The standard treatment for breast cancer patients desiring breast-conserving therapy is partial mastectomy followed by external beam (EB) whole breast radiotherapy (WBRT). Several randomized trials demonstrate that patients who undergo a partial mastectomy alone, and do not receive adjuvant WBRT, have at least a three-fold increase of in-breast recurrences compared with those who receive EBRT. Based on these randomized trial results, the 1990 National Institutes of Health (NIH) Consensus and the 2001 Consensus Conference concluded that breast-conserving surgery should be accompanied by WBRT.

Unfortunately, despite randomized clinical trial results and NIH Consensus Statements, Patterns of Care Studies from the US demonstrate increasing deviation from these recommendations. Data from the Surveillance Epidemiology and End Results (SEER) registry demonstrate that the percentage of patients receiving appropriate breast-conserving therapy declined from 1983 to 1995. Barriers to appropriate RT treatment appear to be multi-factorial including distance to RT centers, decreased socioeconomic status, insurance coverage, and older age. More convenient and less costly RT regimens may improve compliance with adjuvant therapy recommendations and allow more women to choose breast-conserving therapy.

Accelerated partial breast irradiation (APBI) is a potentially attractive way to significantly reduce the duration of time a patient spends on an RT treatment course. The vast majority of in-breast cancer recurrences occur in the same quadrant as the primary tumor, whereas non-tumor bed recurrences and new primaries in the contralateral breast occur with similar frequency in irradiated and non-irradiated patients, suggesting that the primary efficacy of RT in early-stage disease is due to the eradication of residual disease in the region of the tumor bed. The majority of tumors may therefore be controlled by RT delivered only to the region of the tumor bed, sparing the remainder of the breast. APBI options include interstitial catheter-based brachytherapy, endocavitary brachytherapy, three-dimensional (3-D) conformal RT and intra-operative RT (IORT). This article will focus on the two IORT options currently being investigated—partial mastectomy followed by IORT and vice versa.

**IORT Delivered Following a Partial Mastectomy**

Veronesi et al. were the first to report IORT to treat the excised tumor bed with a single dose of RT delivered in the operating room (OR). Briefly, their technique is as follows. A standard sentinel node procedure is performed followed by a standard quadrantectomy down to the pectoralis major fascia with at least 1cm of grossly tumor-free surgical margins. The breast parenchyma is then detached from the overlying skin as well as the underlying pectoralis muscle for 3–4cm. An aluminum-lead disk is then positioned on the surface of the pectoralis muscle to prevent irradiation of the chest wall. The breast parenchyma is temporarily re-approximated over the metal disk and the thickness of the breast tissue is measured with a ruler at multiple locations. The average thickness is then used to calculate the radiation dose. Single fraction radiation is performed with a mobile, linear accelerator (LINAC). The irradiation tube is placed directly onto the re-approximated breast tissue with the skin protected by a moist gauze. Following irradiation, the metal disk is removed and definitive surgical closure is completed.

Two hundred and thirty-seven patients with clinical T1, N0 breast cancers were treated with a quadrantectomy and axillary sentinel node procedure. With a median follow-up of 19 months, four (1.7%) patients developed mild or severe post-treatment breast fibrosis. Furthermore, three (1.4%) patients have developed an ipsilateral breast cancer and two (1%) patients have developed a contralateral breast cancer. With short-term follow-up, IORT appears to have an acceptable cosmetic result, but longer follow-up is necessary before conclusions regarding efficacy can be made.
Single Fraction IORT Delivered In Situ to the Tumor

The IORT technique of Veronesi et al. presents significant technical challenges for the radiation oncologist including the accuracy of tumor bed definition when tissues are re-approximated and the variable margin of normal tissue irradiated in the reopposed tissues. In order to address these issues, the authors modified the Veronesi IORT technique. Instead of delivering the IORT after the tumor is excised by quadrantectomy and the tissues re-approximated, the authors elected to treat the tumor and surrounding tissues with IORT prior to excision. This allowed them to clearly define the target tumor, and normal tissue margin in conventional terms, using ultrasound.

The author’s technique has previously been described in detail. Briefly, their modified technique is as follows. Patients aged 55 or older diagnosed by core biopsy with clinically node-negative infiltrating ductal carcinoma less than 3cm in greatest diameter and visible by pre-operative breast ultrasound were eligible. Pre-operatively, each patient underwent breast ultrasound and ultrasound-guided needle localization of the cancer by a radiologist trained in breast imaging. After the tumor is identified, the optimal angle of approach is determined to minimize the distance to tumor while maximizing distance to lung. At this angle, the width of the tumor, depth from skin to posterior–anterior (PA) and posterior edges of the tumor and from skin to the pleural surface is measured. Dosimetric pre-planning is performed using these parameters to determine the cone size necessary to cover the tumor width plus 1.5–2cm margin and the electron energy necessary to cover a depth of 1cm deep to the posterior edge of the tumor with the 90% isodose line, while delivering at least 1,500cGy to the tumor isocenter.

