Early Experience With Balloon Brachytherapy for Breast Cancer

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Hypothesis: Partial-breast irradiation for carcinoma by a single source of radiation placed in the center of a balloon inserted in the lumpectomy cavity is an effective method of treating breast cancer. Previous interstitial radiation therapy using iridium seeds placed within multiple catheters has been shown to be effective but impractical and cosmetically unacceptable to women.

Design: Prospective registry study.

Setting: Three university and community hospitals.

Patients: Women 40 years and older with histologically diagnosed in situ and invasive T1 through T2 and N0 or N1 breast cancer treated with lumpectomy and axillary node sampling were invited to enter this institutional review board–approved study.

Main Outcome Measures: Evaluation of immediate and short-term complications, patients’ acceptance of the treatment, and cosmesis are reported.

Results: Of the 129 eligible patients enrolled, 112 completed the treatment. Of these, transient skin erythema was noted in 28, localized edema in 3, and skin blisters adjacent to the balloon in 9. Infection developed in 7, necessitating drainage and antibiotic administration. In 10 patients, sonographically demonstrated seromas that developed after removal of the device were aspirated percutaneously. In 4 patients, punctured or ruptured balloons had to be replaced before the treatment could be completed. Patients quickly adjusted to the breast distension caused by the balloon, and their acceptance of the procedure was good. The cosmetic outcome was rated high. There were no recurrences during this very short follow-up.

Conclusions: Our early short-term experience indicates balloon brachytherapy to be an acceptable alternative to external beam radiation for selected operable breast cancers. The 1-week treatment time allows working women and those who live at a distance from radiation centers to choose breast conservation rather than mastectomy.

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BREAST CONSERVATION therapy (BCT), defined as surgical removal of the tumor and sampling of the regional nodes followed by whole-breast irradiation, is generally considered an option for patients with operable breast cancer. Long-term follow-up reports indicate equally good results in terms of disease-free and overall survival compared with mastectomy.1,2 The major advantages of BCT compared with mastectomy are the cosmetic outcome and reduced psychological trauma to the patient. Its main disadvantages are the treatment time of 6 weeks and inconvenience of traveling, especially for older patients living in parts of the country with difficult access to a radiation therapy center. Brachytherapy, a limited irradiation of the tissue adjacent to the primary cancer, is an alternative to external beam radiation in BCT. The rationale for this approach is that 80% of breast recurrences appear at the site of the primary tumor.3,4 Conventional brachytherapy requires the insertion of up to 20 catheters with indwelling needles into the breast around the lumpectomy site. At each treatment, the needles are removed and replaced with iridium Ir 192 radioisotope seeds for approximately 15 minutes. Brachytherapy performed with the MammoSite applicator (Proxima Therapeutics, Inc, Alpharetta, Ga) allows an easier implantation for radiation delivery to the breast tissue around the lumpectomy cavity. The applicator consists of a double-lumen catheter with a balloon similar to that of a Foley catheter, which is inflated once the catheter is inserted into the lumpectomy cavity (Figure 1).

The overall objective of this study was to evaluate the safety and efficacy of the
MammoSite as the sole modality of irradiation in patients with pathological stages I and II breast cancer. The focus of this study is the safety of the device and the immediate and short-term surgical and radiation problems related to the procedure. This study was approved by the respective institutional review boards of the 3 participating medical centers.

