Many women with early-stage breast cancer are treated with breast-conserving surgery followed by radiation. Standard whole breast external beam radiation therapy achieves the best results but is inconvenient and carries a risk of painful skin reactions. A number of methods for delivering partial breast irradiation have been developed, and usually offer improved convenience. This article describes a technique for delivering partial breast irradiation using permanent breast seed implants (PBSI) — which takes only 1 hour and requires no overnight stay in hospital — and summarizes procedures for assessing patient eligibility, seed implantation, and follow-up care. Results to date indicate good coverage of the targeted area, with excellent patient safety, tolerance and satisfaction. A registry is being formed so that the treatment can be offered to other women while results mature, especially regarding disease recurrence. Plans are under way to study PBSI in other centres and in treatment of women with ductal carcinoma in situ.

Today, due to mammography screening, a majority of women with breast cancer are diagnosed at an early stage. Treatment for many of these women includes breast-conserving surgery that removes the bulk of the tumour, followed by adjuvant irradiation for locoregional control.

This approach has been shown to achieve survival rates similar to mastectomy. Standard whole breast external beam radiation therapy (EBRT) uses tangential opposed high-energy x-ray beams delivered daily over 4 to 7 weeks. This is extremely inconvenient, interfering with a woman’s home and work life. Further, roughly 50% of patients suffer painful, acute skin reactions, varying in severity from redness to skin breakdown.

PARTIAL BREAST IRRADIATION
As 96% of breast cancer recurrences occur in the surgical cavity, the concept arose of irradiating only part of the breast, focusing on the fibrotic scar surrounding the surgical area. It was found that higher doses could be delivered at each treatment session without increasing delayed radiation toxicity, since less of the breast was irradiated. Eventually, adjuvant radiation treatment began to be delivered over a shorter period of time, a revolutionary concept called accelerated partial breast irradiation (APBI). Studies of APBI have been conducted since 1992, primarily in the U.S. Initially, iridium wires were implanted, yielding low-dose-rate (LDR) brachytherapy, with patients staying in hospital for 5 days. Later, to avoid overnight hospital stays, a high-dose-rate (HDR) brachytherapy technique using 2 HDR treatments was developed. This technique requires temporary placement of a series of catheters in and around the lumpectomy site. Planned doses of radiation are delivered through the catheters for a few minutes each morning and afternoon, usually for 4 to 5 days, providing 8 to 10 fractions. In 2003, Vicini et al reported long-term results...
on a series of 199 patients treated with this technique who were compared to another group of 199 patients receiving whole breast EBRT. The 2 groups showed similar rates of local recurrence of 1% at 5 years, sparking tremendous enthusiasm for the new method in the oncology community. Benefits included:7-9

- the treatment proceeds much faster
- the patient does not need to attend daily treatments for such a long time
- far fewer side effects because the volume treated is smaller and because the skin receives much less radiation

A number of other techniques for delivering APBI have been developed since then, including external beam conformal irradiation,10 intraoperative radiation therapy,11,12 and the MammoSite breast brachytherapy applicator.13

PERMANENT SEED IMPLANTS

Our group at Sunnybrook Health Sciences Centre pioneered the use of permanent breast seed implants (PBSI). We performed the world’s first permanent implantation of stranded radioactive seeds as the sole adjuvant radiation treatment in a courageous first volunteer patient in 2004. Subsequent patients were enrolled in a Phase I–II study evaluating the safety, tolerance and efficacy of PBSI.14 The seed implantation is achieved using ultrasound image guidance in a single 1-hour procedure. The patient is lightly sedated using intravenous propofol and a local anesthetic that lasts several hours. Patients may remain awake, and assessment has confirmed that they feel no pain.

While prostate seed implantation is a 20-year-old, well-standardized procedure, the transposition of this technique to the breast presented several technical challenges. The first was to achieve accurate seed placement in a mobile target. A stereotactic breast implantation device was developed that uses a “fiducial” 14G brachytherapy needle, lightly sanded to allow better ultrasound visualization. When implanted it hooks and immobilizes the clinical target volume. The fiducial needle is then attached to a template that guides brachytherapy needles loaded with the radioactive seeds, as shown in Figure 1 (page 10).

