Breast Conserving Surgery and Accelerated Partial Breast Irradiation Using the MammoSite System

Initial Clinical Experience

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Hypothesis: Balloon catheter–based accelerated partial breast irradiation (APBI) may result in desirable short-term outcomes in patients undergoing breast conserving surgery.

Design: Prospective consecutive case series.

Setting: Tertiary multidisciplinary referral center.

Patients: Forty selected patients with invasive breast carcinoma undergoing breast conserving surgery and MammoSite device placement.

Interventions: Breast conserving surgery, sentinel and/or axillary node dissection, placement of the new balloon catheter applicator (MammoSite device), and APBI.

Main Outcome Measures: Infection, early and late seroma, device explantation, time to initiating APBI, acute toxic effects on the skin, and cosmesis using the Harvard Scale.

Results: Thirty-nine patients underwent MammoSite device placement at the time of lumpectomy; 1 patient underwent percutaneous device placement after lumpectomy. Nineteen patients (49%) had drainage catheters placed in the breast cavity at the time of lumpectomy. Wound infection developed in 3 patients (8%). Five devices (12%) were explanted because of unfavorable final pathological findings or infection. The mean time to the start of APBI in patients who did not undergo simultaneous drain placement was 7.2 days (range, 5-12 days), compared with 5.1 days (range, 3-8 days) in patients who did (P=.008). With a mean follow-up of 13.3 months (range, 2-28 months), patients completing APBI had limited toxic effects on the skin, with excellent or good cosmetic results in 39 patients (97%).

Conclusions: Use of the MammoSite system in APBI has favorable short-term outcomes. Infection and radiation treatment delay are common and may warrant use of perioperative antibiotics and drain placement, respectively. A small number of patients who have device placement at the time of lumpectomy will require explantation because of unfavorable final pathological findings. Short-term outcomes of MammoSite brachytherapy support further studies comparing APBI with standard whole breast irradiation in patients undergoing breast conserving surgery.

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STANDARD BREAST CONSERVATION therapy for cancer consists of breast conserving surgery (BCS) to excise the cancer with adequate margins, followed by postoperative external beam whole breast irradiation (WBI) targeting the entire breast. Evidence from randomized controlled trials and retrospective studies has shown that long-term survival after BCS and radiation therapy is equivalent to survival after mastectomy.1-6 However, only 60% to 66% of women who undergo BCS actually undergo radiation treatment.7,8 This may be a result of the inconvenience of 5 to 6 weeks of daily radiation treatments and the difficulty of traveling long distances to treatment facilities.9-11 As a result, there is growing interest in providing shorter treatment courses and more limited radiation techniques for women at risk for tumor recurrence.

Accelerated partial breast irradiation (APBI), typically performed as standard interstitial brachytherapy using indwelling needles, may improve patient compliance with radiation therapy after BCS. However, standard multicatheter brachytherapy has the disadvantages of a steep technical learning curve, few clinicians who are familiar with the technique, and an appearance that patients may find disturbing and “barbaric.”12 Additional methods of APBI that are being investigated in-

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include intraoperative radiation therapy, using a mobile linear accelerator or low-energy x-rays, and 3-dimensional conformal external beam radiation. Recently, intracavitary APBI using a new balloon catheter applicator called the MammoSite (MammoSite RTS; Proxima Therapeutics Inc, Alpharetta, Ga) has been explored and shown to deliver radiation successfully during 5 to 7 elapsed days, in addition to being easy to place technically and acceptable to patients.13-16

The purpose of our study was to assess short-term outcomes, complications, and technical considerations of APBI using the MammoSite device. In addition, we evaluated whether simultaneous placement of a drain in the lumpectomy cavity may optimize tissue conformity to the balloon catheter and therefore shorten the time from placement of the MammoSite device to initiation of APBI.

Generally, patients who presented to our multidisciplinary center for consideration of APBI using the MammoSite device had the following indications: a contraindication to WBI, a strong personal preference for using this approach, or, later in the study, tumors that appeared highly favorable for inclusion on the basis of imaging and initial histopathologic findings obtained by means of core needle biopsy in older patients.

With the exception of patients who had a contraindication to WBI, for whom selection criteria were somewhat less strict, patients undergoing BCS for invasive cancer were considered for APBI using the MammoSite device only if the following specific minimum criteria were met: tumor size of 2 cm or less, negative surgical margins, age of 43 years or younger, and N0 node status. Patients were excluded under the following circumstances: noninvasive carcinoma, lobular carcinoma, presence of an extensive intraductal component (>25% of the primary tumor consisted of intraductal carcinoma), known distant metastases, and a distance from the lumpectomy cavity edge to the skin surface of less than 5 mm. These criteria were identical to those of the original US Food and Drug Administration MammoSite clinical study13 and similar to those advised in a consensus statement on APBI (Table 1) written by the American Society of Breast Surgeons.17

The patients who were initially considered for APBI on the basis of favorable primary tumor characteristics had to meet stricter inclusion criteria. These included being postmenopausal, having well-circumscribed tumors that measured less than 1.5 cm on preoperative imaging, and having core biopsy findings that demonstrated histopathologic grades of 1 or 2 and positive expression of estrogen receptors (ERs).