### METHODS

From May 6, 2002, through September 15, 2003, 129 consecutive cases of histologically confirmed breast carcinoma were entered into this single-arm prospective study. The participants were women 40 years and older with pathologically diagnosed in situ and invasive ductal or lobular carcinoma (T1-T2 and N0-N1). Two of the 3 participating institutions excluded patients with positive node findings. Resection margins with negative findings were reported in all cases. Thus, of the initial 129 patients enrolled in the study, 3 patients did not have balloons implanted, 4 because of positive node findings, and 1 because of persistent positive margin findings (Figure 2). A MammoSite catheter was inserted into the lumpectomy cavity in 124 patients. However, 12 patients did not complete brachytherapy: 1 patient had positive margin; 6, closed spacing between balloon and the skin; 3, nonconformance of balloon; 1, infection; and 1, for personal reasons. The balloon was inserted into the biopsy cavity at the time of lumpectomy in 29 patients, which was the policy in the earlier phase of our experience, and at a later date (average of 1 week) in 83 patients. The main reason for this practice change was to ensure (1) clear margin of resection, (2) absence of extensive intraductal carcinoma, and (3) negative node findings in 2 of the institutions. The catheter was inserted into the lumpectomy cavity through the main incision or tunneled from a small counter-incision. Based on the size of the resected specimen, the balloon was inflated with 30 to 70 mL of isotonic sodium chloride solution (average, 48 mL) to give it a diameter of 3 to 4 cm. This was sometimes determined by means of fluid displacement when the lumpectomy specimen was immersed in a marked fluid container. Twelve other patients were withdrawn from the study for various reasons, including nonconformity of the balloon to the lumpectomy cavity or a balloon-to-skin distance of less than 5 mm on computed tomographic (CT) images before treatment (Figure 2). After appropriate dosimetry planning, brachytherapy was performed on 112 patients beginning 2 to 7 days after catheter implantation. Treatment was delivered twice a day during 5 days with a high-dose rate remote after-loader device at 340 rad (340 cGy) per fraction for a total of 10 fractions, with a minimum 6-hour interval between treatments.

### RESULTS

Treatment was completed in 112 (87%) of 129 patients. Ages ranged from 41 to 89 years (mean age, 64 years). Twelve women (11%) were premenopausal; 7 (6%), perimenopausal; and 93 (83%), postmenopausal. The tumor location was the upper outer quadrant in 55 (49%), upper inner quadrant in 11 (10%), lower outer quadrant in 11 (10%), lower inner quadrant in 7 (6%), and central in 28 (25%). The tumor characteristics were Tis in 27 (24%), T1 in 72 (64%; T1a in 16 [14%], T1b in 37 [33%], and T1c in 19 [17%]), and T2 in 13 (12%). Of the 85 patients with non-Tis disease, node status was N0 in 78 (92%), N1 in 6 (7%), and unknown in 1 patient (1%). The balloon-to-skin distance is given in the following tabulation:

<table>
<thead>
<tr>
<th>Distance, mm</th>
<th>Patients, No. (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;5</td>
<td>4 (4)</td>
</tr>
<tr>
<td>5-7</td>
<td>38 (34)</td>
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<tr>
<td>&gt;7-10</td>
<td>32 (29)</td>
</tr>
<tr>
<td>11-20</td>
<td>33 (29)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>5 (4)</td>
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</tbody>
</table>

Whole-breast irradiation has been an integral part of BCT and has yielded results equivalent to mastectomy for operable breast cancers. The practice of irradiating the entire breast was based on results of the detailed histological examination of patients with T1 through T2 breast cancers revealing residual in situ and invasive carcinoma after simulated partial mastectomy. This concept of multifocality and the implied need for whole-breast irradiation was subsequently emphasized by Holland et al. Indeed, the National Surgical Adjuvant Breast Project B-06 randomized prospective trial confirmed that at 10 years, the recurrence rate of 53% in nonirradiated breasts was significantly higher than that of 12% in irradiated breasts ($P < .001$).

