

**RAPID COMMUNICATION**

**INITIAL CLINICAL EXPERIENCE WITH THE MAMMOSITE BREAST BRACHYTHERAPY APPLICATOR IN WOMEN WITH EARLY-STAGE BREAST CANCER TREATED WITH BREAST-CONSERVING THERAPY**

MARTIN KEISCH, M.D.,\* FRANK VICINI, M.D.,<sup>†</sup> ROBERT R. KUSKE, M.D.,<sup>‡</sup> MARY HEBERT, M.D.,<sup>§</sup> JULIA WHITE, M.D.,<sup>||</sup> CORAL QUIET, M.D.,<sup>¶</sup> DOUG ARTHUR, M.D.,<sup>#</sup> TROY SCROGGINS, M.D.,<sup>\*\*</sup> AND OSCAR STREETER, M.D.<sup>††</sup>

\*Department of Radiation Oncology, Mount Sinai Medical Center, Miami Beach, FL; <sup>†</sup>Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI; <sup>‡</sup>Department of Radiation Oncology, University of Wisconsin, Madison, WI; <sup>§</sup>Department of Radiation Oncology, US Oncology, Sherman, TX; <sup>||</sup>Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; <sup>¶</sup>Department of Radiation Oncology, Arizona Oncology, Phoenix, AZ; <sup>#</sup>Department of Radiation Oncology, Virginia Commonwealth University, Richmond, VA; <sup>\*\*</sup>Department of Radiation Oncology, Ochsner Clinic, New Orleans, LA; <sup>††</sup>Department of Radiation Oncology, University of Southern California Norris Cancer Center, Los Angeles, CA

**Purpose:** We present the results of the initial clinical testing of the MammoSite balloon breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy.

**Methods and Materials:** Seventy patients were enrolled in a multicenter prospective trial testing the applicator for safety and performance. Fifty-four patients were implanted, and 43 patients were ultimately eligible for and received brachytherapy as the sole radiation modality after lumpectomy. Patients were staged T1N0M0 with negative pathologic margins and age >45 years. A dose of 34 Gy was delivered in 10 fractions over 5 days prescribed to 1 cm from the applicator surface using <sup>192</sup>Ir high-dose-rate brachytherapy. A minimum skin-to-balloon surface distance of 5 mm was required for treatment. Device performance, complications, and cosmesis were assessed.

**Results:** Computed tomography imaging post-balloon inflation showed 8, 14, and 21 patients with 5–6 mm, 7–9 mm, and >10 mm of skin spacing, respectively. Two patients were explanted because of inadequate skin spacing and 7 because of suboptimal conformance of the surgical cavity to the applicator balloon. One patient was explanted because of positive nodal status and another because of age. The most common side effects related to device placement included mild erythema, drainage, pain, and echymosis. No severe side effects related to implantation, brachytherapy, or explantation occurred. Side effects related to radiation therapy were generally mild with erythema, pain, and dry desquamation being the most common. At 1 month, 88% of patients were evaluated as having good-to-excellent cosmetic results.

**Conclusions:** The MammoSite balloon breast brachytherapy applicator performed well clinically. All eligible patients completed treatment. Side effects were mild to moderate and self-limiting. Skin–balloon surface distance and balloon–cavity conformance were the main factors limiting the initial use of the device. © 2003 Elsevier Science Inc.

**Breast cancer, Brachytherapy, Lumpectomy, Breast-conserving therapy, Radiation.**

**INTRODUCTION**

Interest in accelerated partial breast irradiation after conservation surgery has increased over the past decade as a result of many factors, including both clinical and pathologic data questioning the efficacy of whole-breast radiation in selected patients, as well as factors related to patient convenience, radiotherapy access, and acceptance of radiotherapy. Currently, multicatheter-based implants are the best-studied means of accelerated partial breast irradiation. Data for interstitial implantation used in this setting suggest that

in properly selected patients, high rates of local control and cosmesis can be expected (1–11). Despite these encouraging results, acceptance of interstitial brachytherapy has been limited for several reasons, including the complexity of the procedure and treatment planning, the lack of formal training, and the steep learning curve related to the procedure. The MammoSite balloon brachytherapy applicator was developed to provide a simpler, more assured technique for performing breast brachytherapy. In this report, the results of the initial clinical experience with the device are presented.

