Comparative Acute Toxicity from Whole Breast Irradiation Using 3-Week Accelerated Schedule With Concomitant Boost and the 6.5-Week Conventional Schedule With Sequential Boost for Early-Stage Breast Cancer

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Abstract

There is increased interest in establishing the therapeutic efficacy of shorter RT schedules in the treatment of early-stage breast cancer. In this study, we compared the acute toxicity of 3-week accelerated whole-breast irradiation with a concomitant boost to conventional fractionation delivered over 6 to 7 weeks. The results suggested no increased radiation toxicity with the shorter schedule.

Background: We aimed to evaluate the incidence of acute toxicity in a 3-week accelerated radiation therapy (RT) schedule with a concomitant boost compared with the 6.5-week conventional schedule with a sequential boost for early-stage, node-negative breast cancer. **Materials and Methods:** This study included the first 50 patients treated on protocol using the accelerated schedule as well as 74 patients with comparable stages of disease treated over the same period using the conventional schedule. An accelerated schedule of 40.5 Gy × 2.7 Gy/fraction to the whole breast with 4.5 Gy × 0.3 Gy/fraction concomitant boost, for a delivered total dose of 45.0 Gy × 3.0 Gy/fraction in 15 fractions to the lumpectomy site. The conventional schedule used 46.8 Gy × 1.8 Gy to the whole breast with a sequential boost of 14.0 Gy × 2.0 Gy/fraction, delivering a total dose of 60.8 Gy × 33 fractions to the lumpectomy site. The side effects observed during RT and through the initial 8 weeks after treatment were scored for acute toxicity. **Results:** A lower incidence of ≥ grade 2 skin toxicity was observed among patients treated on the accelerated schedule compared with those treated on the conventional schedule ($p = .0015$). There was a higher incidence of breast pain among patients receiving the conventional schedule ($p = .045$). No significant difference in the incidence of breast edema, fatigue, or hematologic side effects was observed between the 2 groups. **Conclusion:** Our observations suggest that there is acceptable toxicity with the accelerated schedule as used in this study. Further, it is not associated with a higher risk of acute toxicity when compared with the conventional schedule. Patients in the study are being followed, and clinical outcomes will be reported as the data mature.

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Introduction

Lumpectomy, with or without axillary lymph node sampling, followed by RT is a widely accepted treatment alternative to mastectomy for early-stage breast cancer.[1,2] RT is consistently shown to lower rates of local relapse in the ipsilateral breast. More recent data have also illustrated that the application of RT improves overall long-term survival. [3-5] In addition, randomized trials note that a 6.5- to 7-week RT course that includes delivering a boost after whole-breast irradiation improves local control.[6,7] Despite this clinical evidence, there is a lower use of RT and overall compliance with breast-conserving therapy. Among the various explanations for this practice pattern, 1 of the contributing factors suggested relates to a protracted 6- to 7-week duration of treatment.[8] Others have also suggested that the length of the RT course may negatively impact the quality of life of patients undergoing therapy.[9]

Outcome data from various studies suggests that the α/β ratio for breast cancer is closer to that of late-reacting tissues and may range between 3 and 4 Gy, a value higher than traditionally accepted for squamous cell cancer. This suggests that there may be a therapeutic benefit from accelerated schedules using a larger dose/fraction.[10-13] Accordingly there has been an interest in evaluating the effectiveness of a larger dose/fraction and a shorter RT schedule as an alternative to conventional fractionation. Published results from phase III randomized trials comparing accelerated and standard fractionated courses of whole-breast RT have reported equivalent results in patients with early-stage breast cancer.[14-16] The dose fractionation schedules in these trials did not routinely prescribe a boost, and when a boost dose was planned it was administered sequentially after whole-breast RT. In this article we report the incidence of acute toxicity of an accelerated dose fractionation schedule and compare it with the acute toxicity observed in patients treated contemporaneously with conventional fractionation.