A closer look at the in-breast failure pattern reveals that most (67%-100%) of the recurrences appear in the
immediate vicinity of the primary tumor.\textsuperscript{5,8-10} In addition, more recent publications on the pathological examination of lumpectomy and mastectomy specimens reveal that the microscopic foci of malignancy are within 1 cm of the primary tumor.\textsuperscript{11}

Based on these observations and reports, several investigators began to treat patients with brachytherapy alone after lumpectomy. King et al\textsuperscript{12} from the Oschner Clinic, New Orleans, La, described 50 patients treated with segmental mastectomy and interstitial brachytherapy for Tis, T1, and T2 breast cancer and compared the outcome with that of a matched group of patients treated with external beam radiation. At a median follow-up of 75 months, the 2 groups were similar for grade III toxic effects, locoregional recurrence rates, and cosmesis scores. Vicini et al\textsuperscript{13} reported 174 cases of early breast cancer managed with lumpectomy followed by radiotherapy restricted to the tumor bed using an interstitial implant. They compared the results with those of a matched series of cases from the same institution treated with external beam radiation and found no difference in terms of local recurrence, distant metastasis, and disease-free survival at 5 years.

Edmundson et al\textsuperscript{14} were first to report on the partial irradiation of the breast for carcinoma using the MammoSite device. The investigators achieved satisfactory irradiation to 1 cm of the breast tissue immediately adjacent to the balloon surface and noted that the device was easy to use. They also reported that at a minimum distance of 5 mm between the balloon surface and the skin, the latter received less than 150% of the calculated dose, which was deemed to be safe. Subsequently, Keisch et al\textsuperscript{15} used the MammoSite balloon device for brachytherapy in women with early-stage (T1 N0 M0) breast cancer who had undergone partial mastectomy. Of the 70 patients enrolled in the study, 43 (61%) completed the treatment. The main factors limiting the initial use of the device were skin-to-balloon surface distance and balloon-cavity conformance. In the present series, the completion rate was higher (87%), probably due to gained experience, but we still encountered similar complications, some of which may be resolved in the future.

**COMPLICATIONS AND SUGGESTED SOLUTIONS**

**Balloon Puncture and/or Rupture**

Early in our experience, we encountered fluid leakage from the balloon and its deflation in 4 cases. On 1 occasion, the balloon had been punctured by metallic clips inserted in the breast parenchyma at the time of lumpectomy. The operative field was reexplored, the clips were removed, and a new balloon was inserted. Clip placement practice was discontinued afterward. In another case, the inflated balloon was inadvertently punctured by a needle during closure of the incision. Since then, the balloon has been inflated to its predetermined volume after the incision is closed. Two of the balloon ruptures were spontaneous with no identifiable causes.

**Balloon-to-Skin Distance**

Close proximity of the iridium seed to the breast skin has been reported to cause skin necrosis. The minimum acceptable distance between the balloon surface and the skin as determined by CT images during prebrachytherapy simulation is generally considered to be 5 mm. In 6 cases in this series, the device was removed and the patients were treated with external beam radiation because of unacceptable skin distance. This problem is encountered when the tumor is too close to the skin or the breast is small with little subcutaneous tissue. To overcome this problem, we suggest the following solutions.

First, with tumors close to the surface, an ellipse of skin 1 to 2 cm wide immediately above the palpable anterior surface of the tumor should be removed. The subcutaneous layer is approximated with interrupted sutures while the balloon remains deflated.

Second, in most cases the maneuver described in the previous paragraph provides the minimum 5-mm distance between the outer surface of the balloon and the skin. However, in slim women when the tumor is located in the inner half of the breast (16% in this series), the goal might not be attained. In 2 cases, 1 of us (K.D.) used ultrasound guidance to temporarily increase the distance from 2 to 3 mm to 5 mm by injecting 20 mL of isotonic sodium chloride solution subcutaneously before each treatment. This process may be further facilitated by leaving a 20-gauge angiocath in the subcutaneous space for the duration of the treatment. Clearly the whole process has to be performed with strict attention to sterility. The patients cited herein completed their brachytherapy without infection but with a moderate degree of overlying erythema lasting 2 to 3 weeks.