Patients selected for treatment underwent BCS with sentinel node biopsy and/or axillary node dissection after informed consent was obtained. All patients were specifically and explicitly informed that the efficacy of this form of radiation therapy has not been established. Patients who had a contraindication to WBI were specifically informed that the standard treatment in that setting is mastectomy. None of the patients in this study were enrolled in a device registry. This study was approved by the institutional review board.

Preoperative imaging included mammography and ultrasonography in all cases; breast magnetic resonance imaging was not obtained in any patient. All patients underwent lumpectomy with the intent to obtain clear surgical margins; generally, if the surgical margin was less than 2 mm, reexcision was performed. The device was placed at the time of initial lumpectomy, at reexcision, or after the lumpectomy via a percutaneous approach with ultrasound guidance. If the device was placed intraoperatively, it was inserted into the lumpectomy cavity, with the lumpectomy incision still open, after being tunneled through a small counterincision. Breast parenchyma was then reapproximated with suture to help ensure the cavity was a spherical shape that would conform well to the balloon. The balloon was inflated with 30 to 70 mL of an isotonic sodium chloride solution–contrast mixture, depending on the size of the resected specimen as determined by the surgeon. Metallic clips were not placed in the lumpectomy cavity. Skin was excised if necessary, and the subcutaneous fat and skin were closed in layers to ensure a balloon-to-skin thickness of approximately 1 cm.

In the initial part of the study, drains were not placed in the lumpectomy cavity at the time of surgery. Later in the study, drain placement was undertaken at the request of the radiation oncologist, and then was at the discretion of the attending surgeon. Drains used included 5F infant feeding tubes and small round or flat closed-suction silicone drains; these were placed immediately adjacent to the device balloon in the lumpectomy cavity, at the time of the initial lumpectomy, and secured to the device externally.

Three to 4 days after BCS, the patient underwent evaluation by computed tomography, and the final pathological findings were reviewed. After verifying appropriate dosimetry, a minimum balloon-to-skin distance of 5 mm, tissue conformance, and absence of an air pocket or a seroma, intracavitary APBI was administered twice daily using high-dose iridium Ir 192. Treatment was prescribed 1 cm from the surface of the device balloon and delivered in fractions of 340 rad (3.4 Gy) given in the course of 3 days for a total dose of 3400 rad (34 Gy). A minimum of 6 hours elapsed between treatments. If an air pocket or seroma was present at initial computed tomography, treatment was delayed until resolution, as verified by repeat computed tomography 1 to 2 days after the initial scan was obtained. Alternatively, an attempt was made to aspirate the air or fluid percutaneously with ultrasound guidance. Accelerated partial breast irradiation was the only radiation therapy administered.

All patients completing APBI underwent evaluation by the primary surgeon 7 to 10 days after the operation, and then at 6-month intervals. Patients were examined by the treating radiation oncologist during treatment, at 2 and 8 weeks after APBI (at which times acute toxic effects on the skin were evaluated and graded), and thereafter at 6-month intervals.

Table 1. Consensus Statement on APBI Written by the American Society of Breast Surgeons

| The published data on APBI are not extensive or definitive; it is preferable that APBI be performed as part of ongoing investigative protocols. | Patients should be carefully selected for APBI and should be adequately trained. |
| Surgeons and radiation oncologists using APBI techniques should be well trained. | The following selection criteria should be used when considering patients for APBI instead of whole breast irradiation: |
| Age $\geq 50$ y | Invasive ductal carcinoma or ductal carcinoma in situ |
| Tumor size $\leq 2$ cm | Microscopically negative surgical margins |
| Node-negative disease (axillary/sentinel lymph nodes) | Treating physicians should follow up all patients closely to identify adverse events as well as local disease recurrence |

Abbreviation: APBI, accelerated partial breast irradiation.
The main outcome measures analyzed included complications, incidence of infection, development of early and late seroma, device explantation, total treatment times, and time to the start of radiation treatment. Additional short-term outcomes recorded were acute toxic effects on the skin, graded according to Radiation Therapy Oncology Group (RTOG) guidelines,15 and cosmesis using the Harvard Scale. Long-term outcomes, although not the focus of this study, included the development of ipsilateral breast tumor recurrence, development of distant metastases, and death.