Materials and Methods

This study included the first 50 patients who completed treatment in an institutional review board–approved protocol using a 3-week accelerated schedule with a concomitant boost and a group of 74 patients treated during that same period who met the inclusion criteria for the accelerated RT protocol but were treated using a conventional dose fractionation schedule. The eligibility criteria for the accelerated protocol, which also applied to the selection of the comparative group, included patients with stage Tis, T1, and T2 tumors up to 3 cm in size that were N0/N0i+. Patients of all ages and all histologic subtypes were eligible. Antiestrogen therapy was permitted when indicated. Patients with resection margins positive for disease and those receiving any adjuvant chemotherapy were not eligible.

On the accelerated RT schedule, the whole breast received a dose of 40.5 Gy in 15 fractions of 2.7 Gy each, and the lumpectomy site received a concomitant boost dose of 4.5 Gy in 15 fractions of 0.3 Gy each, thereby giving a total dose of 45 Gy in 15 fractions to the lumpectomy site. Patients treated on a conventional RT schedule received 46.8 Gy in 26 fractions to the whole breast, followed by a sequential boost of 14 Gy in 7 fractions of 2.0 Gy each to the lumpectomy site.

At simulation, custom immobilization was used to ensure reproducibility of patient positioning. All patients underwent computed tomography (CT) simulation. The whole-breast planning target volume (PTV) included the extent of breast volume identified on CT, excluding chest wall and 0.5-cm skin thickness. The boost PTV was identified using the lumpectomy cavity seroma and/or radiopaque clips plus a 1.5- to 2-cm margin except in proximity to skin or chest wall. The heart and lung volumes were also contoured. The 3-dimensional conformal RT plan using 2 tangent fields with dynamic wedge for the whole breast and 1 to 3 conformal fields for the boost dose was used for 16 patients in the accelerated-schedule group and 29 patients in the conventional-schedule group. With completion of the linear accelerator technology upgrade in our department, all subsequent patients were treated using a 4- to 7-segment field-in-field forward plan for the whole breast and a boost dose with either photons or electrons using 1 to 3 conformal fields. For dosimetric calculations, we routinely accounted for tissue density corrections.

Individualized treatment plans used either a photon/electron or photon/photon combination in order to achieve optimal coverage of the breast and boost volume by the prescription isodose (Figures 1 and 2). The RT plan was evaluated using a dose-volume histogram and conformance index, defined as the ratio of volume receiving the prescription dose to the PTV volume. In addition, we also defined V_{95} and V_{107} as the volumes receiving 95% and 107% of the prescribed dose, respectively. The dose to adjoining lung and heart was recorded using lung V_{20} and heart D_{05}, respectively. Further, the chest wall separation along the central axis of the tangents was recorded as a surrogate for body habitus and breast size.

The observation period for acute toxicity included weeks of therapy with follow-up through the first 8 weeks after treatment. As standard practice, the first follow-up for patients receiving conventional fractionation was at 8 weeks, whereas patients treated on protocol using the accelerated schedule were followed 1 week after completion and then again at 8 weeks. Acute radiation side effects were scored at weekly on-treatment visits using the National Cancer Institute Common Toxicity Criteria, version 3 toxicity scale.[17] Patient self-assessment of physical and emotional well-being using a 10-point scale (Symptom Distress Thermometer)[18] was also completed weekly while they received treatment. Patients continue to be followed at regularly scheduled intervals. At follow-up, directed breast examination is performed and breast imaging is obtained as clinically indicated. All patients are evaluated by the multidisciplinary team.

