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Boost for Early Stage Breast Cancer

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Abstract

Purpose—Conventional radiation fractionation of 1.8 – 2 Gy per day for early stage breast
cancer requires daily treatment for 6–7 weeks. We report the five-year results of a phase II study
of intensity modulated radiation therapy (IMRT), hypofractionation and incorporated boost that
shortened treatment time to four weeks.

Methods and methods—The study design was phase II with a planned accrual of 75 patients.
Eligibility included age ≥18, Tis-T2, Stage 0 – II, and breast conservation. Using photon IMRT
and an incorporated boost, the whole breast received 2.25 Gy per fraction total 45 Gy and the
tumor bed 2.8 Gy per fraction total 56 Gy in 20 treatments over four weeks. Patients were
followed every six months for five years.

Results—75 patients were treated from 12/03 to 11/05. The median follow-up is 69 months.
Median age was 52 years (range 31–81). Median tumor size was 1.4 cm (range 0.1–3.5). 80%
were node negative. 93% had negative and 7% close (> 0 and < 2 mm) margins. 76% were
invasive ductal, 15% DCIS, 5% lobular and 4% other histology. 29% had grade 3 and 20%
extensive in-situ carcinoma. 11% received chemotherapy, 36% received endocrine therapy, 33%
received both and 20% neither. There were 3 local recurrences for a 5-year actuarial rate of 2.7%.

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Conclusions—This 4-week course of hypofractionated radiation with incorporated boost is associated with excellent local control comparable to historical results of 6–7 weeks of conventional whole-breast fractionation with sequential boost.

Keywords
Breast cancer; radiation therapy; IMRT; Hypofractionation; Breast Boost

Introduction
Radiation therapy following lumpectomy is a standard part of breast-conserving therapy for invasive breast cancer (1, 2) because it significantly reduces the risk of local recurrence in the breast and increases patient survival (3). In spite of these benefits of radiation, the number of women treated with breast-conserving surgery but without radiation is approximately 15–20%, and the percentage of women in whom radiation is omitted is even higher for patients aged ≥70–80 years (4–6).

One problem with standard radiation to the whole breast may be the extended 6–7 week length of treatment. Delivering postoperative radiation therapy in a shorter period of time could result in greater convenience for patients and therefore greater utilization of postoperative radiation. Partial breast irradiation is one method of shortening treatment time, by treating the lumpectomy bed with a small margin twice a day for 1 week. However, partial breast irradiation remains under investigation in randomized trials and lacks long term results. In addition, most patients will not meet the strict eligibility requirements for partial breast irradiation and require whole breast irradiation. Cost is also an increasingly important consideration, both to the individual and to society as a whole. A typical fractionation schedule for breast radiation of 30 – 35 treatments is associated with costs to patients including a daily deductible for each radiation treatment, costs to a personal medical savings account, expenses for travel to radiation, or lost hours of work. The cost to payers is passed on to the end user ultimately by increased premiums or higher taxes.

In 2003, we began a clinical study using hypofractionation to shorten the number of required radiation fractions and shorten overall treatment length. This was achieved by means of hypofractionation of the breast volume, or use of greater than standard 2 Gy fractions per day, and daily incorporation of a tumor bed boost rather than a standard sequential boost. The advantages of this schedule would be a shortened treatment time to a 4-week course of radiation therapy, and continued treatment of the same tumor bed and breast volumes that have been associated with excellent results using conventional radiation therapy fractionation. The primary endpoint of acute toxicity has been previously reported (7). We now present the local control endpoint of the study with a minimum potential follow up of five years.