Radioprotection

Radiation safety was another major concern in developing PBSI, as the radioactivity is released at a shallower depth from the skin surface than in prostate brachytherapy. As the iodine-125 isotope used in prostate brachytherapy was found to be unsuitable, we researched alternative isotopes. We settled on palladium-103 seeds, which have such low energy and short half-life that even a partner who spends a lot of time very close to the implanted patient receives a very low dose of radiation, lower than the National Council on Radiation Protection and Measurements standard of 5mSv.15 As well, we tested the radiation oncologists with thermoluminescent detectors (TLD), and found them to be receiving a zero dose of radiation.

Eligibility

One of the most important safety factors for APBI is careful patient selection. Only early-stage patients with disease corresponding to Holland’s description of breast cancer with limited extent (BCLE) should receive such treatment,6 as was well summarized by Vicini et al in a recent editorial.17 To be eligible for our PBSI study and the subsequent registry phase, a patient must be at least 40 years old, and the pathology report must show early-stage (Grade I and II on the Scarf-Bloom-Richardson scale) infiltrating ductal carcinoma with a maximal diameter size of 3 cm. We do not treat lobular carcinomas with brachytherapy, because of published reports that lobular disease is more likely to be multifocal, incurring a higher rate of local recurrence if treated with partial breast radiation.17 To ensure absence of residual disease, the surgical margins must be clear, with more than 2 mm between the surgical cut and the beginning of the tumour. The cancer must be node-negative (< 3 of 10 positive lymph nodes or a negative sentinel lymph node biopsy), with no extensive intraductal components (EIC) or extensive in situ carcinoma, and no lymphovascular invasion (LVI).

In addition to eligibility by disease characteristics, the implantation must also be technically feasible. The post-surgical fluid cavity, or seroma, must be ≤ 3 cm so that the seeds will not float to undesired positions and fail to irradiate where needed. Further, we limit the total implant volume to a maximum of 100 cc. If the target volume is larger than this, we believe that EBRT is preferable because the very large number of seeds required might increase the risk of seed misplacement and also the potential radiation exposure to the public. Finally, the distance from the implanted area to the skin must be sufficient (≥ 5 mm) to avoid the possibility of radiation affecting the skin, which would negate one of the important advantages of this approach.

Preparation

Planning involves ultrasound imaging and computed tomography (CT) simulation. An ultrasound is done first to determine the feasibility of identifying and assessing the target volume, rule out a large fluid cavity and highlight potential implantation problems. Then the planned target volume is defined and calculated using CT, allowing a
The fiducial needle is inserted under ultrasound guidance into the seroma. The template is positioned and immobilized to the table.

decision about whether permanent seed implant is an option for this patient.

**Implantation**

We have developed a very specific dosimetry algorithm to optimize seed placement that will both improve radiation dose distribution and minimize the risk of “cold spots” in case of seed motion. The algorithm also ensures that we minimize the number of seeds and the number of needles used to insert them. To keep them in place, the seeds are stranded on a polyglactin copolymer suture, so motion or displacement of the seeds is less likely to create a geographical miss that puts the patient at risk of tumour recurrence.

**RESULTS TO DATE**

About half of the 144 patients enrolled in the study eventually received the seeds. Despite being eligible based on the pathology report, 77 patients did not receive the seeds because at the time of planning a large fluid cavity (in 30%) or an excessively large volume to be implanted (in 35%) was found, making the implantation technically challenging, or because they had personal issues with the treatment (25%).

**Target coverage**

The main endpoint of the study, started in May, 2004, was to assess if seed migration occurs, since this would decrease the quality of the radiation treatment. Seed migration was measured by weekly chest x-rays and CT scans performed the day of implantation and 2 months later (see Figure 2). These CT scans were used to rebuild the dose distribution and evaluate the size of the target volume receiving 100% or more (V100) of the prescribed radiation dose.

As shown in Table 1, the target coverage with PBSI is comparable to that obtained with the MammoSite system. Weed et al at William Beaumont Hospital compared HDR brachytherapy using tubes or the MammoSite system and partial breast irradiation using 3D-conformal external beam radiotherapy (3D-CRT). As expected, the coverage of the target was better with 3D-CRT, but as it entails treating a large proportion of the breast tissue (generally over half of the breast) there are concerns about long-term side effects. Coverage with MammoSite was very good, and (surprisingly) very poor with HDR brachytherapy. Patel et al reviewed these data and evaluated HDR brachytherapy using ultrasound image guidance and a larger number of catheters. This time the results for HDR were much better than those of Weed et al and even better than for the MammoSite, emphasizing once again how the individual skill of the radiation oncologist can impact on the final quality of an implant. In our series, despite the use of much smaller safety margins, our V100 showed that 86% of the target volume had received the prescribed dose, which is at least comparable to the MammoSite device. Importantly, coverage improved as we gained skill with the procedure.

