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Increased Rates of Long-Term Complications after MammoSite Brachytherapy Compared with Whole Breast Radiation Therapy

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Abstract

BACKGROUND—Due to its short duration of therapy and low rates of local recurrence, women undergoing breast conservation are increasingly opting for partial breast irradiation with the MammoSite (Cytyc/Hologic) catheter. In early follow-up studies, few complications were reported. Few data, however, exist regarding longer-term complications. We compared the long-term local toxicities of MammoSite partial breast irradiation with those resulting from whole breast radiation.

STUDY DESIGN—This was a retrospective study performed in a single academic medical center. All patients who underwent breast-conserving surgery between 2003 and 2008, who met institutional criteria for brachytherapy, were included. We compared women treated with MammoSite with patients treated with whole breast radiation therapy (WBRT). Endpoints included incidence of palpable masses at the lumpectomy site, telangiectasias, and local recurrence.

RESULTS—Seventy-one MammoSite patients and 245 WBRT patients were well matched with regard to clinical characteristics. Median follow-up was 4 years. A palpable mass developed at the site of lumpectomy in 27% of the MammoSite patients compared with 7% of the WBRT patients ($p < 0.0001$). Telangiectasias developed more frequently in the MammoSite group than in the WBRT group (24% vs 4%, $p < 0.001$). Forty-two percent of patients treated with MammoSite developed a palpable mass, telangiectasia, or both.

CONCLUSIONS—Palpable masses and telangiectasias are frequent long-term complications after MammoSite brachytherapy and occur at a significantly higher rate after MammoSite brachytherapy than after WBRT. This increased rate of long-term local toxicity should be considered when counseling women on options for adjuvant radiation therapy after breast-conserving surgery.

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Clinical trials beginning in the late 1970s documented the safety of breast conservation therapy (BCT) in lieu of mastectomy for the treatment of many women with breast cancer. Recurrence rates in women undergoing breast conserving surgery without adjuvant whole breast radiation therapy (WBRT), however, are significantly higher than the recurrence rates in women treated with partial mastectomy and radiation therapy.

Accelerated partial breast irradiation (APBI) is becoming increasingly popular with breast cancer providers and patients due to reduced length of radiation, patient convenience, and decreased radiation dosage. MammoSite (Cytac/Hologic) was one of the first devices of delivery of APBI using intracavitary brachytherapy. There are, however, limited reports on longer-term outcomes in this patient population. We hypothesized that the long-term local complication rates in women treated with MammoSite APBI were higher than those identified in women treated with conventional WBRT.

METHODS

After obtaining approval from the Dartmouth Committee for the Protection of Human Subjects, we performed a retrospective chart review of all women treated with BCT in our institution between January 1, 2003 and January 1, 2008. From this group, we selected for further analysis those patients who were candidates for APBI based on our institutional criteria during the study period. These criteria included unifocal invasive cancer, maximum tumor diameter ≤ 3 cm, negative nodes, negative resection margins, and patient age ≤ 45 years. We identified a subset of these patients who chose MammoSite therapy and a control group that included all patients eligible for APBI but who chose treatment with WBRT. Women who did not meet the above criteria for brachytherapy were excluded.

Once we compiled our study groups, we extracted data from the medical records including age, date of initial diagnosis, date of last follow-up, type of carcinoma, tumor size, stage of carcinoma, receptor status, adjuvant treatment received (chemotherapy and/or hormonal therapy, APBI vs WBRT), postoperative infection, telangiectasias, palpable masses, need for repeat biopsy, indication for repeat biopsy (physical finding or radiographic finding), location of repeat biopsy, dates of repeat biopsies, and incidence of and date of recurrences.

Our main outcomes measures were the development of a palpable mass post-treatment, need for repeat biopsy at the site of lumpectomy, telangiectasia, and local recurrence. Chi-square test was used to compare the 2 treatment groups. Standard follow-up for all patients who underwent BCT consisted of physical examinations by the attending oncologic surgeon at 6 and 12 months and then annually for 5 years. Follow-up did not differ between the APBI and the whole breast radiation groups. Mammograms were obtained at 6 months and 12 months post-treatment and then annually.