Study Population and Methods
The study population consisted of 75 women who were enrolled and completed radiation therapy on a hospital Institutional Review Board-approved clinical trial 03-026. Inclusion criteria were histologically confirmed invasive or in-situ carcinoma of the breast, American Joint Committee on Cancer stages Tis, T1 or T2 and stages 0, I or II breast cancer (8), treatment by breast-conserving surgery, performance status 0–2, age ≥18 years, and absolute neutrophil count ≥1,500/μl and platelets ≥75,000/μl. Exclusion criteria for the study included positive resection margins (defined as tumor at the specimen edge), concurrent chemotherapy, pregnancy, T3 or T4 disease, stage IV disease, mastectomy, prior radiation therapy to the ipsilateral breast, active systemic lupus or history of scleroderma, or medical or psychiatric conditions that could prevent the patient from providing informed consent.
consent, maintaining compliance, or receiving protocol treatment. A history and physical exam, complete blood count, and serum pregnancy test where applicable were required prior to radiation simulation. All outside pathology was confirmed by Fox Chase Cancer Center pathologists. Patients with ductal carcinoma in situ (DCIS) detected by calcifications on mammography underwent post-biopsy mammograms to confirm removal of all malignant calcifications. The study did not stipulate a specific course of chemotherapy prior to radiation, and any endocrine therapy was allowed after radiation. Chemotherapy was given prior to radiation in 33 (44%) patients. 52 patients were estrogen receptor positive but none of the patients had concurrent endocrine therapy with radiation. Three women were enrolled but removed from the study prior to radiation and so were not included in the study population – their physicians determined that they should be treated with standard therapy because of large postoperative seromas at the lumpectomy sites in 2 cases and the need for radiation in a support bra in 1 case.

All 75 patients were treated with an IMRT technique. Patients had simulation with a dedicated CT scanner to define the clinical target volume of the breast tissue and normal structures. Patients were placed in an alpha-cradle cast on a 10–15° wedged breast board. The physician defined the clinical target volume (CTV) as the palpable breast tissue anterior to the chest wall to within 5 mm of the skin, with a margin of 2 cm in the superior, inferior, and lateral directions. We have previously reported our IMRT technique that involves an iteration method for optimization to generate the IMRT plan, Monte Carlo dose calculation, and a step-and-shoot technique using multi-leaf collimation for beam delivery (9). Treatment energy was 6 or 10 MV depending upon patient chest wall separation, and a beam spoiler was used with treatment energies of 10 MV. The whole breast was treated to a dose of 2.25 Gy per day for 20 fractions for a total of 45 Gy. Electrons were used to increase the dose to the small volume of the boost to a dose of 2.8 Gy per fraction for 20 days for a total of 56 Gy. Five fractions per week were given for 4 weeks.

The primary study endpoint was acute skin toxicity using the common terminology criteria for adverse events (CTC) for acute radiation dermatitis (10). The primary endpoint has been previously reported (7). Patients were to be followed every six months for 5 years for regular physician follow up with mammography performed every year until study closure. Cosmetic and quality of life assessments were to be obtained prior to radiation, 6 weeks after radiation, and then every 6 months for the 5-year study period. Cosmetic outcome was assessed by physicians using a modified version of the EORTC breast cancer rating system for cosmetic results of breast conserving treatment (11). This included a global rating of cosmesis, in addition to specific scoring for breast size, shape, color, nipple location and shape, appearance of the surgical scar, and telangiectasias. Patient self-assessment data was collected using the Breast Cancer Treatment Outcome Scale (BCTOS). The BCTOS is a 22-item measure of perceived aesthetic (e.g., breast shape) and functional status (e.g., pain, mobility) after breast-conserving surgical treatment (BCT) and radiotherapy. The BCTOS produces a factor structure with three internally consistent subscales for cosmetic status, functional status, and breast specific pain that has demonstrated predictive validity (12, 13).

Results

The characteristics of the 75 patients are shown in Table 1. The median age was 52 years (range 31 – 81 years). The median tumor size was 1.4 cm. Margins were negative in 93% and close (> 0 mm and < 2 mm) in 7%. Grade was 1 in 9%, 2 in 40%, 3 in 29% and unknown in 21%. Extensive in-situ carcinoma was reported in 20%, negative in 51% and unknown in 29%. Systemic therapy was chemotherapy (all prior to radiation) in 11%, endocrine therapy in 36%, both in 33%, and neither in 20%. The mean chest wall separation was 21.0 cm (range 16 – 32.5 cm). The whole-breast CTV volume was mean 584 cc (range...
97 – 2079 cc). The incorporated boost volume of the tumor bed CTV volume was mean 24 cc (range 3 – 123 cc).

After a median follow-up of 69 months (mean 67 months, range 11 – 92 months), there have been 3 local recurrences in the 75 patients. The 3 local in-breast recurrences occurred at an interval of 16, 38- and 61 months, respectively. The 5-year rate of local recurrence is 2.7% (Figure 1).

Table 2 shows the patient-reported scores using the BCTOS for cosmesis, breast-specific pain, and function. For the BCTOS, scores represent from 1–4 the difference between the involved breast and the uninvolved breast, with a score of 1 representing no difference compared with the untreated breast, 2 a mild difference, 3 moderate, and 4 severe. Table 2 also shows the physician-reported score for cosmesis, 0 representing excellent, 1 good, 2 fair, and 3 poor cosmesis. There are no significant differences over time in the mean scores through the five-year period of the study.

