

# Intraoperative Electron Radiotherapy Boost as a Component of Adjuvant Radiation for Breast Cancer in the Community Setting

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To reduce toxicity/treatment time and improve accuracy, intraoperative electron radiotherapy (IOERT) was used as an alternative to electron beam radiation therapy boost. Primary objective was to determine feasibility and acute toxicity. From August 2009 to June 2011, 50 patients (age 32 to 76 years) with *in situ* or invasive breast cancer (Stage 0 to IIIA) were treated. Toxicity assessed according to standard National Cancer Institute scales. Median tumor size was 20 mm (range, 6 to 80 mm) with 43 infiltrating ductal, two infiltrating lobular, and five ductal *in situ* carcinoma. A single 10-Gy fraction boost was given to the tumor bed after resection followed by whole-breast radiotherapy. After IOERT, three patients required completion axillary lymph node dissection, eight had reexcision resulting from positive margins, and four opted for completion mastectomy. The median follow-up was 10 months (range, 2 to 24 months). Ten patients had Grade 1 and one reported Grade 2 breast pain 2 weeks after IOERT; all resolved at 6 weeks. Two patients had delay in wound healing, but none developed a wound infection. Three patients reported symptomatic fat necrosis. No other toxicities were reported. IOERT resulted in a reduction in treatment time, was not associated with additional toxicity or change in the acute toxicity profile, and is a feasible treatment option in a community hospital setting.

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THE CURRENT STANDARD of care for early-stage breast cancer is considered breast-conserving therapy (BCT) followed by postoperative radiation therapy. Many randomized prospective clinical trials have demonstrated no significant difference in therapeutic outcome when comparing radical surgery with BCT.<sup>1</sup> Local control and overall survival are not compromised when BCT is followed by whole breast irradiation.<sup>2, 3</sup> During whole breast radiation therapy (WBRT), cumulative doses in the range between 40 to 50.4 Gy in single fractional doses of 1.8 to 2.67 Gy (5 fractions/week) are commonly used to sterilize subclinical disease to decrease the probability of local recurrence. However, the tumor bed itself represents a region with the highest probability of local tumor recurrences comprising approximately 65 to 80 per cent of all events. Prospective and retrospective clinical trials show a lower

local recurrence rate if the dose is escalated by adding a “boost,” defined as focused irradiation to the former tumor bed. By the additional use of an *en face* electron boost of 10 to 16 Gy (5 to 8 fractions  $\times$  2 Gy) or, alternatively, interstitial implants (high-dose rate brachytherapy), it is possible to halve the local recurrence rates in comparison to WBRT only.<sup>4</sup>

However, there are some concerns regarding the boost portion of radiation therapy. There is controversy as to the exact definition of the boost target volume. Furthermore, because conventional boost techniques are applied after completion of WBRT, the possibility of a geographic miss exists, especially with the increasing popularity of oncoplastic reconstruction. There are also concerns regarding maintaining a good cosmetic outcome.<sup>5</sup>

Intraoperative electron radiotherapy (IOERT) has a number of potential advantages compared with conventional boost techniques. The tumor bed is directly visualized at the time of the procedure eliminating the concerns of a geographic miss. Normal tissue-sparing occurs because the overlying skin is not exposed to any radiation. There is also a more homogeneous dose distribution to the directly visualized tumor bed cavity. IOERT also reduces overall treatment time by 1 to 2

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weeks, thus improving patient convenience and comfort.<sup>6</sup> Some recent publications using IOERT boost for breast cancer have reported excellent local control with good to excellent cosmetic outcomes.

To date, the available interim analyses have demonstrated lower local recurrence rates with IOERT boost than with standard treatment schedules.<sup>6, 7</sup>

## Methods and Materials

### *Patient Selection Criteria*

From August 2009 to June 2011, 50 consecutive patients with biopsy-proven invasive or *in situ* breast cancer were treated with IOERT (Mobetron<sup>®</sup>; IntraOp Medical, Sunnyvale, CA) boost as part of their adjuvant radiation therapy. All patients were older than age 35 years and had staging work-up including mammograms and breast sonography, breast magnetic resonance imaging, and metastatic evaluation as deemed clinically necessary. IOERT was used in cases of breast-conserving surgery in which a boost treatment would have been part of the adjuvant radiation therapy. Written informed consent was obtained from all patients for radiation treatment. An Institutional Review Board-approved retrospective chart review was obtained for data review, analysis, and distribution.

### *Procedure*

The operative procedures were as follows: the lumpectomy was performed with an incision centered over the tumor or periareolar region depending on the surgeon's preference. A pathologist performed a microscopic assessment of margins by frozen section to ensure tumor-free margins. Sentinel node or axillary lymph node dissection was carried out in all patients with invasive disease. Patients with ductal carcinoma *in situ* (DCIS) did not undergo nodal evaluation. After excision of the tumor, the tissue surrounding the excision cavity was mobilized and temporarily approximated using sutures. This tissue was brought into the radiation-planning target volume. The appropriate size applicator tube was selected by the radiation oncologist and together with the surgeon positioned to encompass the entire tumor bed plus a margin of at least 1 cm. Intraoperative ultrasound was used to determine both depth to the chest wall and target volume. The appropriate radiation energy was selected based on these measurements. Careful attention was paid to ensure that the skin was spared from the radiation field.