**Other endpoints**

A clinical research assistant running an independent review clinic assessed skin reactions every other week for 2 months following the implantation. Also, the radiation exposure to a partner (if any) was assessed using wrist badges. The patients’ acceptance of the procedure, satisfaction and health-related quality of life were recorded using well-established questionnaires.

The study is now closed as 65 patients have undergone the procedure. Our group presented an interim analysis of 45 patients at the American Brachytherapy Society Annual Meeting in Philadelphia in May, 2006. The satisfaction rate was excellent: 25% reported being satisfied and 75% very satisfied. The acute skin tolerance to radiation was excellent with 19% of patients presenting no reaction and 57% presenting Grade I reactions according to the NCI CTC Scale 3.0. These were mainly indurations, so a combined 76% rate of good skin tolerance was noted. Grade II skin effects — mainly erythema and edema — occurred in 21% of patients. Only 3% presented a moist desquamation, which is 15-fold fewer compared to the rate seen with standard EBRT.

Another advantage of PBSI is that once the insertion scars heal, the patient has no visible or palpable evidence of the implant, unlike MammoSite or HDR brachytherapy which entail carrying percutaneous catheters for about a week.

**Disease recurrence**

The maximum followup of the present series is about 3.5 years, with a median of 2 years. So far no breast cancer recurrences have occurred. While 5–7 years will be needed...
to judge the true value of this new technique and its efficacy, these short-term results are very encouraging.

**NEXT STEPS**

We are receiving many requests for this technique from patients throughout Ontario as well as other Canadian provinces and even the U.S. and Europe. Clearly women like the idea of not going every day to the hospital for treatment. To enable us to continue to offer this treatment to eligible women during the 5–7 years needed to ascertain the long-term results in terms of local control, we are developing a registry similar to the one set up by the American Society of Breast Surgeons for the MammoSite system. The idea is to maintain our skills while the data are maturing. Patient treatment would continue for those who request it, with capture and monitoring of tolerance, quality assurance and efficiency data. If a problem develops the treatment will be halted.

We were amazed by the amount of public and media attention generated by the press release issued by our institution in September 2004. We learned how disruptive it is for a woman to go daily to a cancer centre, put on a gown, wait, and undergo treatment. It will be very worthwhile if this technique can improve the quality of life of these patients, especially those with early-stage, curable disease.

**Further research**

Once we are satisfied regarding patient tolerance and confidence of the efficacy of this technique, the hope is to expand its use to a new category of patients: those with ductal carcinoma in situ (DCIS). The prognosis is very good when DCIS presents as a single nodule. As none of these women are likely to die of cancer, it makes sense for them to avoid daily treatments and side effects, and to maximize their cosmetic outcome. Another important question is how outcomes will be when radiation oncologists in other centres perform this technique. We are presently seeking funding for a multicentre study combining both questions that would offer the treatment to DCIS patients in 4 Canadian centres: Centre Hospitalier Universitaire de Québec, the Ottawa Regional Cancer Centre, the Sunnybrook Health Sciences Centre and the Vancouver Island Centre–British Columbia Cancer Agency. Further, we are currently developing new imaging devices to allow online real-time guidance of the seed implantation and correction of suboptimal implants.

**Disclosure and acknowledgment**

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**References**


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**TABLE 1. Percentage of target volume receiving at least 100% of the prescribed dose (V100) for different techniques of accelerated partial breast irradiation**

<table>
<thead>
<tr>
<th></th>
<th>PBSI</th>
<th>MammoSite</th>
<th>HDR</th>
<th>3D-CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pignol et al</td>
<td>86%</td>
<td>76%</td>
<td>58%</td>
<td>100%</td>
</tr>
<tr>
<td>Weed et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al</td>
<td>86%</td>
<td>96%</td>
<td></td>
<td></td>
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**FIGURE 2. CT scan image after seed implantation**

The seroma is identified by the orange dots, and the radioactive seeds by the green dots. Radiation is delivered to the seroma and extends an additional 1.5 cm into the surrounding area.