Patients received APBI within 12 weeks of final surgery. We strictly followed the technical guidelines for APBI treatment published by the American Brachytherapy Society.¹ All plans were based on CT scan with 0.5 cm or smaller slices. Balloon catheters were placed >7 mm from skin. Total dose to 3,400 cGy was administered in 2 fractions per day (3.4 Gy per fraction) for 10 fractions. Doses were separated by at least 6 hours. Whole breast radiation was administered in 25 cycles to 4,600 cGy followed by a tumor boost to 6,100 cGy in additional cycles or 16 cycles to 4,260 cGy with a boost to 5,250 cGy in 5 additional cycles.

RESULTS

Between January 2003 and January 2008, 941 patients were treated with BCT at our institution. Of these patients, 316 met institutional criteria for APBI. Seventy-one patients elected MammoSite APBI and 245 women were treated with whole breast irradiation

(Table 1). Of the women who underwent whole breast irradiation, the majority (200 patients) received whole breast irradiation with a boost to 6,100 cGy, 5 patients were treated with whole breast irradiation without a boost to 4,600 cGy, 26 patients had hypofractionated whole breast irradiation with a boost to 5,000 cGy, and 14 had hypofractionated radiation without a boost to a total dose of 4,260 cGy. The average patient age was 63.5 years. The average tumor size was 1.1 cm. Ninety-two percent of the tumors were estrogen receptor (ER) positive. Median follow-up time was 4 years (range 0.9 to 8.1 years). There were no significant differences between the 2 study groups in the age of the patients, the mean tumor size, the percent of women with estrogen receptor positive tumors or the length of follow-up. The majority of hormone receptor positive women in each group (83% in the MammoSite group and 94% in the WBRT group) received adjuvant endocrine therapy. Nine percent of MammoSite patients and 13% of the WBRT group received adjuvant chemotherapy. There was no significant difference in systemic chemotherapy rates.

Discrete palpable masses developed at the lumpectomy site in 26.7% (19 of 71) of the patients in the Mammo-Site group compared with 7.3% (18 of 245) of women in the WBRT group ($p < 0.001$) (Table 2). Due to concerns that these masses were recurrent cancer, 12 patients in each group underwent diagnostic core biopsy. The decision to biopsy palpable masses with normal imaging was made at the discretion of the surgical oncologist based on interval change and clinical suspicion of recurrence. There was no difference in the percentage of patients with palpable masses in each group who underwent core biopsy: 63% (12 of 19) of masses in the MammoSite group were biopsied compared with 67% (12 of 18) of masses in the WBRT group. The palpable masses that did not undergo biopsy were followed closely with clinical examination to exclude interval growth. Patients in the MammoSite group were significantly more likely than patients in the WBRT group to develop a palpable mass at the lumpectomy site that required core biopsy to exclude malignancy (16.9% vs 4.9% $p = 0.02$).

The time course to development of a palpable mass requiring core biopsy is displayed in Figure 1. Only 2 patients in the MammoSite group underwent biopsy in the first year after their BCT, suggesting that clinical concern was not prompted by postoperative seroma or other immediate postoperative change. Most biopsies were performed 2 to 3 years after lumpectomy and radiation.

Pathology of the biopsied masses revealed fat necrosis, stromal scarring, and fibrosis in the majority of women treated with MammoSite brachytherapy. Only 1 patient had biopsy of a cystic lesion consistent with a seroma. A local recurrence at the lumpectomy site was diagnosed in 2.8% (2 of 71) of the patients in the MammoSite group and in 1.6% (4 of 245) of women in the WBRT group ($p = \text{NS}$).

There was a nonsignificant trend toward an increased incidence of postoperative infections in patients undergoing MammoSite brachytherapy: 7% (5 of 71) compared with 3.7% (9 of 245) of patients receiving whole breast irradiation. None of the MammoSite patients who developed an infection, however, went on to develop palpable masses requiring biopsy.

Telangiectasias more frequently developed in patients in the MammoSite group than in the WBRT group (24% vs 4%, $p < 0.001$) (Table 2). Overall, 42% of the patients in the MammoSite group and 9% of the WBRT group developed either a palpable mass at the lumpectomy site or telangiectasias.