**Infection**

Seven cases of wound infection involving the lumpectomy cavity (6%) were recorded in 112 patients treated with brachytherapy using the MammoSite device. Perioperative intravenous antibiotics were given to most but not all patients. In 1 patient, the indolent wound was eventually operatively debrided and did not completely heal until 11 months after balloon insertion, leaving an unsightly indentation in the breast. It is likely that the combination of the infection and the close balloon-to-skin distance acting in concert made the complication far more severe than it would have been with only 1 of the factors alone. Our infection rate, however, is in line with the incidence reported by other investigators.\textsuperscript{12}

Close observation of the entry point of the catheter into the breast during 10 sessions of treatment in the radiation therapy department revealed that adequate sterilization was not maintained during insertion of the iridium seed into the balloon. An externally located part of the catheter measuring 2 to 3 cm in length moved in and out of the breast when the patient changed from supine to upright positions. One of us (K.D.) has begun anchoring the catheter to the skin with 2 nonconstricting sutures in an attempt to avoid this movement. Topical antibiotics should be applied to the catheter entry point, and attention should be paid to good catheter care during the treatment week.

**OTHER ADVERSE EFFECTS**

**Skin Reactions**

With some exceptions, the following minor to moderate degrees of skin reactions lasting up to 3 months were
noted: erythema in 28 patients, edema in 3, and blisters in 9. Minimal degree of telangiectasia of the skin overlying the balloon was noted in 10% of patients. One patient who had a 5-mm balloon-to-skin distance and in whom an abscess also developed has had a chronic, slowly healing skin ulceration during a period of 10 months.

Seroma

Results of postbrachytherapy ultrasound examination in 10 patients revealed variable amounts of fluid collection (seromas) after the balloon was removed. In symptomatic cases, the fluid was aspirated in the office with ultrasound guidance.

PATIENT ACCEPTANCE AND COSMETIC EVALUATION

During the early phase of our experience, the MammoSite device was placed in the breast at the time of lumpectomy (26% in the series). This policy was changed after realizing that several patients required reexcision for positive margin findings. It was then decided to insert the device at the time of reexcision, or if the margins were reported to be clear, at a separate session (74% of cases). The procedure was performed with ultrasound guidance through a small skin incision under local anesthesia and/or sedation.

During the initial 24 hours after insertion, all patients experienced a variable degree of discomfort due to the breast distension by the balloon. However, they adjusted to this temporary discomfort and completed the 5-day course of radiation treatment.

The cosmetic result was judged primarily by the patients with input from the medical personnel during the follow-up visit 1 to 6 months after the completion of brachytherapy. Although photographs were taken to objectively compare the treated with the untreated breast, this comparison was not uniformly performed. Based on a modified Harvard Scale, the cosmesis was rated excellent/good in 80%, fair in 15%, and poor in 5%.

We concede that not all patients with operable breast cancer who may choose BCT are candidates for brachytherapy. In our series of 129 patients from 3 medical centers, 112 (87%) completed the prescribed 1 week of treatment. Compared with 6 weeks of conventional external beam radiation, the difference is a significant saving of time. However, there are still some unresolved problems. Seventeen (13%) of 129 patients who enrolled in the study were not treated (Figure 2). Four patients with axillary node metastases were excluded by 2 investigators. The rationale for this policy was based on the recommendation of the American Brachytherapy Society that such patients should be treated with whole-breast irradiation due to possible increased risk of local recurrence. In the present study, 1 investigator (K.D.) included 6 patients with positive node findings and small metastases in 1 to 3 axillary lymph nodes. All 6 patients were treated with chemotherapy after their course of brachytherapy was completed. To date, none have shown local recurrence.

In addition, 6 of 129 patients were not treated because the balloon-to-skin distance was less than 5 mm. We have suggested maneuvers that can circumvent this problem.

Of 112 patients who completed brachytherapy, the major complication was infection in 7 patients. We believe that this morbidity can be avoided by meticulous attention to catheter care in addition to the steps suggested herein.