Reprint requests to: Martin Keisch, M.D., 1 Blum Bldg., Radiation Oncology, 4306 Alton Rd., Miami Beach, FL 33140. Tel: (305) 535-3400; Fax: (305) 535-3422; E-mail: mkeisch@salick.com

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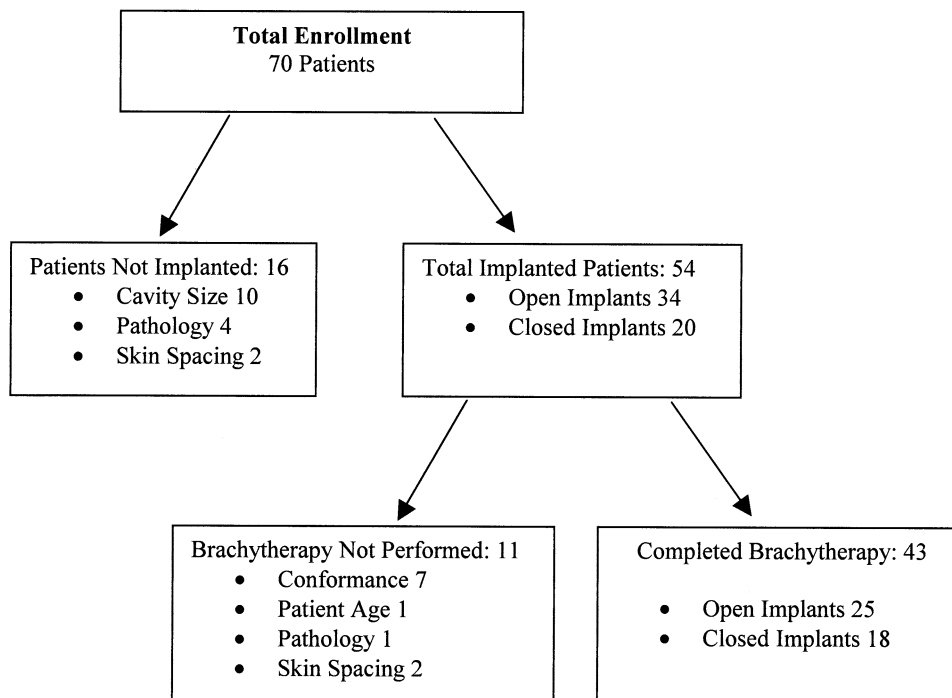


Fig. 1. Patient enrollment. The total enrollment shown step-by-step during evaluation and implantation phase through actual brachytherapy, including reasons for ineligibility.

## METHODS AND MATERIALS

Between May 2000 and October 2001, 70 patients were enrolled in a multi-institutional investigational review board–approved prospective trial designed to test the MammoSite device’s safety and performance, either as the sole modality of irradiation or as a boost dose. However, all patients entered on the trial were enrolled in the sole-modality arm. The device is a dual lumen spherical balloon catheter inflatable to 4–5 cm with a central lumen for the high-dose-rate  $^{192}\text{Ir}$  source. Eligibility requirements included the following: age >45 years, tumor <2 cm, invasive ductal histology, negative nodal status, negative marginal status (National Surgical Adjuvant Breast and Bowel Project definition), applicator placement within 10 weeks of final lumpectomy procedure, and a cavity post-lumpectomy with one dimension of at least 3.0 cm. Ineligibility criteria included the following: an extensive intraductal component, pure intraductal cancers, lobular histology, or collagen vascular disease. Additionally, patients were deemed ineligible for technical issues, including inadequate balloon–skin distance, excessive cavity size, or poor balloon–cavity conformance. Patients could be enrolled before final lumpectomy to allow device placement in an open fashion during that procedure; other patients were enrolled post-lumpectomy and implanted using a closed technique (typically under ultrasound guidance).