There have been 6 distant recurrences of breast cancer. There have been 10 new primary cancers in 8 patients. There were 2 lung cancers, 1 ovarian cancer, 1 colon cancer, 1 endometrial cancer, 1 ductal carcinoma in situ of the contralateral breast, and 1 squamous cell carcinoma of the skin. One patient had 3 documented new primaries – bladder cancer, melanoma of the skin, and hepatocellular carcinoma. There have been 7 deaths: 2 patients from breast cancer, 1 patient from lung cancer, 1 patient from breast or ovarian cancer (cause undetermined), 1 from hepatocellular cancer, and 2 from undetermined causes who were without evidence of recurrence at last follow up. One patient deceased from breast cancer had initial disease T2N1M0, ER and PR negative, and HER-2 positive and was treated with adriamycin, cytoxan and paclitaxel but no herceptin (standard adjuvant therapy in the early years of the protocol). The other patient with breast cancer death had initial disease T1N0M0 stage I, ER and PR negative, and Her-2 negative and did not receive adjuvant chemotherapy due to age and comorbidities.

**Discussion**

Hypofractionation, or delivery of greater than standard 1.8 – 2 Gy fraction sizes per day, is one method of shortening overall treatment time required for postoperative radiation in early stage breast cancer. Four prospective randomized clinical trials have shown promising results with hypofractionated schedules for WBI (14–18). In each of these studies, the goal was to deliver a hypofractionated dose schedule that was biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions of 2 Gy. With 5–10 year follow-up of these studies, there has been similar in-breast local control between the hypofractionated and standard fractionated arms. The prospective randomized clinical trial conducted in Canada tested 42.5 Gy in 16 fractions over 22 days compared with a standard dose of 50 Gy in 25 fractions over 35 days (19). There was equivalent 5-year local recurrence-free survival of 97%, and no significant differences in radiation toxicity or cosmesis.

One possible reason that the Canadian radiation therapy fractionation schedule was not widely adopted in the United States may have been the absence of a boost. In two prospective randomized studies in invasive breast cancer, the use of a boost after WBI reduced the risk of local recurrence even in patients with negative resection margins(20, 21). An international survey of Radiation Oncologists in 2001–2002 showed that 85% of American and 75% of European respondents would deliver a boost even with negative margins after WBI(22). None of the 4 prospective studies for hypofractionated WBI examined a hypofractionated dose schedule that is biologically equivalent to the cumulative
dose from a tumor bed boost (typically 60–66 Gy in 30–33 fractions). A standard fractionated sequential boost (5 fractions of 2 Gy) was employed in the United Kingdom START A and B trials in a nonrandomized fashion based on individual investigator discretion and not as part of the protocol therapy. The use of a sequential boost of 1–2 weeks in these studies extended the overall treatment time reducing the potential time-saving benefit to patients from the incorporated boost used in the present study. Standard fractionated radiation therapy consists of radiation to the whole breast for 4 ½ to 5 weeks with a sequentially sequenced boost to the tumor bed for an additional 1 ½ to 2 weeks. Therefore, the present study aimed to achieve the highest possible rate of local control by maintaining the differentially higher dose to the tumor bed compared to the remainder of the breast.

This series represents one of only a few with the longest followup combining a concurrent boost with whole breast hypofractionation. Formenti has reported a trial of IMRT, hypofractionation, and concomitant boost (23). A dose of 40.5 Gy was delivered in 15 fractions with a concomitant boost of 0.5 Gy per day for a total tumor bed dose of 48 Gy. The results in 91 patients treated were reported with a median follow-up of 12 months. The major acute toxicity was reversible grade 1–2 dermatitis in 67%. There were no treatment breaks. There were 2 acute grade 3 toxicities, 1 skin and 1 fatigue. There were no late grade 3 toxicities. Late fibrosis was reported grade 1 in 48%, grade 2 in 3%. Grade 1 pigmentation change was noted in 70%. Breast pain was grade 1 in 8% and grade 2 in 2%. Skin telangiectasias were grade 1 in 3% and grade 2 in 2%. There was 1 regional node recurrence. Chadha has reported a trial of conventional whole breast irradiation with a concomitant boost over 3 weeks for early stage breast cancer (24). The whole breast dose was 2.7 Gy per fraction for 15 fractions to a dose of 40.5 Gy. The concomitant boost to the lumpectomy site was a total of 3 Gy per fraction for 15 fractions to a total dose of 45 Gy. The results of 105 patients were reported at a median follow-up of 24 months. There was no acute grade 3 or 4 toxicity. There were no reported late soft tissue toxicities. There was no significant negative effect reported on cosmesis.