In the OR each patient underwent lymphatic mapping (LM) and sentinel lymphadenectomy (SL) with a combined isosulfan blue dye and technetium 99m (99mTc)-labeled sulfur colloid technique. After completion of LM/SL, a curvilinear incision is made in the standard fashion over the appropriate quadrant of the breast. The incision is long enough (approximately 6–7cm) to ensure adequate exposure of the breast tissue and to allow for placement of the appropriate size radiation cone, as determined pre-operatively by the ultrasound measurements and dosimetric planning. Subcutaneous skin flaps are raised circumferential from the incision for approximately 2–3cm. The skin edges are protected with moist gauze sponges and retracted from the radiation field using a circular retractor with metal hooks. The radiation cone is then locked into position so that the edge is just abutting the breast tissue, at the angle of approach pre-determined by ultrasound guidance, with the tumor as localized by the needle and pre-operative ultrasound in the center of the radiation field. After the surgeon and radiation oncologist have placed and secured the cone, the patient is brought to the position underneath the mobile, self-shielded, linear accelerator for docking. Once docked, the entire team exits the room. The pre-planned dose is delivered at a dose rate of 1,000 monitor units per minute. It typically takes approximately one to two minutes for the actual radiation delivery. The entire procedure adds 20–30 minutes to the case. Once the radiation phase of the procedure is complete, partial mastectomy is performed in the standard fashion.

Twenty-three patients have been enrolled with a median age of 63 and a range of 55 to 82 years. The median follow-up is six months, with a range of one to 22 months. The median clinical tumor size as defined by ultrasound was 1.1cm, with a range of 0.5–2.1cm. Five patients did not receive IORT. In one patient, IORT was not delivered due to a machine fault. In two patients, the tumor could not be conclusively located by ultrasound after initial biopsy; therefore, dosimetric planning could not be accomplished with confidence. In two additional patients the tumor was adjacent to the chest wall so that the radiation dose constraints to the lung could not be satisfied. Five of the first 18 patients received WBRT, and three received mastectomy. Only 10 in 18 patients were therefore treated with IORT partial-breast RT. The reasons for receiving WBRT were extensive intraductal component, invasive lobular carcinoma, and involved lymph nodes (LN). Reasons for mastectomy included an inability to achieve negative margins with re-excision, and patient request in lieu of WBRT recommended for extensive intraductal component.

Discussion

Since the vast majority of in-breast recurrences occur in the lumpectomy bed, several approaches to accelerated partial breast irradiation (APBI) have emerged to treat only the portion of the breast harboring the index lesion. The rationale for this approach is that with smaller treatment volumes the treatment can be delivered over a significantly shorter period by using a larger dose per fraction, without excess normal tissue toxicity. Options for APBI include interstitial catheter-based brachytherapy, endocavitary, brachytherapy, and conformal 3-D RT. All of these approaches still require the patient to travel numerous times to the radiation facility following surgery to complete their PBRT. Only IORT affords the patient the opportunity of having the area at highest risk, the tumor bed, managed in a single visit by both the surgery and radiation oncology team.
While certainly very convenient for patients, delivery of the entire course of therapy in a single dose raises concerns regarding accuracy of the RT delivery, tumor control, and normal tissue toxicity. When IORT is delivered after the tumor has been excised and normal breast tissue re-approximated, it is theoretically more difficult to define the target volume for the radiation oncology team. This uncertainty may be compensated by irradiating a wider margin of surrounding breast tissue. With the authors’ technique of irradiating the tumor in situ, they precisely calculated the target volume by pre-operative ultrasound, which allowed them to select the appropriate cone size and electron energy, as well as the incision site and cone angle, for each tumor individually prior to skin incision. The skin is then retracted to expose the undisturbed tumor bed and tumor and a smaller margin of surrounding breast tissue are treated. However, a potential drawback to the authors’ approach is the smaller treatment volume. The optimal dose for IORT is not known. Veronesi et al. found 21Gy to be well-tolerated after a dose-escalation study. However, a single dose of 15Gy is estimated to be biologically equivalent to standard dose and fractionation (25 treatments of 50Gy) for breast cancer.26–29

The lower dose and smaller volume may result in better cosmesis, but it may also result in increased risk of local recurrence, an issue that the authors are studying. For this reason, they have carefully chosen criteria, including age, that must be satisfied for delivery of IORT as sole treatment; disease not meeting these restrictions requires additional EBRT per protocol.

With short-term follow-up, the initial analysis of toxicity and feasibility of the authors’ in situ IORT indicates that the technique is well-tolerated to date. The authors have had two cases of acute toxicity in 18 patients, one WB mastitis and one delayed wound healing. In either case, it is not certain that IORT was related to the complication. To date, the authors have seen no grade 3 or 4 subcutaneous toxicity in the 20 patients with >90 day follow-up.

In conclusion, the early results of single-fraction IORT, delivered either prior to or following partial mastectomy, seem encouraging. Acute toxicity and cosmetic result does not appear to be adversely affected by delivering RT at the same time as performing a partial mastectomy. While longer follow-up is awaited to determine actual tumor-bed recurrence rates, optimizing target volume and delivery and continued attention to acute and chronic toxicity must be primary goals for investigators. If successful, IORT could dramatically increase the number of women who choose breast-preserving therapy because of the convenience of surgical resection and tumor-bed RT in a single visit.

References