Final determination of suitability of high-dose-rate brachytherapy treatment was made after device placement using computed tomography (CT) imaging in all patients to measure the applicator–skin distance (minimum require-

ment 5 mm). Conformance was assessed by CT imaging after device placement and was deemed acceptable if the balloon was in contact with the lumpectomy margin uniformly, without air- or fluid-filled gaps. CT and fluoroscopic simulation were used for treatment planning, both to determine the single dwell position in the center of the balloon and to make daily confirmation of balloon diameter. Acceptable diameters ranged from 4 to 5 cm, corresponding to a 35–70 cc fill volume. In all cases, 34 Gy was delivered at a point 1 cm from the surface of the balloon in 3.4 Gy fractions (twice daily) over 5–7 elapsed days with various commercially available remote afterloaders. Interfraction separation was a minimum of 6 hours.

Data collection included twice-daily physician assessment of the treatment site and applicator status (during treatment), ultrasound assessment of the site, device- and radiotherapy-related adverse events, and cosmesis (at 24 h, 1 week, and 4 weeks posttreatment).

## RESULTS

Seventy patients, of whom 43 ultimately were found eligible for brachytherapy, were enrolled in the trial. Patient eligibility for the protocol was assessed at each step of the treatment process (i.e., before implant, at the time of implant, and after postimplant imaging before brachytherapy). The two most common reasons for ineligibility for implantation of the device were excessive cavity size and final pathology (see Fig. 1). The 54 patients implanted included 34 placed at the time of lumpectomy and 20 in a closed

Table 1. Patient and tumor characteristics

Demographics	
Age (years) ( <i>n</i> = 43)	
Average ± SD (range)	69 ± 10.4 (50–90)
Breast size ( <i>n</i> = 43)	
A	1 (2%)
B	9 (21%)
C	15 (35%)
D+	11 (26%)
Unknown	7 (16%)
Menopausal status ( <i>n</i> = 43)	
Post	41 (95%)
Peri	2 (5%)
Histology ( <i>n</i> = 43)	
G1	17 (40%)
G2	16 (37%)
G3	6 (14%)
Gx	4 (9%)
AJCC tumor class ( <i>n</i> = 43)	
T1a	9 (21%)
T1b	16 (37%)
T1c	18 (42%)
Tumor location ( <i>n</i> = 43)	
Right breast	(35%)
Left breast	(65%)
Upper outer	(30%)
Upper midline	(30%)
Upper inner	(19%)
Lower outer	(9%)
Lower midline	(5%)
Lower inner	(5%)
Areola	(2%)
Method of implant ( <i>n</i> = 43)	
Closed cavity	18 (42%)
Open cavity	25 (58%)

fashion after final pathologic review. Brachytherapy was ultimately performed in 43 patients, including 25 from the open group and 18 from the closed group. Cavity size was measured directly during the open procedures and ultrasonographically for patients enrolled post-lumpectomy. Poor balloon conformance was the most common reason for ineligibility for brachytherapy and device explantation (7 of 11 patients). Conformance was assessed by CT imaging after device placement, and was deemed acceptable if the balloon was in contact with the lumpectomy margin uniformly, without air- or fluid-filled gaps. Skin spacing, generally determined by ultrasound measurement and CT, was also an important issue for determination of both implantation and treatment. Overall, 4 patients enrolled became ineligible because of skin spacing.

Demographic and tumor characteristics of the 43 treated patients are listed in Table 1. The average tumor size was 1.0 cm (range: 0.4–2.0 cm). Tumors were located most commonly in the upper outer and upper mid-breast region, representing 60% of all treated patients. Pretreatment CT required good cavity–balloon conformance and acceptable balloon–skin distance. Figure 2 demonstrates the balloon–skin distances determined by CT measurement.

All patients initiated on their course of brachytherapy

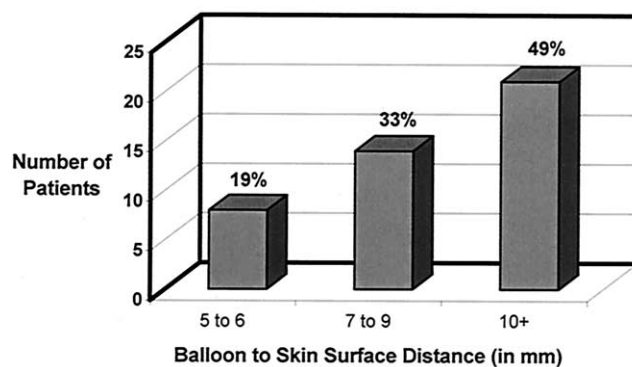


Fig. 2. Skin-spacing distances.

completed the prescribed dose. Three patients had balloon rupture, all before the first fraction, and in all cases the balloon was replaced without difficulty, and the treatment was completed. The manufacturer analyzed the devices, and in each case, evidence of contact with a sharp object was noted. In two cases, a needle was felt to be a likely cause; in the third case, surgical clips in the cavity were implicated. Investigators were required to assess the device and site both clinically and by imaging with each fraction, and all fractions were delivered without incident. Explantation of the device was performed after the final fraction with excellent tolerance by patients in all cases.