CONCLUSIONS

We have presented the initial encouraging experience of 3 groups of surgeons and radiation therapists at 3 medical centers treating operable breast cancers with lumpectomy and brachytherapy using the MammoSite device. Based on available data, we believe that the suitable candidate for this treatment is a perimenopausal or a postmenopausal patient with a moderate to large breast and less than 3 cm of invasive or in situ tumor located in the midlateral part of the breast. Brachytherapy with the MammoSite catheter has distinct advantages compared with whole-breast irradiation, including a much shorter treatment time that enables working women and those at a distance from radiation centers to consider breast conservation. The single catheter placement is technically easier to learn and apply than the multiple catheters. The long-term results, including the incidence of local recurrence, will be the subject of future reports.

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This study was presented at the 111th Scientific Session of the Western Surgical Association; November 12, 2003; Tucson, Ariz; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

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**DISCUSSION**

John H. Donohue, MD, Rochester, Minn: Whole-breast tele-
therapy radiation administered over 5-1/2 to 6 weeks is the stan-
dard of care for women undergoing BCT. Because most in-
breast tumor recurrences occur in the vicinity of the primary tumor, recent attention has focused on the efficacy of limited field radia-
tion therapy in breast cancer patients. Several small, mostly
single-institution publications have reported 5-year results with this technique. These studies have included external beam, in-
trooperative, implant, and balloon catheter radiation therapy tech-
niques. The data reveal high local control rates with these treat-
ments, all of which were completed in less than a week. The patient acceptance and cosmetic results have generally been excellent.

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The alternative treatment techniques are the subject for a future clinical trial. I think National Surgical Adjuvant Breast Project is considering doing a large-scale clinical trial on this method of therapy.

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: I have 2 questions. If you placed a balloon at the time of lumpectomy and your pathologist returns a positive margin on permanent sections, how do you handle that? Secondly, there is a theoretical risk of seeding of the balloon tract. Has that been borne out in practice? That is, the catheter comes out through a tract. Is that tract actually radiated by the brachytherapy? In other words, presumably that is a risk that there would be seeding of that tract as the catheter comes out of the breast.

Dr Dowlatshahi: The answer to your first question is every time we had to get negative margins. If there were positive margins, the patient had to be reexcised, and that was the reason why we went from the immediate to delayed insertion of the device to make sure that we had clear margins. As for removal of the catheter, if there is no cancer in the cavity, we don't expect any seeding, and we have not given any radiation treatment to the breast subsequent to the removal of the catheter.

Norman C. Estes, MD, Peoria, Ill: Were the wound infections that you had with the intraoperative balloon placement, or were a number of those when you actually reopened the site and placed the catheter postoperatively?

Dr Dowlatshahi: No, the wound infection was noted after the radiation therapy was completed. In fact, 2 to 3 days after the completion of radiation therapy, and I don't think it had to do with the breakage of the sterile field during the time of placement.

Dr Estes: But I thought you said that you would do an excision, and then at another setting the wound was reopened and the catheter placed which is a modification of the initial technique.

Dr Dowlatshahi: The catheters were placed into the wound subsequent to the pathology report, and the infection occurred after the completion of radiation therapy.

Dr Estes: I have a long experience with brachytherapy and there is a very high infection rate, but the difference is that you don't reenter the wound. The wound infections in brachytherapy done traditionally are mainly after the radiation has been done or if you have to reenter the wound. At all costs I would try not to reenter the wound, and I wondered if that was a factor here.

Dr Dowlatshahi: Well, you do reenter the wound either by not opening it or you may go through a stab incision and place the catheter into the space.

Nora M. Hansen, MD, Santa Monica, Calif: If the catheter is placed in a delayed fashion, is it the radiologist or the surgeon who places the catheter? Can you describe the technical aspects of placing the catheter? Do you have to take the patient back to the operating room or do you use ultrasound or CT guidance to assist you with the placement of the catheter?

Dr Dowlatshahi: Surgeons insert the catheter. Ultrasound-guided catheter placement is practiced if the margins are clean. In several cases where we had positive margin, we reexcised and placed the catheter under direct vision.

Correction

Error in Text. In the article titled “Image of the Month,” published in the March issue of the ARCHIVES (2004; 139:341), the breast mass is on the left side, not the right.