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Clinical outcomes with the MammoSite radiation therapy system: results of a prospective trial

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Abstract

Objective—The purpose of this study was to report the treatment-induced adverse events and cosmetic and treatment outcomes of accelerated partial breast irradiation (APBI) delivered with the MammoSite radiation therapy system (RTS) in breast cancer patients undergoing breast-conserving therapy (BCT).

Methods—This is a prospective clinical trial that was approved by the institutional review board. The study included female breast cancer patients undergoing breast-conserving therapy in the form of surgery and APBI delivered with the MammoSite RTS. Patients and tumor characteristics, treatment-induced acute adverse events based on the Common Toxicity Criteria for Adverse

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Conflict of interest The authors declare that they have no competing interests.

Compliance with ethical standards: Statement of ethical standards All human studies have been approved by the appropriate ethics committee—Northwestern University Institutional Review Board—and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

Events (CTCAE) version 2.0, chronic AEs according to Radiation Therapy Oncology Group (RTOG) scale, treatment outcomes (including local control, disease-free survival, and overall survival), and cosmetic outcomes are reported.

Results—The study included 36 eligible patients treated consecutively in our institution between November 2003 and August 2009. The age range was 45–83 years. A total of 29 patients had invasive disease (median size 1.1 cm), while 7 patients had in situ disease only (median size 0.8 cm). The skin distance in most of the patients (91.7 %) was ≥ 1 cm; only three patients (8.3 %) had skin distance < 1 cm. The median balloon diameter was 5 cm (range 4–6 cm). At a median follow-up of 42 months (range 4–65 months), local control, disease-free survival, and overall survival were 100 %. None of the patients experienced any grade 3 or 4 toxicities; 16.7 and 5.6 % of the patients had late grade 2 fibrosis and telangiectasia, respectively. At last follow-up, cosmetic outcome was rated as good or excellent in 94 % of the patients.

Conclusion—APBI delivered with the MammoSite RTS is a feasible, tolerable, and effective treatment modality. Multicenter, randomized, controlled clinical trials with a larger number of patients are required for verification.

Keywords

Accelerated partial breast irradiation; MammoSite; Brachytherapy

Introduction

For several decades, early-stage breast cancer has been treated with breast-conserving therapy (BCT), which consists of breast-conserving surgery followed by whole-breast radiotherapy (WBRT). This organ-preserving approach has been shown to be equivalent in survival to modified radical mastectomy in large randomized trials with 20-year follow-up [1, 2]. Postoperative radiotherapy is an integral component of BCT; WBRT has been shown to improve both local control and overall survival after lumpectomy [3]. Despite its benefits, in clinical practice, radiotherapy (RT) is often omitted in BCT [4]. The rate of omission of RT in BCT appears to be due, at least in part, to the logistical difficulties associated with a 6–7-week course of WBRT [5]. Accelerated partial breast irradiation (APBI) is a new therapy that offers a dramatic reduction in the logistical burden of a course of RT and consequently, may increase its utilization after lumpectomy.

APBI limits the target volume to the tissue immediately surrounding the operative bed. This approach is predicated on the observation that treatment failure outside of the operative bed is rare in early breast cancer [2]. By limiting the treatment volume and increasing fraction size, APBI can be completed in a single week of twice daily treatments. APBI is currently being compared to WBRT in randomized controlled trials [6, 7]. Prior to the publication of these trials, non-randomized experiences may help to define the patient population for whom APBI may be an appropriate therapy. We report the results of a single-institution prospective trial evaluating the safety, efficacy, and cosmetic outcomes of APBI delivered with the MammoSite radiation therapy system (RTS).

Methods

Between November 2003 and August 2009, qualifying patients undergoing BCT at Northwestern Memorial Hospital were offered enrollment on a prospective trial evaluating the MammoSite RTS for the delivery of APBI. The Institutional Review Board of Northwestern University approved this prospective clinical trial. Written informed consent for participation in the study was received from all patients prior to enrollment. Patients were screened for eligibility with regard to patient, tumor, and technical factors as described in Table 1.

Treatment

For each patient, the MammoSite applicator was placed after surgery under ultrasound guidance through a stab incision. The balloon was then inflated with a saline/contrast mixture to conform to the surgical cavity. Prior to treatment, a CT scan was obtained to assess the balloon to skin distance, the conformance of the balloon to the operative bed, and the symmetry of the source channel. Dose was prescribed to a single point 1 cm from the balloon surface. Treatment was delivered using an Iridium-192 high-dose-rate (HDR) brachytherapy remote after-loading system. The total treatment dose was 34 Gy divided in 10 fractions. The MammoSite RTS treatments were accomplished at the time of lumpectomy—prior to systemic therapy. Treatments were delivered twice daily over a period of 5–7 days. An interval of at least 6 h was required between fractions. Prior to each fraction, the location and inflation status of the balloon applicator were confirmed with fluoroscopy or CT scan (Fig. 1).