To calculate the lumpectomy excision volumes, 3 dimensions measured at the specimen axis (width, length, and height) were required. Because it has been demonstrated that simple calculation of width × length × height can overestimate the true volume of breast lesions, the excision volume was calculated using the formula \(\frac{4}{3} \pi r^3\) for an ellipsoid volume, with \(r^3\) defined as the radius of the width multiplied by the radius of the length multiplied by the radius of the height.19

The means between the group of patients who underwent simultaneous drain placement vs those who did not undergo drain placement were compared using a 2-tailed \(t\) test, with \(\alpha = .05\). Linear regression was used to test the effect of excision volume on time to the initiation of APBI.

## RESULTS

Forty women underwent BCS and APBI from June 1, 2002, to January 31, 2005. Three surgeons performed the procedures; almost half (19 procedures [48%]) were performed by the senior author (L.A.D.). All radiation treatment was performed at a single center; 33 (82%) of the treated patients underwent evaluation and were followed up by a single radiation oncologist (M.C.R.), and all treatment planning was overseen by 2 senior radiation oncologists (M.C.R. and M.T.). Additional radiation oncologists covered individual treatment sessions as necessary. The mean patient age was 65 years (range, 49-82 years). The mean primary tumor size was 1.2 cm (range, 0.6-2.8 cm). Most cancers were invasive ductal carcinoma; 33 tumors (82%) were positive for ERs; and 32 (80%) were Bloom-Richardson grade 1 or 2. Thirty-three cancers (83%) were node negative (Table 2). All patients had negative surgical margins; 25 (62%) had margins of 1 cm or more, and 37 (92%) had margins of 2 mm or more. Twenty-seven patients (68%) received some form of adjuvant systemic therapy. Twenty patients (50%) underwent hormonal therapy only; 7 patients (18%) underwent systemic chemotherapy.

The indications for MammoSite device placement were patient preference in 18 cases (45%), primary tumors with favorable imaging and initial histopathologic findings in 13 (32%), and a contraindication to WBI in 9 (22%). Two thirds of patients who had a contraindication to WBI had substantial lung disease, and it was believed that even a small loss of pulmonary function could not be tolerated. The remaining patients had undergone previous lung radiation therapy or radiation therapy for Hodgkin disease and expressed a strong preference for BCS over mastectomy. Patients who initially preferred to undergo APBI using the MammoSite device or who initially had favorable-appearing tumors but later had final pathological findings consistent with an unfavorable tumor (size >2 cm, histopathologic grade 3, node-positive disease, and negative ER findings) were advised to undergo WBI. Some patients who ultimately had less favorable tumors were advised to undergo WBI or mastectomy but refused to do so and proceeded with APBI.

Thirty-nine patients (98%) underwent operative placement of the device at the time of lumpectomy; the remaining patient had successful percutaneous placement under ultrasound guidance. Four patients (10%) had the device placed at a reexcision lumpectomy, including 1 patient who underwent an unsuccessful attempt at percutaneous placement. The mean fill volume used in the device balloon was 55.3 mL (median, 60 mL; range, 30-70 mL). In 12 cases (30%), an ellipse of skin was excised to help obtain a negative surgical margin and maintain a balloon-to-skin distance of at least 5 mm. The mean distance between the device balloon and breast skin was 9.6 mm (median, 10 mm; range, 5-50 mm). The balloon-to-skin distance was 5 to 7 mm in 15 cases (38%), 8 to 10 mm in 17 (42%), and more than 10 mm in 8 (20%).

In 19 (49%) of 39 cases, drainage catheters were placed adjacent to the device to prevent or to treat a seroma or an air pocket. The mean specimen volume excised by lumpectomy was 57.7 cm³ (range, 14.1-164.0 cm³). There was no difference in mean specimen volume between patients who underwent drain placement (mean, 58.7 cm³; range, 21.9-164.0 cm³) and patients who did not (mean, 55.9 cm³; range, 14.1-107.0 cm³) (\(P = .17\)).

## Table 2. Patient and Tumor Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>65 (49-82)</td>
</tr>
<tr>
<td>Mean tumor size (range), cm</td>
<td>1.2 (0.6-2.8)</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>2 (5)</td>
</tr>
<tr>
<td>T1b</td>
<td>14 (35)</td>
</tr>
<tr>
<td>T1c</td>
<td>21 (52)</td>
</tr>
<tr>
<td>T2</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Node stage</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>33 (82)</td>
</tr>
<tr>
<td>N1</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Metastatic stage</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>40 (100)</td>
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<tr>
<td>Tumor grade†</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (58)</td>
</tr>
<tr>
<td>2</td>
<td>9 (22)</td>
</tr>
<tr>
<td>3</td>
<td>7 (18)</td>
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<tr>
<td>Hormone receptor status</td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>33 (82)</td>
</tr>
<tr>
<td>ER−</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>37 (92)</td>
</tr>
<tr>
<td>Invasive mammary carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: ER−, negative findings for estrogen receptor; ER+, positive findings for estrogen receptor.

*Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

†One patient with a metaplastic carcinoma did not have a tumor grade assigned.
Thirty-five patients (88%) were able to complete APBI using the MammoSite system. Five (12%) of the 40 devices were explanted before radiation therapy, including 2 (5%) because of unfavorable final pathological findings (specifically, tumor-positive nodes), 2 (5%) because of diffusely involved margins despite attempts at reexcision, and 1 (2%) because of severe cellulitis that required hospitalization and intravenous antibiotics. Three of these patients ultimately underwent standard WBI; 2 patients had a mastectomy. Two devices (5%) were displaced after the balloon spontaneously burst, but the devices were replaced and brachytherapy was successfully completed. No patient required device explantation as a result of a balloon-to-skin distance of less than 5 mm.

In patients who underwent surgical device placement and completed treatment, the mean time to the start of APBI after device placement was 6.1 days (range, 3-12 days); the mean total time from MammoSite implantation to explantation at the completion of radiation therapy was 11.7 days (range, 9-18 days). The mean time to the start of APBI in the 17 patients who did not undergo simultaneous drain placement and who completed APBI was 7.2 days (range, 5-12 days). This was significantly longer than the mean time to the start of APBI in those 17 patients who had drains placed at the original operation and who completed brachytherapy (5.1 days; range, 3-8 days; \( P = .008 \)). In addition, the total time the device was in place was 12.7 days (range, 10-18 days) in the group without drains vs 10.7 days (range, 9-13 days) in the group with drain placement \( (P = .008) \).

Nine (26%) of the 34 patients who had surgical placement of the device and who completed APBI had an excision volume greater than that of the device balloon. The mean time to the start of APBI in this group was 7.1 days, which was not significantly different from the mean time to the start of APBI in the group of patients who had an excision volume of less than 70 cm\(^3\) (5.8 days; \( P = .41 \)). Based on linear regression analysis, there was no correlation between excision volume and time to the start of radiation treatment.

Two (12%) of the 16 patients who did not undergo initial drain placement required ultrasound-guided aspiration of a seroma in an attempt to improve tissue conformance and proceed with radiation treatment. In 1 case, the device balloon was punctured by the aspiration needle, and the device was successfully replaced. In both cases, there was a significant delay before the initiation of radiation treatment and a prolonged total time that the device was in place.

Three patients (7.5%) had infectious complications, including 1 with an infected postradiation seroma requiring drainage and prolonged antibiotic treatment. This particular patient required ultrasound-guided aspiration of a postlumpectomy seroma to start APBI, and had the balloon punctured and the device replaced. A severe breast cellulitis developed in 1 patient within days of the operation, with treatment by hospital admission, intravenous antibiotics, and immediate explantation of the device before starting brachytherapy; this patient received WBI after the cellulitis resolved.

Toxic effects on the skin occurred in 13 (37%) of 35 patients completing APBI; most of these had hyperpigmentation and/or dry desquamation (RTOG grade 1), but patchy moist desquamation (RTOG grade 2) developed in 3 (9%). There were no grade 3 or 4 toxic effects, and no skin necrosis developed after brachytherapy. A late seroma that was symptomatic and required aspiration or drainage developed in 4 patients (11%).

In the 30 patients who completed APBI and had a minimum of 6 months of follow-up, most patients had an excellent (14 patients [47%]) or a good (15 patients [50%]) cosmetic result based on the Harvard Scale. Only 1 patient (3%) was rated as having a fair result, and no patients were rated as having poor results. There was no correlation between balloon-to-skin thickness and cosmesis.

With respect to longer-term outcomes that were based on a mean follow-up of 13.3 months (median, 14 months; range, 2-28 months), no ipsilateral breast recurrences developed in any of the 35 treated patients. Brain metastases developed in 2 patients (6%), and one of those patients died 23 months after the initial operation. Both patients had unfavorable tumors: in one case, the patient had a 3-cm, node-positive cancer and a history of radiation therapy for lung cancer; in the other, the patient had a 1.5-cm, node-negative, ER-negative cancer with a histopathologic grade of 3.

**COMMENT**

Breast-conserving surgery followed by WBI is currently the standard of care for patients undergoing breast conservation therapy for cancer. It is well established that the frequency of ipsilateral breast tumor recurrence for patients who undergo lumpectomy without postoperative radiation therapy ranges from 10% to more than 30% at 5 years.\(^{1,20-23}\) Despite this, 14% to 40% of women who initially opt for BCS rather than mastectomy do not undergo postoperative radiation therapy.\(^{7,8,10,24,25}\)

As a result of the significant number of patients who do not complete appropriate radiation therapy after BCS, many clinicians believe APBI may increase the use of radiation therapy by providing better patient acceptance secondary to more rapid and focused treatment. In addition, APBI may offer further advantages, including the potential for breast preservation after local tumor recurrence, the completion of all local therapy before initiation of systemic therapy, and decreased costs.