DISCUSSION

The National Surgical Adjuvant Breast Project (NSABP) B06 trial noted a 39% incidence of local recurrence at 20 years in women undergoing surgery alone compared with a 14%

recurrence in women treated with partial mastectomy and WBRT.² Similarly, Veronesi and colleagues³ documented the safety of breast conserving surgery with adjuvant radiation therapy in comparison to mastectomy. Based on a meta-analysis from the Early Breast Cancer Trialists Collaborative Group, the improvement in local control afforded by radiation translated to a survival benefit. This analysis looked at 7,300 women enrolled in trials of BCT from 1995 to 2004, who were treated with and without radiation therapy. In aggregate, the 15-year breast cancer mortality was significantly lower in the women who underwent adjuvant irradiation compared with those treated with partial mastectomy alone. Five-year local recurrence risks (nearly all recurrences were in breast) were 7% vs 26% (reduction 19%) in the irradiated vs the nonirradiated group, and 15-year breast cancer mortality risks were 30.5% vs 35.9% (reduction 5.4%, SE 1.7, 2, $p = 0.0002$).⁴ As a result of these findings, BCT with partial mastectomy and adjuvant radiation therapy has become a mainstay of treatment for women with resectable breast cancer.

Due to the cost and inconvenience of 6 weeks of radiation, novel techniques of APBI have emerged as an alternative to the more traditionally administered whole breast radiation. The majority of local recurrences after BCT occur within 1 to 2 cm of the original tumor.^{5,6} Based on this observation, APBI techniques were developed to treat the tumor bed with a 1- to 2-cm margin rather than the whole breast. Partial breast irradiation delivers radiation to the highest risk area of the breast while sparing unaffected tissue. The total dosage is lower (typically 34 Gy compared with 50 to 60 Gy) and is delivered in fewer fractions (10 total at 2 fractions/day compared with 33 fractions, 1/day). There are several potential advantages that APBI offers patients including reduced travel time to radiation therapy, a lower dose of total radiation to the heart and lungs, and a high patient-reported quality of life after treatment.⁷⁻¹⁰

Several delivery methods of APBI have developed in the last 10 years. These include interstitial brachytherapy, intraoperative radiotherapy, intracavitary brachytherapy, conformal external beam radiotherapy, and intensity modulated radiotherapy. The Food and Drug Administration approved the MammoSite catheter for breast brachytherapy in May 2002. Several nonrandomized clinical trials with short-term follow-up demonstrated that MammoSite brachytherapy results in rates of local recurrence and acute toxicity that are comparable to those seen in patients receiving WBRT.^{9,11-13} A more complete understanding of the immediate and long-term results of APBI must be garnered, particularly in light of the increasing adoption of this technique. From 2000 to 2007, APBI use increased 1,600% and current estimates suggest that 7% of women in the United States undergoing BCT are treated with APBI via an implantable device.¹⁴ This study reports long-term complication rates in a nonrandomized single institutional experience with the MammoSite breast brachytherapy catheter treatment in patients with early-stage breast cancer.

Data on recurrence and long-term complications of MammoSite brachytherapy, such as palpable masses and telangiectasias, are accumulating (Table 3). Although the initial American Society of Breast Surgeons Registry Trial¹⁵ reported a low incidence of masses at the lumpectomy site (2%) in short-term follow-up, investigators in this trial did not track development of a palpable mass as a long-term (6-year) toxicity. Because this was not an endpoint in this trial, the incidence of mass formation over time is unknown in this large trial of 1,499 women.¹⁶ More recent studies, such as that by Monticciolo and colleagues¹⁷ and our study, with longer follow-up, found that approximately one-quarter of patients developed a mass at the lumpectomy site.

The APBI was delivered in our study in accordance with American Society for Radiation Oncology (ASTRO) guidelines using the same technical specifications implemented by

investigators in these other reports. All MammoSite treatments were performed by 1 radiation oncologist (KU) with specialty training in brachytherapy, making it unlikely that differences in the incidence of masses at the lumpectomy site in this study were due to technical discrepancies in the delivery of radiation to our patients. Only 1 of the core biopsies in our study revealed a seroma, and only 2 of the core biopsies were performed in the first year after surgery; these findings refute the potential argument that the high incidence of mass formation in this study results from overaggressive management of early postoperative changes like seroma or hematoma. As shown in Figure 1, nearly half of the core biopsies we performed were precipitated by new or enlarging masses at the lumpectomy site detected more than 3 years after initial treatment. We suspect that the observed higher incidence of masses at the lumpectomy site reflects the longer follow-up in this study in comparison to other similar studies.

Our threshold to perform a core biopsy was comparable between the MammoSite and WBRT groups and was based on the level of clinical suspicion of local recurrence. Approximately two-thirds of our patients with described masses underwent core biopsy; the masses in the other one-third of patients were documented as unchanged with normal imaging and were therefore followed closely on clinical breast examination. In both patient cohorts a rather high proportion of the core biopsies (6 of 24, 25%) revealed recurrent cancer (Table 2). Although most of the core biopsies in the MammoSite group revealed fibrosis and fat necrosis, the finding of cancer in 17% (2 of 12) of the biopsies supports the decision to do a biopsy in any patients treated with Mammo-Site who develop a new mass at the lumpectomy site.