Data collection

Patient demographic information, tumor characteristics, and technical factors were collected prospectively at enrollment. Information on acute and late treatment-induced adverse events (erythema, desquamation, telangiectasia, fibrosis, and seroma), cosmetic outcome, and tumor recurrence were collected at regular follow-up with treating physicians. Acute treatment-induced adverse events were scored according to the CTCAE version 2.0, and chronic adverse events were graded according to the RTOG scale [8]. Cosmetic outcome was judged by the treating physician according to a scale described in Table 2.

Statistical analysis

Descriptive statistics such as means and medians were calculated. Ninety-five percent approximate confidence intervals, *t* tests for continuous data, and chi-square tests for binary data were provided as appropriate. *P* values of less than 0.05 were reported, and such results were considered “significant” in this study.

Results

Study population

Thirty-six patients were entered on trial; the characteristics of this study population are presented in Table 3. A total of 29 patients had invasive disease (median size 1.1 cm), while 7 patients had in situ disease only (median size 0.8 cm). Median follow-up for this cohort as

a whole was 42 months (range 4–65 months). The source-skin distance in most of the patients (91.7 %) was ≥ 1 cm; only three patients (8.3 %) had source-skin distance < 1 cm. The median balloon diameter was 5 cm (range 4–6 cm).

Disease control

At a median follow-up of 42 months, none of the patients had any local recurrence or distant metastases. We report 100 % local control, disease-free survival, and overall survival in this cohort of patients.

Cosmetic results

Most of the patients had excellent (66.7 %) or good (27.8 %) cosmetic outcome at the last follow-up visit. Only one patient had fair outcome and none had poor outcome. The detailed cosmetic outcomes are presented in Table 4.

Complications

None of the patients had grade 3 or 4 treatment-induced adverse events. Treatment-induced adverse events are detailed in Table 5.

Discussion

This study reports on a single-institution prospective experience of 36 female breast cancer patients treated with the MammoSite RTS. At a median follow-up of 42 months, there were no in-breast tumor recurrences. At last follow-up, cosmetic outcome was rated as good or excellent in 94 % of the patients. Acute and late toxicity were limited to grade 1 or 2 in all patients.

These very favorable results are comparable to those of other series using the MammoSite RTS. A report on the results of a multi-institutional registry trial showed a 3-year actuarial rate of ipsilateral breast tumor recurrence of 2.15 % [9]. At 48 months, 91 % of patients had cosmetic results described as good or excellent. The results of all available series have been summarized elsewhere; in most series, local recurrence rates range between 0 and 4 %, and rates of good or excellent cosmesis range between 75 and 97 %, albeit with relatively short follow-up [10, 11].

Our results are superior to a recent retrospective study reported by Rosenkranz KM et al. [12] who analyzed the long-term complications in 71 MammoSite patients compared to 245 whole-breast external radiation patients. At a median follow-up of 4 years, a palpable mass developed at the site of lumpectomy in 27 versus 7 %, and telangiectasia was developed in 24 versus 4 % of the MammoSite versus the whole-breast external radiation patients, respectively ($p < 0.0001$ and $p < 0.001$). The authors concluded that MammoSite treatment resulted in a statistically significant higher long-term complication rate with 42 % of patients treated with MammoSite developed a palpable mass, telangiectasia, or both. Notably, their inclusion criteria included patients with larger tumors (≥ 3 cm) compared to our study (≥ 2 cm).

Until the publication of the results of randomized trials, the question of which subsets of patients are most appropriate for treatment with APBI outside of the confines of a clinical trial remains an open question. However, our results are promising; stronger evidence is still required to show clear benefit of the MammoSite RTS over the external beam radiation therapy utilizing the advanced technology that is currently available. The American Society for Radiation Oncology published a consensus statement that categorized early-stage breast cancer patients into three groups with regard to their appropriateness for treatment with APBI outside of a clinical trial: suitable, cautionary, and unsuitable [13]. This statement restricted the suitable category to those patients at lowest risk for having disease remote from the operative bed. The criteria for the suitable category included age 60 or older, stage T1N0, ER positive, unicentric, and invasive ductal carcinoma, with no lymphovascular invasion (LVI) and margins ≥ 2 mm. Of the patients enrolled in the present study, 11 fit into the suitable category, 21 into the cautionary category (based on age or the presence of focal LVI, ER negative status, pure DCIS, or invasive lobular histology), and 4 into the unsuitable category (all 4 were between the ages of 45 and 50). The chi-square test for equality among the three propositions is highly significant, (chi-square (1)=12.27) suggesting they differ from a common probability of belonging to a slot of 1/3.