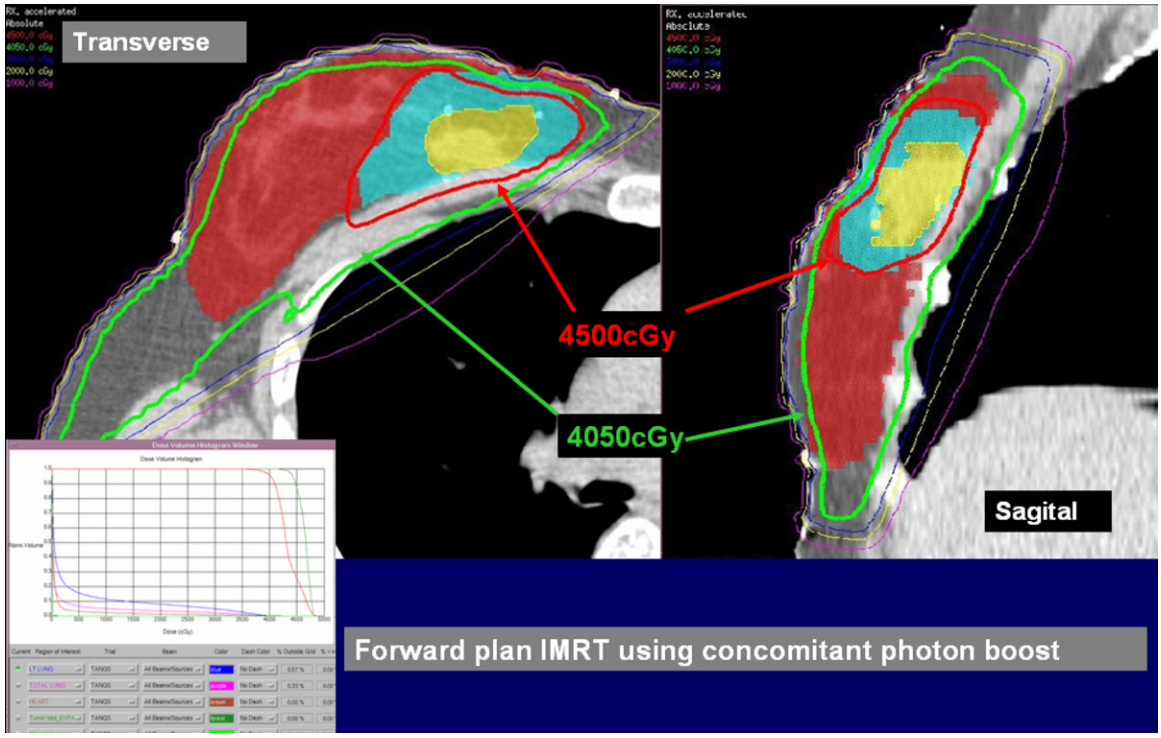
Statistical Analysis

Data was analyzed using the SAS system for data analysis, version 9.1[19] (SAS Institute Inc, Cary, NC). Univariate factors were analyzed using the χ^2 and Fisher's exact tests for categorical variables. Continuous variables were analyzed using the t test. All tests were 2-tailed, and differences were considered statistically significant at $2p \leq .05$.

Results

Table 1 summarizes pertinent treatment variables. The groups were fairly matched with the exception of age and beam modality for delivering the boost dose. The median age of patients treated using the conventional schedule was younger compared with the age of patients treated on the accelerated schedule ($2p < .0001$). While planning accelerated RT, there was a preference to use photons for delivering the concomitant boost even though an electron beam may have provided adequate coverage. Among patients planned for accelerated RT, the

Figure 1 Dosimetry from a Treatment Plan of Whole Breast RT with Concomitant Photon Boost



choice of electrons for the boost was limited to instances in which the boost target volume was shallow or when it was located at the medial or very lateral aspect of the breast. In contrast, conventional RT plans commonly used electrons to deliver the boost dose; this choice of beam is representative of the widely accepted standard of practice.

Analysis of dosimetry data revealed that the ratio of lumpectomy boost volume to breast volume was ≤ 0.35 in 95% of the plans and > 0.35 to 0.5 in 5% of plans. The V_{95} coverage for the whole breast and boost volumes was achieved at 99.4% for the whole breast volume and 99.7% for the boost volume. The 107% hot spot inhomogeneity within the target was not observed in most patients. Median dose received by D_{05} heart was 2.4 Gy; ≤ 5Gy in 90% of plans. The median V_{20Gy} lung was 7.6% and in 85% plans it was < 10%.

The incidence of acute toxicity using the National Cancer Institute Common Toxicity Criteria, version 3 toxicity scale is summarized in Table 2. We observed a significant difference in the grade 2 or higher acute skin toxicity between the 2 groups. There was a higher incidence of breast pain among the patients treated on the conventional schedule. This is probably a secondary effect of the higher rate of skin toxicity among these patients. We noted no difference in the incidence of breast edema, fatigue, or hematologic side effects between the 2 groups.

