Partial Breast Irradiation: **Continuing the Retreat from Halstedian Breast Cancer Management**

by Thomas B. Julian, MD, and Eleftherios P. Mamounas, MD

In Brief

In the last several years, community cancer centers and their patients with cancer have become increasingly interested in the "new" technology of partial breast irradiation. Despite the promise of this new treatment modality, important questions remain. And before partial breast irradiation can be considered in place of the "gold standard" of whole breast irradiation, large-scale randomized clinical trials must compare the clinical safety and efficacy of the two treatments. One such clinical trial—NSABP B-39/RTOG 0413—is underway now in the United States. This clinical trial (which is still enrolling) will compare whole breast irradiation vs. partial breast irradiation in 3,000 women randomly assigned to the two treatment arms, following a successful lumpectomy with clear margins.

A Paradigm Shift

During the last quarter of the 20th century, the surgical management of breast cancer went through significant evolution resulting from profound changes in the biological understanding and clinical presentation of the disease. An alternative hypothesis of tumor dissemination challenged the previously accepted Halstedian principles that had governed the surgical management of the disease up until that time, i.e., tumor dissemination in continuity or by lymphatics.[1-3] This hypothesis was subsequently supported by results from randomized trials demonstrating that the extent of surgical resection did not have significant impact on patient outcome.[4-10] Based on the results from these trials, the radical mastectomy procedures developed at the turn of the 20th century were replaced by breast conserving procedures, such as lumpectomy and quadrantectomy.

The alternative hypothesis was further supported by results from clinical trials indicating that the administration of postoperative systemic therapy significantly improved disease-free and overall survival in patients with early stage breast cancer.[11-14] As a result, systemic therapy consisting of adjuvant chemotherapy, adjuvant hormonal therapy, or both has become standard practice for the majority of patients irrespective of nodal status.[15-17] In addition to reducing the rates of distant recurrence and prolonging overall survival, systemic therapy also had a profound effect in decreasing the rates of locoregional failure after surgery (with or without radiotherapy).[4, 18-21] These findings made the adoption of less radical surgical procedures more widely acceptable.

At the turn of the 21st century, we entered a new phase in the continuing retreat from the Halstedian paradigm of breast cancer management. This new phase is marked by efforts to reduce the extent of breast irradiation and is heralded by the introduction and clinical application of partial breast irradiation (PBI). Over the past decade, PBI has been investigated extensively as a potential substitute for whole breast irradiation (WBI).[22-25]

The rationale for WBI was based on the concept that, following lumpectomy, residual microscopic disease may be present in the vicinity of the lumpectomy cavity or elsewhere in the breast. This concept is the radiotherapy equivalent of the Halsted radical mastectomy. Although widely adopted for many years, the multicentric concept of primary breast cancer has little supporting data. Moreover, recent results support the idea that following lumpectomy, additional disease in the breast is limited to a zone of 1.0 to 2.0 cm around the lumpectomy site.[26-29] Thus, clinicians hypothesized that the need to treat the breast with radiation therapy should only extend to that limit. By limiting the volume of breast that needs to be treated and by increasing the dose per fraction, significant reductions can be achieved in the total time it takes to complete the regimen. Current PBI regimens can deliver the desired total radiation dose in five days.

In addition to the above-noted biologic rationale, which mirrors that for breast conserving surgery, several other significant clinical and practical reasons support the pursuit of PBI. For example, many newly diagnosed breast cancer patients choose to avoid the six to seven weeks of WBI because of time constraints, travel inconvenience, and radiation effects, accepting instead either a mastectomy or lumpectomy without breast irradiation.[30-32] In the end, PBI provides women with an additional option that promotes the use of breast conserving surgery.

Before PBI can be considered in place of the gold standard of WBI, however, large-scale randomized clinical trials must compare the clinical safety and efficacy of the two therapies. In response, the National Cancer Institute (NCI), the National Surgical Adjuvant Breast and Bowel Project (NSABP), and the Radiation Therapy Oncology Group (RTOG) have initiated one such trial in the United States. This clinical trial, NSABP B-39/RTOG 0413, is still enrolling patients today.

Deconstructing Partial Breast Irradiation

PBI can be delivered by four basic techniques: multi-catheter brachytherapy, balloon single-catheter brachytherapy (MammoSite®), three-dimensional conformal external beam radiotherapy (3-D conformal), and intra-operative radiotherapy. In the NSABP B-39/RTOG 0413 trial, only the first three techniques are being used for PBI.

Multi-catheter brachytherapy uses implanted catheters

spaced at regular intervals surrounding the lumpectomy cavity. This procedure is performed either by a free-hand technique or with the use of a template. Multi-cathether brachytherapy was first used as a boost to WBI. Available data confirm this technique's minimal toxicity, its good-to-excellent cosmetic results, and its low rate of in-breast tumor recurrence (less than 5 percent).[22,23,25,33] Multi-catheter brachytherapy is somewhat labor intensive but generally well-tolerated by the patient. The radiation source consists of Irridium[192] seeds placed into the catheter by a high-dose radiation (HDR) device.