Conclusion

APBI delivered with the MammoSite RTS is a feasible, tolerable, and effective treatment modality in females diagnosed with early-stage breast cancer. Multicenter randomized controlled clinical trials with a larger number of patients are required for verification and stronger evidence.

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Fig. 1. Axial and multiplanar views for a single dwell source on a right-sided MammoSite application

Table 1
Inclusion and exclusion criteria

Inclusion		Exclusion
Patient factors		
Age	Postmenopausal or ≥ 45	
Consent	Written informed consent	
Other		Pregnancy or breast feeding Collagen vascular disease (except rheumatoid arthritis) Bleeding disorder Medical inoperability Bilateral breast cancer Prior breast irradiation Postoperative infection
Tumor factors		
Histology/size	Invasive carcinoma ≤ 2 cm Grade 1–2 ductal carcinoma in situ ≤ 2 cm Grade 3 ductal carcinoma in situ ≤ 1 cm	Extensive lobular carcinoma in situ Paget's disease of the breast Multifocal or multicentric tumor Extensive intraductal component (Harvard definition, >25 % DCIS)
Stage	Tis or T1, N0, M0	
Margins	Closest surgical margin >0.2 cm	
Mammography	Appropriate mammography Preoperative mammogram within 2 months or postoperative mammogram	Unbiopsied indeterminate/suspicious calcifications on mammogram
Technical factors		
Skin distance	Skin spacing ≥ 0.6 cm	

Table 2
Cosmetic score

Cosmetic score	Description
Excellent	Minimal or no difference in size, shape, or texture of the treated breast compared to the untreated
Good	Mild asymmetry in the size or shape of the treated breast
Fair	Obvious difference in the size or shape of the treated breast involving 1/4 of the breast
Poor	Marked change in the appearance of the treated breast involving >1/4 of the breast

Table 3
Patients and tumor characteristics

	Invasive±DCIS	DCIS alone
Patients	29	7
Median Age	62 (45–83)	54 (46–79)
Histology		
Ductal	25	
Lobular	2	
Mixed	2	
Focal LVI	3	0
Median tumor size	1.1 cm (range 0.3–2.0)	0.8 cm (range 0.6–0.8)
Tumor grade		
Grade 1	14	1
Grade 2	11	5
Grade 3	4	1
Chemotherapy	3	0
Hormonal Therapy	26	5
Median Follow-up	45 months (4–65)	31 months (19–56)

Table 4

Cosmetic outcomes

Cosmetic outcomes						
	Excellent number (%) ^a	Good number (%) ^a	Fair number (%) ^a	Poor number (%) ^a	NA number (%) ^b	
12 months	23 (74 %)	7 (23 %)	1 (3 %)	0 (0 %)	5 (14 %)	
24 months	19 (79 %)	5 (21 %)	0 (0 %)	0 (0 %)	12 (33 %)	
36 months	11 (73 %)	4 (27 %)	0 (0 %)	0 (0 %)	21 (58 %)	
48 months	8 (89 %)	1 (11 %)	0 (0 %)	0 (0 %)	27 (75 %)	
Last follow-up	24 (69 %)	10 (29 %)	1 (3 %)	0 (0 %)	1 (3 %)	

NA not available

^a Percent among patients available for evaluation, not including patients' lost to follow up

^b Percent among all study patients (36 patients)

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Table 5

Treatment-induced adverse events: N (%)

Adverse events	None	Grade 1	Grade 2	Grade 3/4
Acute skin toxicity				
Erythema	27 (75)	9 (25)	0 (0)	0 (0)
Dermatitis	28 (77.8)	8 (22.2)	0 (0)	0 (0)
Telangiectasia	33 (91.7)	3 (8.3)	0 (0)	0 (0)
Pain	32 (88.9)	3 (8.3)	1 (2.8)	0 (0)
Late skin toxicity				
Fibrosis	25 (69.4)	5 (13.9)	6 (16.7)	0 (0)
Telangiectasia	33 (91.7)	1 (2.8)	2 (5.6)	0 (0)
Seroma	30 (83.3)	3 (8.3)	3 (8.3)	0 (0)