The MammoSite device was approved by the US Food and Drug Administration in May 2002 to provide intracavitary brachytherapy in patients undergoing lumpectomy for breast carcinoma. Edmundson et al\(^{26}\) and Keisch et al\(^{27}\) were among the first to report their early clinical experience with the MammoSite device. In their studies of 12 and 70 patients, respectively, they showed that device placement was easily and reproducibly undertaken, with a short learning curve. However, in both studies, balloon-to-skin distance and tissue conformance limited the applicability of the device, such that only 75% and 61% of their patients, respectively, were able to complete APBI. Since then, additional studies\(^{14-16,27}\) have refined technical factors and increased the percentage of patients able to successfully undergo APBI using the MammoSite device.
Our study confirms the findings of those studies and suggests that drain use may shorten the time to the start of radiation treatment, thereby allowing even more rapid completion of local therapy for the patient with breast cancer. The simultaneous placement of a drainage catheter in the lumpectomy cavity resulted in a 2-day reduction in mean time to the start of radiation therapy. The presence of the drain improved conformance of the balloon catheter to the surrounding tissue by eliminating a seroma and/or an air pocket. In our current practice we routinely place a small, round, closed-suction drain with every device placement and have found that most patients are able to start treatment 3 days after BCS.

A vexing problem associated with the MammoSite device is the concern that patients with larger volumes of excision may be ineligible to undergo balloon catheter-based APBI. Theoretically, a larger volume of excision, particularly an excision volume larger than the maximal balloon fill volume, could result in a larger air pocket or seroma and impaired conformance. Pawlik et al. analyzed the volume of resection in 445 patients undergoing BCS to determine what percentage of patients would be eligible for MammoSite APBI based on the patient selection guidelines of the American Society of Breast Surgeons. Only half of eligible patients were deemed candidates for balloon catheter brachytherapy based on the use of a 70-cm³ device. Edmundson et al. suggested that MammoSite brachytherapy could be used effectively only if the lumpectomy excision volume was 50 cm³ or less.

In the present study, one quarter of the patients had excision volumes greater than that of the device balloon. We found no correlation between the volume of excision and the time to the start of radiation therapy, suggesting that the lumpectomy cavity shrinks with time or that the presence of a drain helps improve tissue conformance despite a volume of excision larger than that of the device balloon. However, it is also possible that folds of breast parenchyma are created by drain suction as the cavity rapidly collapses, and that such folds could affect the internal structure of the cavity and thereby alter dose distribution to the surrounding tissue. To improve tissue conformance further and to increase the number of patients eligible for MammoSite treatment, the device manufacturer has developed a larger spherical catheter and a catheter with an ellipsoidal balloon. Future study will be required to better evaluate the relationship between maximal excision volume, tissue conformance, and time to the start of APBI using the MammoSite device.

Five patients in our study required explantation of the device, primarily as a result of unfavorable final pathological findings. With the exception of patients who had contraindications to WBI, our final selection criteria were fairly strict and, therefore, patients with node-positive disease were advised to convert to WBI. Had node-positive disease been acceptable in this study, the number of patients requiring device removal as a result of unfavorable final pathological findings would have been limited to those subjects with tumor-involved surgical margins. One method to circumvent this problem is to place the device after the final pathological results are obtained, via a percutaneous approach or at a second operation. The benefits of placing the device at the original lumpectomy include undergoing a single operation and anesthetic, accurate placement of the device because of the ability of the surgeon to reshape the lumpectomy cavity, and the ability to proceed rapidly to radiation treatment within days of lumpectomy. In aggregate, these benefits may outweigh the disadvantage of a small number of devices that require explantation after the lumpectomy.

The incidence of infection in this study was not different from that observed in other patients at our institution who underwent BCS for cancer, and also was not significantly different from that reported in previous studies evaluating the MammoSite device for APBI. Although this suggests that the incidence of infection is not increased by use of the device, it is noteworthy that the development of infection in the setting of the MammoSite device resulted in explantation and hospitalization in one severe case and persistent infection in another case. For this reason, it seems prudent to administer prophylactic antibiotics in the perioperative period and to pay close attention to catheter wound care as is currently advised by the device manufacturer and other authors.