Experience with the MammoSite® balloon brachytherapy catheter has been more recent. The device was approved by the U.S. Food and Drug Administration (FDA) in May of 2002, following a Phase I/II trial that demonstrated excellent safety and toxicity results.[34] To date, more than 12,000 catheters have been implanted, and results from a registry of more than 1,500 patients compiled by the American Society of Breast Surgeons have been published.[35] These results demonstrate reliable technical reproducibility between institutions, 92.5 percent good-to-excellent cosmetic results, and low toxicity rates. Available in two shapes and sizes, the device can be placed either at the time of lumpectomy or after lumpectomy when pathology results are known. Placement of the device is more user-friendly than that of the multiple brachytherapy catheters but still requires training. A margin of at least 7.0 mm from the balloon surface to the skin is preferred to minimize skin toxicity. The single channel is readily accessible for Irridium[192] seed placement via an HDR device on a twice-a-day schedule for five days.

A natural evolution from WBI, 3-D conformal external beam PBI provides a noninvasive, uniform dose treatment with fewer potential side effects. This technique requires CT-guided 3-D treatment planning hardware and software and the use of a linear accelerator. Several published reports have validated the feasibility of this technique.[36,37] A recent presentation of the RTOG 0319 3-D conformal study at the 2004 San Antonio Breast Cancer Symposium verified the reproducibility and low toxicity of 3-D conformal external beam PBI in multiple institutions.[38]

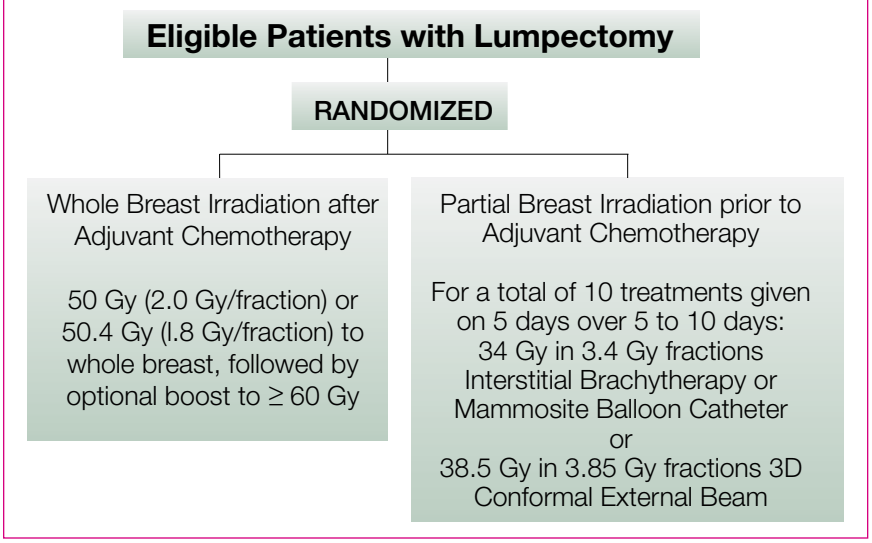
The NSABP B-39/RTOG 0413 Trial

Today, PBI is offered in many cancer centers in lieu of WBI—even though data to support its long-term equivalence to WBI is not available. For this reason, it is important that trials, such as the NSABP B-39/RTOG 0413 trial in the U.S. and others like it, be completed so that this question can be answered quickly.

The NSABP B-39/RTOG 0413 clinical trial will compare WBI vs. PBI in 3,000 women randomly assigned to the two treatment arms, following a successful lumpectomy with clear margins. (See Figure 1.) Patients with invasive or noninvasive breast cancer and with 0-3 positive lymph nodes will be eligible for this trial. WBI (50 Gy with a boost to a total of 60 Gy) will be given over six to seven weeks. PBI (34 to 38.5 Gy) will be delivered by one of the previously described three techniques that is best suited for the patient and available at the institution. Treatment will be given within 5-10 days. Both radiation treatments (WBI and PBI) will be coordinated with the use of hormonal therapy and chemotherapy as necessary.

The primary endpoint of the study is in-breast tumor recurrence. An aggressive quality control and quality assurance program is part of the trial and provides for review of the dosimetry planning data for the PBI arm and the WBI arm. This program includes rapid review of the initial case of each PBI technique performed at a participating site, followed by a timely batched review of the next four PBI cases and then a random review. Review of the WBI cases will occur in a batched fashion. This approach will ensure that the appropriate treatment guidelines for patients are followed consistently.

Figure 1: NSABP B-39/RTOG 0413 Schema



An important component of this clinical trial is the quality-of-life (QOL) substudy. The first 482 patients who receive chemotherapy and the first 482 patients who do not receive chemotherapy will enter into the QOL substudy. The QOL substudy will use a patient self-assessment questionnaire, physician evaluation, and digital photographs over a three-year period to assess cosmetic results and toxicity.

Clinicians who are interested in participating in this trial can contact the NSABP at 412.330.4624 or via the Web at *www.NASBP.Pitt.edu* or RTOG at 215.574.3205 or online at *www.RTOG.org*.

Thomas B. Julian, MD, FACS, is an associate professor of Human Oncology and is the associate director of the Allegheny Breast Care Center at Allegheny General Hospital in Pittsburgh, Pa. He is the associate director of Medical Oversight for the National Surgical Adjuvant Breast and Bowel Project and the Protocol Office for NSABP B-39. Eleftherios P. Mamounas, MD, MPH, FACS, is medical director of the Cancer Center of Aultman Health Foundation in Canton, Ohio, and chairman of the Breast Committee for the National Surgical Adjuvant

Breast and Bowel Project (NSABP). He is also associate professor of surgery at Northeastern Ohio Universities College of Medicine in Rootstown, Ohio.

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