The Mobetron<sup>®</sup> (IntraOp Medical) was used to deliver the IOERT. This is a mobile self-shielding linear accelerator that delivers electron beams. The energy of the electron beam ranges from 6 to 12 MeV. A dose of

10 Gy prescribed to the 90 per cent isodose line was given to each patient.

After IOERT, the sutures used to approximate the tissue were removed and the surgeon continued with the remainder of the surgery. Tumor cavity remodeling was done before closing the incision. In most cases, WBRT in the range of 40 to 50.4 Gy was administered 3 to 6 weeks after completion of surgery using beams ranging from 6 to 18 MV photons. No patients were treated with concurrent chemotherapy during their WBRT.

### *Toxicity Assessments*

The acute and subacute toxicities included breast pain, infection, fat necrosis, skin reaction, and wound healing evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. After surgery, patients were evaluated weekly or every other week for the first 2 months, then in 3-month intervals for the first year. Follow-up evaluations will occur at least every 6 months for 5 years after completion of radiation treatments.

### *Statistical Methods*

Chi-squared analysis was used to compare outcomes in groups. Significance was accepted at  $P < 0.05$ .

## Results

Fifty consecutive patients were followed for a median of 10 months (range, 2 to 24 months) beginning in August 2009 and ending June 2011. The median age was 63 years with a range of 30 to 76 years. Breast cancer stage distribution included Stage 0 to Stage IIIA. Median pathologic tumor size was 20 mm (range, 6 to 80 mm). There were five patients with DCIS, two with invasive lobular breast cancer, and the remaining 43 with invasive ductal carcinoma. All patients received segmental mastectomies with sentinel node evaluation as appropriate. At the time of final pathologic review and based on current standards of practice, three patients underwent completion axillary lymph node dissection. Eight patients (16%) had re-excision of the segmentectomy site as a result of positive margins and four patients opted for completion mastectomy as a result of the extent of parenchymal disease in the breast.

Magnetic resonance imaging (MRI) was performed preoperatively at the discretion of the practitioners. Thirty-six patients had MRI and 14 patients had preoperative imaging limited to mammogram with or without ultrasound. Of the eight patients requiring re-excision, seven (19%) had undergone preoperative MRI. Of the 14 who did not have an MRI, one (7%)

had a re-excision performed. These differences were not statistically significant ( $P > 0.27$ ).

All patients received a single 10-Gy fraction to the tumor bed after resection and before closure. Adjuvant whole-breast radiation therapy was delivered to all patients except those who opted for mastectomy and ranged from 40 to 50.4 Gy. Breast pain was evaluated using standard criteria (CTCAE) and was limited to Grade 1 to 2 pain. At the early reporting phase (2 weeks after IOERT), 10 patients (20%) had Grade 1 pain and only one patient reported Grade 2 pain. The follow-up at 6 weeks (delayed phase) documented complete resolution of the initial pain symptoms.

Oncoplastic surgery (OPS) was included in half (25) of the patients. The remaining patients were closed with standard methodology (SM). There was no significant difference ( $P > 0.37$ ) in breast pain, fat necrosis, or re-excision rates regardless of surgical closure method. Breast pain was reported in seven of 18 OPS cases and five of 20 SM cases. Fat necrosis was observed in two of 23 OPS and one of 24 SM. Re-excision was required in four of 21 patients in each group with two of the four patients in the OPS going on to completion mastectomy.

Wound healing was observed for the entire study group. There were no perioperative infections according to standard criteria of erythema, cellulitis, drainage, leukocytosis, or fever. No patient received a course of antibiotics for infection. Two patients had significant delay in their wound healing. This was consistent with complexities in the breast surgery, not radiation treatment volume (Table 1).

### Discussion

The rationale for boost therapy to the tumor bed is based on the assumption that most recurrences occur in or near the original primary tumor site. This assumption has been supported by the results from randomized clinical trials.<sup>4, 8</sup>

Reports from Europe have emphasized the advantages of IOERT for boost therapy. These advantages include: 1) greater precision of therapy treatments by direct visualization of the tumor bed, which guarantees more accurate dose delivery; 2) improved cosmesis

with smaller treatment volumes and complete skin sparing; 3) shortening postoperative radiotherapy treatment times by 1 to 2 weeks; 4) more homogeneous dose distribution of the boost therapy in the tumor bed and surrounding tissue; and 5) increased use of oncoplastic reconstruction techniques, which involve larger resections and tissue rearrangements to achieve more optimal cosmetic outcomes.<sup>5, 6</sup>