The study assessed side effects according to FDA guidelines without separation of complaints or observation by

Table 2. Device- and radiation-related side effects: A list of all breast and skin symptoms and signs related to the device and/or radiation treatments (*n* = 54)

Adverse event description	Patient incidence (%)
Erythema	31 (57.4)
Catheter site drainage	28 (51.9)
Pain breast	23 (42.6)
Ecchymosis	17 (31.5)
Edema breast	8 (14.8)
Dry desquamation	7 (13.0)
Dry skin	6 (11.1)
Seroma	6 (11.1)
Pruritus	5 (9.3)
Skin discoloration	5 (9.3)
Rash	4 (7.4)
Fibrosis breast	3 (5.6)
Hematoma	3 (5.6)
Induration-skin	3 (5.6)
Moist desquamation	3 (5.6)
Skin irritation	3 (5.6)
Blister	2 (3.7)
Infection	2 (3.7)
Mastitis	2 (3.7)
Telangiectasia	2 (3.7)
Abscess	1 (1.9)
Eschar	1 (1.9)
Induration-breast	1 (1.9)
Serosanguinous leakage	1 (1.9)
Vasodilatation	1 (1.9)

likely cause. Therefore, all side effects are grouped without separation into surgical, device-related, or radiation-related etiologies. The side effects are listed in Table 2. Most commonly, radiation effect was limited to mild or moderate erythema without desquamation. In addition, other less common, but significant, events included the following: moist desquamation in 3 patients; 2 infections, including an abscess requiring drainage; and 3 seromas requiring drainage, because of patient discomfort. No definitely serious device-related events were reported. In four cases, serious adverse events were noted that were potentially related to the device; these were the previously mentioned abscess and seromas.

## DISCUSSION

The MammoSite brachytherapy applicator was tested in a prospective clinical trial to determine its safety as a radiation delivery system for breast brachytherapy to obtain FDA clearance. The trial detected no severe device-related adverse events. The four potentially device-related events, including an abscess and 3 seromas, were all self-limiting and resolved. The device performed well as an applicator for breast brachytherapy; 100% of patients eligible for treatment received the prescribed dose. Patients experienced only mild-to-moderate side effects, including skin erythema (57%), dry desquamation (13%), and moist desquamation (5%) short term, that were related to the radiation therapy

dose. Overall, the study demonstrated that the device was safe and well tolerated, leading to FDA clearance on May 6, 2002 as an applicator suitable for delivery of radiation therapy to the surgical margins of a lumpectomy cavity.

During the study, the device was placed by 14 different investigators at eight sites, with an 80% rate of placement to treatment. Given the novel nature of the applicator, this suggests its relative ease of use. Patients not treated after device placement were most commonly explanted because of excessive cavity size/poor conformance (63%) or skin spacing (18%). Obviously, some limitations exist, particularly in regard to balloon–cavity conformance and balloon–skin spacing. The conformance of the balloon to the cavity wall is essential to assure appropriate dosimetry. Additionally, the balloon–skin distance is critical in not exceeding appropriate doses to the skin over the balloon. A higher implant:treatment ratio was seen in the closed implant group with 90% vs. 73% in the closed and open groups, respectively. Regarding the 9 of 34 (27%) patients requiring explantation in the open setting, the reasons for explantation included mostly technical issues, such as conformance, as well as pathologic issues, such as nodal positivity. In the 2 of 20 (10%) patients requiring explantation in the closed setting, the reasons for explantation included poor conformance with 1 patient and age ineligibility (<45 years) with the other patient.