The crude incidence of 8 patients with new second primary cancers out of 75 women in this phase II trial is 11% with a minimum follow up of 5 years and median potential follow up of 81 months. Fowble et al has reported the incidence of second malignancy in 1,253 women treated with postlumpectomy radiation using conventional fractionation from 1978 to 1994 (25). There were 69 non-breast cancer and non-skin cancer second cancers out of 1,253 women with a median interval of 7 years for a crude incidence of 5.5%. There should be no biologic rationale for an increase in second cancers between this phase II trial of hypofractionation and concurrent boost and our larger patient population of whole breast radiation with a sequential boost. Four of the observed second cancers were pelvic tumors (ovarian, colon, endometrial, bladder) and two were extremity skin cancers where the dose between these two techniques from minimal internal scatter from the breast would be < 1%. Two second cancers were of the lung. The IMRT technique used in this protocol was step and shoot using tangential gantry angles similar to that used for conventional tangent radiation. This technique is associated with decreased lung dose rather than increased compared to conventional wedged tangential radiation (26, 27). None of the large prospective trials of whole breast irradiation with 5–10 year follow-up has reported differences in observed rates of second malignancy.

Randomized and nonrandomized data has shown superiority of WBI delivered with IMRT compared to 2D delivery methods. In one randomized trial from the United Kingdom, there was a negative change in breast appearance in 58% of patients randomized to 2D conventional treatment compared to 40% randomized to IMRT (28). In a second randomized trial from Canada, IMRT was associated with improved dose homogeneity and reduced
moist desquamation (31% vs. 48%, p=0.0019)(29). We have published the Fox Chase Cancer Center results of using breast IMRT compared to conventional radiation (30). The maximum toxicity by technique was grade 0/1 48% and grade 2/3 52% for IMRT, and grade 0/1 25% and grade 2/3 75% for conventional radiation (p<0.0001). For IMRT, 82% of weeks during treatment were spent with grade 0/1 and 18% with grade 2/3 dermatitis, compared with grade 0/1 29% and grade 2/3 71% for conventional radiation (p<0.0001). An important question is whether similar results as IMRT can be achieved with 3DCRT methods that give comparable coverage of the entire breast volume and exclusion of normal tissues on CT. To fully evaluate this, it is first necessary to establish target doses, normal tissue constraints, acceptable heterogeneity, and appropriate quality assurance for the delivery of WBI with CT-based volumes with 3DCRT and IMRT. Data will be forthcoming from a prospective randomized trial RTOG 1005 activated May 2011 that will compare hypofractionation with concurrent boost versus conventional or hypofractionated radiation with a sequential boost. 3DCRT or IMRT are allowable in both treatment arms as long as the same dose volume constraints are met.

Conclusion

This radiation schedule of whole breast hypofractionation with incorporated boost is associated with excellent local control at 5 years. This regimen is a good alternative to 6–7 weeks of conventional whole-breast fractionation with sequential boost, and is an option for most women requiring postoperative whole breast radiation. Patient-reported cosmesis, pain and arm function and physician-reported cosmesis showed no significant changes within 5 years. Whole breast radiation with a concurrent boost in a higher risk population of patients than treated in the previous hypofractionation randomized trials are being studied in a prospective randomized trial RTOG 1005.

Acknowledgments

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References


FIGURE 1.
5-year local control in 75 patients treated with whole-breast hypofractionation and concurrent boost.
Table 1

Pretreatment characteristics of 75 study patients.