CONCLUSIONS

Accelerated partial breast irradiation using the MammoSite system has reasonably favorable short-term outcomes, with limited toxic effects on the skin and good-to-excellent cosmetic results in more than 90% of patients. Infection may occur often enough and is serious enough to warrant judicious use of prophylactic perioperative antibiotics and careful device wound care. The concomitant use of a drain in the lumpectomy cavity appears to decrease the time to the start of APBI by eliminating a postoperative seroma. Use of a drain may also affect tissue conformance in cases of larger excision volume. A few patients who have device placement at the time of lumpectomy will require explantation because of unfavorable final pathological findings. We believe that the short-term procedural outcomes of MammoSite brachytherapy support further study comparing APBI with standard WBI in patients undergoing BCS, to determine critical outcomes such as local recurrence. The National Surgical Adjuvant Breast and Bowel Project (NSABP) is undertaking a phase 3 randomized study of patients with breast carcinoma who will receive WBI or partial breast irradiation. The biological rationale for APBI, as well as the findings of this study and those of previous studies addressing toxic effects, cosmesis, and local control, supports the entry of patients with breast cancer into this important trial.

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REFERENCES


Laura J. Esserman, MD, San Francisco, Calif: This very interesting paper presents the details of the clinical experience with the MammoSite system, an APBI technique.

A number of exciting advances are occurring in the field of radiation therapy, one of which is the introduction of techniques for partial breast irradiation. It has long been known from detailed pathology mapping studies from Holland and others that small foci of tumor can extend in a skip-like fashion to other quadrants of the breast. More recent data from magnetic resonance imaging also suggest that as many as 20% of patients have occult disease elsewhere in the breast. Yet, of women undergoing breast conservation with radiation, only about 10%, on average, recur. In fact, the 20-year follow-up of randomized trials of lumpectomy and radiation vs mastectomy from both the NSABP trial and the Instituto Tumori in Milan shows that 90% of early local recurrences (the first 5 years after initial treatment) occur in the same site or quadrant as the initial tumor. Later recurrences appear in other parts of the breast, but they occur at the same frequency in the contralateral breast. Molecular studies have shown that the recurrences that appear in the same quadrant are identical to the primary. These observations have fueled the interest in radiating part of the breast based on the hypothesis that the key area that needs treatment is the area within 2 cm of the tumor.

Another important driving principle for change in radiation techniques is the relative inconvenience of prolonged radiation relative to the benefit for some women. Although the literature shows that radiation therapy reduces the risk of local recurrence for all women, clearly there are some groups that benefit less than others. The Cancer and Leukemia Group B 9343 showed that women over 70 years who are taking tamoxifen or not have a small benefit, with a reduction in risk of recurrence at 5 years in the 4% range, no difference in distant disease, and not even a significant difference in the rate of mastectomy. Thus local recurrence was low and not associated with significant adverse effects. For these women, extended radiation may not be worth the benefit. For women not taking tamoxifen or aromatase inhibitors, extended therapy may be a distinct advantage. Clearly, biology is an important driver of recurrence. Another randomized trial of radiation therapy vs none in women on tamoxifen, in women 55 years and over, the Canadian trial, also published in The New England Journal of Medicine in August of 2004, showed that the difference in recurrence risk was 10% at 5 years for women with ER-negative tumors but only 2% for women with ER-positive disease. Molecular biology (expression arrays) is allowing us to better understand the types of tumors that arise and the cell
types from which they arise (luminal, basal, HER-2 driven), and how they behave. We know that the majority of tumors that arise in older women are luminal A-type tumors, but not all. So, while age is a reasonable surrogate, it may be possible in the future to be able to tailor radiation techniques to tumor type.

Partial breast irradiation in the well-behaved ER tumors (luminal A) may be sufficient to avoid 5 years of hormonal therapy.

There are 3 main types of partial breast irradiation techniques. All deliver a dose of radiation to an area around the lumpectomy cavity. Interstitial brachytherapy usually refers to the placement of a series of catheters after the lumpectomy through the lumpectomy cavity, allowing the insertion of radioactive iridium seeds through the catheters designed to deliver a dose 1 cm from the catheters. The dose of radiation is delivered over 5 days. The MammoSite technique also involves delivery of radiation over 5 days in 10 doses, but is delivered through a single point source. It requires the insertion of a balloon catheter. The center is where the radiation source is placed, and the dose is designed to deliver radiation directed to 1 cm beyond the edge of the catheter. This is why a seroma around the balloon catheter would interfere with treatment. Intraoperative radiotherapy is the third technique and it involves a single point source of radiation, but it is delivered in 1 dose at the time of operation. A round device of the appropriate size is inserted into the cavity and then [attached] to the radiation delivery device, and the time of treatment controls the dose of radiation to treat 2 cm around the cavity. Zeiss makes a portable device that is easy to use and does not require shielding. In all of the partial breast techniques, the highest dose is delivered to the perimeter of the lumpectomy cavity and rapidly falls off beyond 2 cm.