Discussion

For most cancers, a curative course of RT uses a ≤ 2-Gy fraction size when delivering a therapeutic dose to achieve a favorable therapeutic ratio.[10,13] A recent review of clinical outcomes on breast cancer from retrospective as well as randomized studies suggests that the α/β ratio may be higher than 2 Gy and possibly between 3 and 4 Gy. This higher α/β ratio for breast cancer falls within the same range as that for late-responding tissues in relation to the breast.[11,12] There is increased interest in accumulating clinical experience using a larger dose/fraction and shortened overall treatment time. In a randomized trial, Whelan et al compared 50 Gy in 25 fractions over 35 days and 42.5 Gy in 16 fractions over 22 days delivered using opposed tangential fields to the whole breast.[14] At a median follow-up of 5.75 years there was no difference between the 2 arms in 5-year local control, disease-free survival, and overall survival. Of note, patients in the randomized trial reported by Whelan et al did not receive a boost dose. However in practice when a boost is planned, it is often delivered sequentially after accelerated whole-breast RT. There is only limited experience with accelerated whole-breast RT with a concomitant boost, and this is mainly limited to reports from single-institution studies.[20-22]

The toxicity and cosmetic outcome of conventional fractionation using a dose of 1.8 to 2 Gy with a sequential boost has been well studied; an overall low risk of acute toxicity is well established and good to excellent cosmetic outcome in > 70% of patients has been reported.[1,3,23] The maximum width of breast tissue allowed was < 25 cm. The authors observed no difference in radiation morbidity and cosmetic outcome (defined as good or excellent) at 3 years (77%

Figure 2 Dosimetry from a Treatment Plan of Whole Breast RT with Concomitant Photon Boost

Table 1 Clinical Variables and Data on Treatment Planning

Variable	Conventional	Accelerated	t Test
No. of Patients	74	50	
Median Age (years; range)	55 (29-77)	67 (47-88)	$p < .0001$
Hormones (%)			NS
None	33 (45)	20 (40)	
Tamoxifen	21 (28)	11 (22)	
Aromatase inhibitor	20 (27)	19 (38)	
Technique (%)			NS
3-Dimensional CRT	29 (39)	16 (32)	
Field-in-Field Forward Plan	45 (61)	34 (68)	
Median Separation of Tangents at Central Axis (range)	20.5 (13-29)	21 (15-29)	NS
Boost Modality (%)			
Photons	17 (23)	39 (88)	$2p < .0001$
Electrons	57 (77)	11 (22)	

Abbreviations: CRT = conformal radiation therapy; NS = not significant.

Table 2 Distribution of Acute Toxicity by Dose Fraction Schedule

Toxicity	Conventional RT (%)	Accelerated RT (%)	2*p* Value
Skin			.0025
Grade 0/grade 1	56 (76)	48 (96)	
≥ grade 2	18 (24)	2 (4)	
Edema			0.59
Grade 0/grade 1	73 (98.6)	50 (100)	
≥ grade 2	1(1.4)	0	
Hematologic			.43
Grade 0	72 (97)	49 (98)	
Grade 1	2 (3)	1 (2)	
Pain			.045
Grade 0	40 (54)	34 (68)	
Grade ≥ 1	34 (46)	16 (32)	
Fatigue			.08
Grade 0/grade 1	65 (88)	48 (96)	
≥ grade 2	9 (12)	2 (4)	

Abbreviation: RT = radiation therapy.

vs. 76.8%) or 5 years (77.4% vs. 76.8%).[14] The observed toxicity on the conventional fractionation has been further reduced with the application of technical advances in RT planning and delivery. The potential advantage of using either a 3-dimensional conformal RT field-in-field forward plan or inverse plan intensity-modulated RT (IMRT) over 2-dimensional dosimetry reduces the dose inhomogeneity and hot spots within the target. In a randomized study by Pignol et al, the RT technique of field-in-field, 5 to 7 segments, was associated with a lower skin reaction when compared with historical