Telangiectasia of the skin of the breast was also commonly found in our patients (24%). This complication has also been reported by others to occur in 10% to 40% of patients undergoing MammoSite brachytherapy (Table 3). Because higher rates of telangiectasias have been reported in patients whose balloon-to-skin distance was less than 7 mm, we were careful to ensure that this distance was greater than 7 mm in all patients.¹²

Our study demonstrates that palpable masses and telangiectasias at the lumpectomy site are common events in patients after MammoSite brachytherapy. Overall, 42% of our patients receiving MammoSite brachytherapy developed a long-term complication of therapy (mass or telangiectasia or both). When we compared these patients with a well matched control group of patients treated by the same surgeons and radiation oncologists during the same time period, we observed that these complications developed significantly more frequently in women treated with MammoSite than in women who received WBRT.

The development of masses and telangiectasias after BCT and radiation therapy are adverse events. Telangiectasias are unsightly. Masses at the biopsy site are emotionally stressful to patients and often mandate the pain and expense of core biopsy. Even if proven benign, some palpable masses also cause chronic pain.¹⁵

Further institutional experience and randomized clinical trials are needed to determine the long-term safety and efficacy of MammoSite brachytherapy. Additionally, as newer techniques have developed for APBI, they need to be carefully evaluated regarding short, intermediate, and long-term potential risk. A multicenter randomized clinical trial sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP)/Radiation Therapy Oncology Group (RTOG) is underway comparing whole breast radiation therapy to partial breast radiation therapy in women who have undergone surgery for ductal carcinoma in situ or stage I or stage II breast cancer. The primary endpoint in this study is in breast tumor recurrence. Secondary endpoints include toxicity. This study began accrual in 2005 and is expected to reach a primary endpoint in 2015.¹⁸ Until this prospective, randomized trial

reports, the increased rate of long-term local toxicity found in our institution's experience with MammoSite brachytherapy should be considered when counseling women on options for adjuvant radiation therapy after breast-conserving surgery.

Abbreviations and Acronyms

APBI	accelerated partial breast irradiation
BCT	breast conservation therapy
WBRT	whole breast radiation therapy

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Figure 1.
Time to biopsy of palpable mass.

Table 1

Patient Characteristics

Characteristic	MammoSite	Whole breast radiation
n	71	245
Mean age, y (range)	63.9 (46–86)	63.4 (46–88)
Mean tumor size, cm	1.1	1.2
Estrogen receptor (ER) or progesterone receptor (PR) positive, %	91.6	93.8
ER/PR+ patients who received adjuvant hormonal therapy, %	81.5	94.5
Adjuvant chemotherapy, %	8.5	13.4
Median follow-up, y (range)	4.2 (0.9–7.2)	4.0 (1–8.1)

Table 2

Long-Term Complications

Complication	MammoSite APBI		WBRT		p Value
	n	%	n	%	
Patients developed a palpable mass	19/71	26.7	18/245	7.3	<0.001
Palpable masses biopsied	12/19	63	12/18	67	NS
Patients with palpable masses undergoing biopsy	12/71	16.9	12/245	4.9	0.02
Patients with local recurrence	2/71	2.8	4/245	1.6	NS
Patients with ipsilateral in-breast recurrence	3/71	4.2	5/245	2.0	NS
Patients developing telangiectasia	17/71	24	10/245	4	<0.001

APBI, accelerated partial breast irradiation; WBRT, whole breast radiation therapy.

Table 3

Long-Term Complications of MammoSite: A Literature Review

First author	Mass on examination requiring biopsy			Mass on examination			Telangiectasia			Local recurrence			Follow-up, mo
	n	n	%	n	n	%	n	n	%	n	n	%	
Kahn ¹⁶	1,449	5	0.3	30	2	9.3	141	9.7	NR	25	1.7	38	
Benitez ¹³	43	NR		4	9.3	NR	17	39.5	NR	0		65	
Chao ¹⁹	80	NR		7	8.8	NR	NR		NR	2	2.5	22	
Monticciolo ¹⁷	97	8	8	23	24	NR	3	3	NR	1	1	NR	
Current study	71	12	17	19	27	17	24	3	4.2	2	2.8	50	