A phase 2 trial of the MammoSite technique was recently reported in the *Journal of the National Cancer Institute* by Vicini et al (2003;95:1205-1210). After 5 years of follow-up, the local recurrence was found to be 1% and not statistically different from matched-pair analysis. The current paper gives us information about how long the catheters stay in place, the infection rate, and the need to remove them. There was a 7.5% wound infection rate, and while they did not find this rate higher than in breast-conserving patients without the implant catheter, and infection required the removal of the catheter, 12% failed and were removed because of pathology or infection. This compares to about a 20% failure in the multicenter trial. In the multicenter trial MammoSite phase 2 trial (reported in *International Journal of Radiation Oncology and Biology Physics*, 2003 [Gittleman et al.†]), placement of catheters percutaneously resulted in a higher rate of treatment (90%) compared to open placement (63%), probably because of prior knowledge of the pathology report. Women had the catheters in place for 9 to 18 days. The use of drains appeared to shorten the time by 2 days.

It is important to recognize the role that economics will play in the diffusion of these technologies. Placement of the MammoSite device is reimbursed much better than placement of the intraoperative radiotherapy (IORT) device ($9000 vs $3000), and the radiotherapy fees for the 5-day treatment is the same as the external beam treatment, where the IORT device reimbursement is only 25% to 33%. Certainly the barrier to change is least for the MammoSite device, as it does not require new equipment in the operating room.

I have a few technical questions. First, the use of a drain seems to decrease the time that a device is in place, and it avoids secondary procedures to drain seromas. Drains in the setting of lumpectomy usually adversely affect cosmesis, so can you explain how they affect cosmesis, and are they removed prior to the catheter explantation? Has the long-term follow-up with drains affected cosmesis?

Second, it is possible to perform the lumpectomy and to place the device once the margins are known to be clear. Is it simpler to just warn patients that there is a 10% to 20% risk of reoperation and to place the device in an open fashion rather than plan to reoperate on everyone? Percutaneous technique does not appear to be the best solution in your study, but others report a better experience. What are the problems with percutaneous placement?

Third, should antibiotics probably be used routinely because the consequence of an infection is a lost implant? Should it be a single perioperative dose? I also have some questions about how these treatments compare and how they should be offered. Fourth, given your experience, how would you estimate the acceptability of the device relative to interstitial brachytherapy or intraoperative delivery?

Fifth, a number of randomized clinical trials are starting to compare partial breast irradiation to standard WBI. These devices are clearly ready for phase 3 randomized trials; however, easy access to partial breast irradiation will make it more difficult to complete the randomized trials. Should partial breast irradiation be offered outside of a trial? And from your experience, how should such trials be presented and which patients, if any, should be offered partial breast irradiation outside of a trial?

Finally, should there be a registry for all patients treated off trial with partial breast irradiation, and what are the key outcomes to collect?

**Jon M. Greif, MD, San Diego, Calif:** This was an excellent paper, and I very much appreciate the technical information that you presented. It is going to help us with our MammSite use. We currently limit our use of the MammSite to patients who cannot undergo WBI, eg, patients with underlying lung disease, and patients with connective tissue disorders. We are planning to participate in the NSABP-RTOG Trial, and I assume that you are also. My question is, will you continue to offer patients MammSite off of trial? If you do, will you now move to the indication that NSABP-RTOG has added to MammSite use, treatment of noninvasive cancers?

Dr Esserman asked many of the other questions I wanted to ask, but I want to put a different spin on the cost question because I think you may have an answer that is apropos to our institution, Kaiser Permanente. We don't get reimbursed more for the MammSite than for any other type of radiation therapy, and it may add to our costs of treating breast cancer patients. How does the cost of the MammSite device compare with standard radiation therapy following BCS for breast cancer?

**Dr Difronzo:** Thank you, Dr Wilson. I would like to first thank the Pacific Coast Surgical Association for the privilege of being able to present our data on early outcomes using this new brachytherapy device. I would also like to thank the discussants for their comments and insightful questions, particularly Dr Esserman for her overall comments and thoughtful questions. The questions tend to fall into 2 categories: technical questions and general concepts regarding issues of implementing new technology off trial, and so forth. I will split up the responses in this manner.

I also want to echo Dr Esserman’s comments about change. I think that what we are witnessing, and perhaps more importantly, participating in, is a paradigm shift in the way we deliver care to patients with breast cancer. Years ago, we were doing radical mastectomy with extended lymph node dissections and whatnot, and eventually that shifted to modified radical mastectomy, and that shifted then to breast conservation with WBI therapy. I think now we have the data to support looking critically at partial breast irradiation, and that this may be the shift that we are witnessing and participating in now.

