higher rates of telangiectasia after MSBT (18, 19). However, in our series only seven patients (7%) developed grade 1 telangiectasia, which is due to the fact that we used the MammoSite device for application of the boost only. Thus, the applied total dose and dose per fraction *via* MammoSite was lower in our study. The incidence of telangiectasia was significantly associated with lower skin spacing in our study, which is in line with other studies (14, 18). With longer follow-up, rates of telangiectasia are likely to increase. It is also known from the European multi-center study that boost RT increases the risk of long-term fibrosis compared to WBI alone (8). Moreover, at 3 years, the panel evaluation showed that 86% of patients in the no-boost group had an excellent or good global result compared to 71% of patients in the boost group (p=0.0001) (20). On the other hand, local control improved significantly, especially for younger patients.

Ideally, future studies would include assessments of patient preference, quality of life and cost-effectiveness when comparing different sequential or simultaneous boost techniques. Single-arm studies can only provide preliminary data, that need confirmation in randomized trials. Interstudy comparisons might suffer from different patient selection criteria and variable experience of the treating institutions (learning curve), amongst others.

We observed no local or locoregional failure during the study, which indicates an excellent efficacy. It should be mentioned that the characteristics of 54 patients (50%) in our study did not conform to the inclusion criteria of the APBI guidelines of the American Society for Radiation Oncology (21). Importantly, in our study all patients received WBI after MSBT. A large study of 1,379 patients also reported low failure rates (22). Most patients (n=1052) received an electron boost, 225 a brachytherapy boost and 76 a photon boost. At a median follow-up of 8.8 years, 35 patients (2.5%) had developed a local or locoregional recurrence. Boost technique was not associated with recurrence rate. In a different study, intraoperative boost RT yielded a 2.6% local recurrence rate at 5 years (23). According to current recommendations, many patients included in our study would now be eligible for hypofractionated WBI (24).

Conclusion

The technique used in this series of patients seems to provide excellent local control with acceptable toxicity, similar to the results observed with other types of interstitial accelerated partial-breast irradiation as a boost. Long-term follow-up is necessary to refine the patient selection criteria and to assess efficacy and late toxicities.

Conflicts of Interest

The Authors indicated no potential conflicts of interest with regard to this article.

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