The advantage to open placement includes elimination of a separate procedure (albeit a simple one). In the post-

Table 3. Studies of partial breast irradiation using brachytherapy

Institution	No. of cases	Median F/U (mo)	Scheme (cGy)	Total dose (cGy)	% Local recurrence	% Good/excellent cosmetic result
<b>HDR brachytherapy series</b>						
MammoSite (current study)	43	1	340 × 10	3400	–	88
Ochsner Clinic (4), New Orleans, Louisiana	26	75	400 × 8	3200	2*	75*
Royal Devon/Exeter Hospital, Exeter, England (13)	45	18	1000 × 2 700 × 4 600 × 6	2000 2800 3600	8.8	95
National Institute of Oncology, Budapest, Hungary Phase I/II Trial (3)	45	57	520 × 7 433 × 7	3640 3030	4.4	97
National Institute of Oncology, Budapest, Hungary Phase III Trial (3)	126	30	520 × 7 (HDR) 200 × 25 <sup>†</sup> (EBRT)	3640 5000	0	Not stated
London Regional Cancer Center London, Ontario (14,15)	39	20	372 × 10	3720	2.6*	Not stated
William Beaumont Hospital (1,2)	54	36	400 × 8	3200	0	100
Radiation Therapy Oncology Group (16)	66	32	340 × 10	3400	–	–
Tufts-New England Medical Center (11)	32	33	340 × 10	3400	3	88
<b>LDR brachytherapy series</b>						
Ochsner Clinic (4)	26	75	>40 cGy/h	4500	2*	75*
Guy's Hospital (5,6)	27	72	40 cGy/h	5500	37	83
Florence, Italy (9)	90	27	Not stated	5000–6000	4.4	Not stated
University of Kansas (10)	25	47	–	2000–2500	0	100
William Beaumont Hospital (2)	120	36	52 cGy/h	4992	0	98
Radiation Therapy Oncology Group (16)	33	36	–	4500	–	–

\* LDR/HDR patients combined.

<sup>†</sup> Whole-breast radiation.

Abbreviations: HDR = high-dose-rate brachytherapy; LDR = low-dose-rate brachytherapy; EBRT = external beam radiation therapy.

lumpectomy setting, the device can be placed quite easily under ultrasound guidance by the radiation oncologist or surgeon. Later placement eliminates the issue of unknown pathologic findings requiring alternate or additional treatment (extensive intraductal component, positive margins, multiple positive nodes, etc.), as well as the ability to assess the patient's cavity for anatomic suitability. Close communication between the surgeon and radiation oncologist is therefore essential.

Long-term follow-up data on all patients are being collected for analysis of local control and cosmesis. Short-term cosmesis has been good to excellent on the Harvard scale in 88% of women treated. Current follow-up does not provide sufficient data for long-term assessment of these end points. However, dose-volume histogram analyses of the device in patients treated in this trial have been published previously and compare favorably with catheter-based breast brachytherapy systems. These systems have previously demonstrated excellent 5-year results (See Table 3). For example, Edmundson *et al.* demonstrated that the treatment volume with the MammoSite device was typically larger than with interstitial brachytherapy (by 14%) in a comparable group of patients (12). Additionally, coverage of the margins of the resection cavity was dramatically improved when ana-

lyzed in terms of the mean  $D_{90}$  (dose received by 90% of the volume) coverage (90% vs. 69.8%) and reproducibility ( $D_{90}$  range: 89.2%–90.8% vs. 61.1%–83.5%). In addition, Wazer *et al.* (8) found an association between clinically evident fat necrosis and volumes receiving 200%, 150%, and 100% of the prescribed dose with interstitial brachytherapy. The MammoSite device never exceeded these dose-volume cut-offs in the study by Edmundson *et al.* (12), suggesting that fat necrosis is relatively unlikely. These data attest to the device's dosimetric comparability to interstitial brachytherapy in providing a safe and effective dose. Just as important, they also demonstrate a high degree of reproducibility and ease of use. These characteristics are obvious prerequisites for the acceptance of the device by the medical community as an effective means of delivering accelerated partial breast irradiation.

## CONCLUSIONS

The initial MammoSite balloon trial demonstrated good treatment delivery performance and safety and has received FDA clearance for clinical use. The applicator provides a simpler method for performing reproducible breast brachytherapy.

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