Technical questions. Dr Esserman asked how the drains affect cosmesis. I was trained certain things about doing lumpectomies. One of them was to never place a drain. I had to relearn how to do a lumpectomy when I learned how to place this de-
vice. The things that I was taught were never excise skin, never place a drain, never reapproach breast parenchyma with suture, and always clip the cavity to help the radiation oncologist deliver a radiation boost. Well, all of those things you don’t do when you place this device. The manufacturer’s feeling on drainage is to let the seroma drain spontaneously via the stab incision in the breast. What you have to do is place a lot of gauze around this, and it becomes distinctly uncomfortable for the patient. Then what realistically happens is that the stab incision seals within a day or two. The seroma and air pocket accumulate. So drains placed simultaneously with the device seem to help decrease the seroma formation, or at least remove seroma as well as air.

How do they affect cosmesis? In our study it didn’t seem to affect cosmesis at all, though we don’t have long-term follow-up. In the short run, it didn’t seem to affect cosmesis, and my impression of that is that it’s the balloon that essentially starts open the cavity, so that counteracts the effect of the drain. In addition, you are getting very intense radiation over a short course that may induce a fibrosis that I think will keep these “propped open,” if you will, in the long run.

The next question was about placing the device percutaneously once the pathology is known. In our study we placed the vast majority of these at the time of the initial lumpectomy. There were 2 cases where we attempted percutaneous placement several weeks after lumpectomy. In one case we were successful, and in the second case the interventional radiologist was unsuccessful because the cavity had shrunk down and it was no longer pliable enough to accept the balloon. In that case I took the patient back to the operating room and had to actually reexcise a bit to make room for the balloon. I think that with authors who have looked at percutaneous placement, if you are going to do it right, you do it within days after lumpectomy before the cavity has a chance to shrink down. Even then, I think there are some patients whose cavities shrink very quickly, and you may still have a problem in those patients trying to get the balloon to really conform to the cavity.

There was a question about antibiotics and how we should use antibiotics. The consequences of infection can be quite significant. One patient in our study had to have the device explanted because of a serious cellulitis. Another patient had to have antibiotics for a persistent infection and finally had to have the cavity opened and drained. So the consequences are serious and, given that and given the lack of data about the use or the benefit of prophylactic antibiotics, I think we are safest at this point to use them. Our current practice is actually fairly aggressive. We use a single dose of a perioperative first-generation cephalosporin and then send patients home on an oral first-generation cephalosporin. In addition, careful catheter care seems to be helpful. We haven’t had any major infections since we instituted that policy.

As far as the larger questions go regarding broader issues like implementing new technology into practice before good randomized data support it, there were several questions regarding that. One was estimating the acceptability of the device, especially with comparison to IORT. The whole goal here is to make this easy on patients, in addition, of course, to obtaining local control, etc. The ultimate in patient acceptance is going to be IORT. That is a single dose. It’s the ultimate acceleration, if you will, and patients are under anesthesia. There are some questions about IORT, of course, and those include getting a linear accelerator into the operating room. If you are using a more accessible device that emits low-energy x-rays, there are still questions about how efficacious it will be beyond several millimeters in the breast cavity. So there are some issues with IORT that have to be worked out before we can really answer that question.

I think that this device is relatively acceptable to patients given the currently available comparisons, which are 5 to 7 weeks of WBI therapy, or multicatheter brachytherapy.

Should APBI be offered off trial? The answer is no, in my opinion. However, I think that realistically it’s already happening and going to happen more. Keep in mind that this device has been placed in about 7000 patients since it was approved by the Food and Drug Administration. Only about 1500 of those were actually registered to the American Society of Breast Surgeons APBI Registry, so the reality is it is already happening a lot. I don’t know whom it is happening in elsewhere. I can tell you whom it is happening in at our institution. It’s mainly patients with favorable tumors and so forth.

In my opinion, the patients whom we should consider offering it to off trial will be patients who have contraindications to WBI yet are committed to breast preservation. Those are patients who have had prior irradiation, for instance mantle radiation for Hodgkin’s, and underlying lung disease. Otherwise we should adhere to trying to get patients on study.

The final question Dr Esserman asked was about registry.

Yes, I think we should have a registry if we are not enrolling patients on trials. I am uncertain as to why the American Society of Breast Surgeons chose to stop accruing at 1500 patients. I think it may be beneficial to consider reopening that registry so we can keep an eye on the major outcomes, which would be things like local control, recurrence, distant failure, cosmesis, etc.

Dr Greif, I think I probably answered your question about whom we should offer this to off trial. As far as costs go, we are in the same institution, so our radiation oncologists tell us that it’s a wash: 5 to 7 weeks of radiation therapy cost about the same as this device. As far as where the money came from to pay for this device, it came from the Radiation Oncology Department. If these patients are enrolled in trials, hopefully they will be in trials like the NSABP-RTOG trial, perhaps endorsed by the American College of Surgeons Oncology Group, and that will allow others who don’t have the kind of system that we have to enroll patients freely in this study.