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median years)</td>
<td>52</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71  96</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2   3</td>
</tr>
<tr>
<td>African-American</td>
<td>1   1</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>11  15</td>
</tr>
<tr>
<td>T1</td>
<td>50  67</td>
</tr>
<tr>
<td>T2</td>
<td>14  19</td>
</tr>
<tr>
<td>Bra Size</td>
<td></td>
</tr>
<tr>
<td>32, 34A, B; 36 A</td>
<td>12  16</td>
</tr>
<tr>
<td>34C, 36B, C; 38 A, B, C</td>
<td>35  47</td>
</tr>
<tr>
<td>Any D or 40 +</td>
<td>23  31</td>
</tr>
<tr>
<td>Unknown</td>
<td>5   6</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>53  71</td>
</tr>
<tr>
<td>N1</td>
<td>13  17</td>
</tr>
<tr>
<td>NX</td>
<td>9*  12</td>
</tr>
<tr>
<td>Side</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>33  44</td>
</tr>
<tr>
<td>Right</td>
<td>42  56</td>
</tr>
<tr>
<td>Chemotherapy prior to radiation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33  44</td>
</tr>
<tr>
<td>No</td>
<td>42  56</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>52  69</td>
</tr>
<tr>
<td>Negative</td>
<td>19  25</td>
</tr>
<tr>
<td>Unknown</td>
<td>4   5</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Invasive ductal</td>
<td>55  74</td>
</tr>
<tr>
<td>DCIS</td>
<td>13  17</td>
</tr>
<tr>
<td>Other</td>
<td>7   9</td>
</tr>
</tbody>
</table>

*All 9 NX patients had DCIS
Table 2

Patient-reported BCTOS scores for pain, function and cosmesis and physician-reported scores for cosmesis

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Time relative to radiation</th>
<th>Pain Mean ± STD</th>
<th>Function Mean ± STD</th>
<th>Cosmesis Mean ± STD</th>
<th>Physician-Reported Cosmesis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>Pre-treatment</td>
<td>1.64 ± 0.73</td>
<td>1.28 ± 0.44</td>
<td>1.64 ± 0.54</td>
<td>0.40 ± 0.60</td>
<td>72</td>
</tr>
<tr>
<td>56</td>
<td>6 weeks</td>
<td>1.81 ± 0.78</td>
<td>1.30 ± 0.56</td>
<td>1.67 ± 0.49</td>
<td>0.42 ± 0.53</td>
<td>60</td>
</tr>
<tr>
<td>57</td>
<td>8 months</td>
<td>1.66 ± 0.76</td>
<td>1.22 ± 0.42</td>
<td>1.69 ± 0.46</td>
<td>0.41 ± 0.62</td>
<td>58</td>
</tr>
<tr>
<td>46</td>
<td>14 months</td>
<td>1.67 ± 0.78</td>
<td>1.22 ± 0.40</td>
<td>1.66 ± 0.54</td>
<td>0.43 ± 0.54</td>
<td>46</td>
</tr>
<tr>
<td>37</td>
<td>20 months</td>
<td>1.50 ± 0.73</td>
<td>1.18 ± 0.55</td>
<td>1.64 ± 0.59</td>
<td>0.46 ± 0.64</td>
<td>39</td>
</tr>
<tr>
<td>37</td>
<td>26 months</td>
<td>1.63 ± 0.72</td>
<td>1.27 ± 0.57</td>
<td>1.71 ± 0.52</td>
<td>0.53 ± 0.70</td>
<td>36</td>
</tr>
<tr>
<td>29</td>
<td>32 months</td>
<td>1.39 ± 0.48</td>
<td>1.15 ± 0.25</td>
<td>1.69 ± 0.53</td>
<td>0.58 ± 0.72</td>
<td>31</td>
</tr>
<tr>
<td>20</td>
<td>38 months</td>
<td>1.30 ± 0.61</td>
<td>1.19 ± 0.36</td>
<td>1.73 ± 0.57</td>
<td>0.68 ± 0.75</td>
<td>19</td>
</tr>
<tr>
<td>17</td>
<td>44 months</td>
<td>1.57 ± 0.78</td>
<td>1.31 ± 0.74</td>
<td>1.63 ± 0.63</td>
<td>0.63 ± 0.83</td>
<td>19</td>
</tr>
<tr>
<td>13</td>
<td>50 months</td>
<td>1.30 ± 0.47</td>
<td>1.19 ± 0.44</td>
<td>1.75 ± 0.61</td>
<td>0.71 ± 0.83</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>56 months</td>
<td>1.33 ± 0.52</td>
<td>1.08 ± 0.23</td>
<td>1.79 ± 0.68</td>
<td>0.88 ± 0.64</td>
<td>8</td>
</tr>
</tbody>
</table>

Note: For patient-reported BCTOS, score of 1 is best and 4 is worst. For physician-reported cosmesis, score of 0 is best and 3 is worst.