A pooled analysis from seven European institutions using electrons as a boost therapy during breast-conserving surgery followed by WBRT was presented at the combined European Society for Radiotherapy & Oncology and the International Society of Intraoperative Radiation Therapy meeting in London, U.K., in May of 2011.<sup>9</sup> The report involved 1110 patients with a median follow-up of 73.3 months. The local tumor control rate was 99.2 per cent. The annual in-breast recurrence rates were 0.64 per cent for patients 40 years and younger, 0.34 per cent for patients 40 to 49 years, 0.21 per cent for patients 50 to 59 years, and 0.16 per cent for patients 60 years and older.<sup>9</sup> At the same London meeting, the 10-year follow-up data for the IOERT boost modality from the Salzburg group was presented. The in-breast tumor recurrence rate for the IOERT group was 1.6 per cent. The 10-year ipsilateral tumor recurrence rate for the group receiving the boost therapy after WBRT was 7.2 per cent. This report is only currently available as an abstract.<sup>10</sup>

At our community hospital, we are aware of a building trend for single-fraction IOERT for selected cases of breast cancer treated with breast conservation. Meaningful reports of institutional and clinical trial results with single-fraction IOERT have steadily increased over the past decade.<sup>11, 12</sup> We began our experience with IOERT by performing single-fraction boost treatments in August of 2009. Our boost therapy was then followed by standard WBRT of 48 to 50.4 Gy. There was a “learning curve” for our IOERT team. Presently, IOERT adds approximately 25 to 30 minutes of additional operative time per case.

The largest U.S. experience with IOERT boost and WBRT has only been reported in 2010 as an ASTRO abstract.<sup>13</sup> Fifty-two patients were treated at the Mayo Clinic in Scottsdale, Arizona, from February of 2003 until January of 2005. With a median follow-up of 61 months, only one patient had an in-field relapse. The 5-year local control rate was 98 per cent. Ten percent of patients had fat necrosis, 8 per cent had late infections, and one patient had a nonhealing wound requiring mastectomy with flap reconstruction.<sup>13</sup>

Our initial experience with IOERT boost therapy has been very positive. Our median follow-up time is too short to comment on the effectiveness of this approach to lower in-breast rate recurrence rates. Our data on postoperative pain, fat necrosis, wound healing, and

TABLE 1. Number and Type of Intraoperative Electron Radiotherapy Postoperative Complications

Toxicity	No.	%
Grade 2 or greater pain	1	2
Delayed healing	2	4
Infection	0	0
Symptoms of fat necrosis	3	6
Radiotherapy dermatitis	0	0

infections were comparable to those series already reported on this subject.<sup>5, 6</sup> The additional operating room time for IOERT boost therapy of 25 to 30 minutes is also comparable with those who have reported such data.<sup>13</sup>

We have in place two additional institutional protocols for IOERT therapies. One combines IOERT with 3 weeks of hypofraction WBRT. The second protocol is for a single-fraction of IOERT partial breast radiation therapy of 21 Gy for selected cases of early breast cancer.

We believe that IOERT will have an increasing role in the treatment of patients undergoing breast conservation. Because nearly 85 per cent of all breast cancer treatment in the United States is performed at the community level, we believe that it is vital that community hospitals embrace and study emerging technologies like IOERT.

#### REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
2. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast conserving therapy in small breast carcinoma: long term results of a randomized trial. *Ann Oncol* 2001;12:997–1003.
3. Van de Steene J, Vinh-Hung V, Cutuli B, Storme G. Adjuvant radiotherapy for breast cancer: effects of longer follow-up. *Radiother Oncol* 2004;72:35–43.
4. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. EORTC 22881. *N Engl J Med* 2001; 345:1378–87.
5. Pezner RD. Cosmetic breast fibrosis: it's the local boost! *IJROBP* 1994;30:1251–2.
6. Sedlmayer F, Fastner G, Merz F, et al. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: results of an ISORT pooled analysis. *Strahlenther Onkol* 2007;183:32–4.
7. Reitsamer R, Sedlmayer F, Kopp M, et al. The Salzburg concept of intraoperative radiotherapy for breast cancer: results and considerations. *Int J Cancer* 2006;118:2882–7.
8. Roestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15: 963–8.
9. Sedlmayer F, Fastner G, Merz F, et al. 312 oral results of an ISORT pooled analysis with Linac-based IORT with electrons (IOERT) as boost strategy during breast conserving therapy in limited stage breast cancer. *Radiother Oncol* 2011;99(suppl 1): S124.
10. Reitsamer R, Kopp M, Fastner G, et al. 10-year results of intraoperative electron radiotherapy (IOERT) in boost modality in breast cancer patients treated with breast conserving surgery. *Radiother Oncol* 2011;99(suppl 1):S0167.
11. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intra-operative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010;376: 91–102.
12. Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study of 1,822 cases treated with electrons. *Breast Cancer Res Treat* 2010;124: 141–51.
13. Wong WW, Pockaj BA, Vora SA, et al. Five-year outcome of a prospective study evaluating tumor bed boost with intra-operative electron irradiation (IOERT) in breast conserving treatment for T1/T2 N0 breast cancer. *Int J Radiat Oncol Biol Phys* 2010;78(suppl):S207–8.