Table 3 Summary of Acute Toxicity Relative to Dose Fractionation Schedule and Overall Treatment Time

Reference (N)	Whole-Breast Dose Fractionation Schedule	Boost Sequence Dose Fractionation Schedule	Total Dose to Lumpectomy Site/ Treatment Time	Grade 0/1	Grade ≥ 2
Fisher et al[26] N = 171	2 Gy in 23 fractions	Sequential 2 Gy × 7 fractions	60 Gy/6 weeks	62%	38%
van der Laan et al[27] N = 90	1.81 Gy in 28 fractions	Simultaneous 0.49 Gy × 28 fractions	64.4 Gy/5.5 weeks	68%	32%
Freedman et al[28] N = 73	2 Gy in 23-25 fractions	Sequential 2 Gy × 7 fractions	60-66 Gy/6.5 weeks	79%	21%
Freedman et al[20] N = 74	2.25 Gy in 20 fractions	Simultaneous 0.55 Gy × 20 fractions	56 Gy/4 weeks	77%	23%
Vicini et al[29] N = 262	1.8 Gy in 25 fractions	Sequential 2 Gy × 8 fractions	61 Gy/6.5 weeks	56%	44%
Chadha[a] N = 74	1.8 Gy in 23 fractions	Sequential 2 Gy × 7 fractions	60.8 Gy/6.5 weeks	76%	24%
Chadha[a] n = 50	2.7 Gy in 15 fractions	Simultaneous 0.3 Gy × 15 fractions	45 Gy 3 weeks	96%	04%

[a] Current study.

2-dimensional wedge-pair plans evaluated on the isocenter slice only.[24] There is level 1 evidence from a Canadian multicenter randomized double-blind clinical trial that breast IMRT reduces acute dermatitis, and there is level 1 evidence from a UK randomized clinical trial[25] that breast IMRT improves long-term cosmetic results.

In our study of accelerated whole-breast RT with a concomitant boost, the radiation dosimetry plan favored using a photon beam for delivering the concomitant boost, even though in conventional dosimetry the electron beam may have provided adequate coverage. The concomitant boost selectively used an electron beam only when the boost volume was shallow or was placed at the edge of the breast volume. Table 3 summarizes acute toxicity reported in the literature.[17,26-29] The lower rates of toxicity we observed on the accelerated schedule are probably the result of a number of factors, including the total dose used, modality for delivering the boost dose, and the short overall treatment duration of RT. Acute toxicities were noted during the weeks of therapy and at the 8-week follow-up; because of the difference in length of treatment, the number of weeks for observation on the accelerated schedule were fewer than with the conventional schedule. To offset this observation period, patients on the accelerated schedule returned for evaluation of toxicity 1 week after completion of therapy. In both groups, an 8-week posttreatment evaluation was performed. Whether this difference in observation period contributed to the observed difference in skin toxicity is unclear. The most significant difference observed was a lower incidence of grade 2 skin toxicity with the accelerated schedule compared with the conventional schedule.

Fox Chase Cancer Center treated 75 patients with ductal carcinoma in situ and early-stage invasive breast cancer on a phase II IMRT whole-breast accelerated hypofractionation protocol.[20] The dose delivered to the whole breast was 45 Gy in 2.25-Gy fractions, and a concomitant electron boost of 0.55 Gy was used to deliver a total dose of 56 Gy in 2.8-Gy fractions to the lumpectomy site over 4 weeks. The authors reported acceptable acute toxicity, with no grade 3 or higher skin reactions. The maximum acute skin toxicity at the end of treatment was grade 0 in 9 patients (12%), grade 1 in 49 patients (65%), and grade 2 in 17 patients (23%). Cosmesis was good, with no significant differences between baseline and 6-week posttreatment patient-reported or physician-reported cosmetic scores.

DeWyngaert et al reported results in patients with stage I and stage II breast cancer treated on an accelerated schedule delivering 40.5 Gy to the entire breast in 2.7-Gy fractions and an additional dose of 0.5 Gy as a concomitant boost to the lumpectomy site for a total dose of 48 Gy in 15 fractions.[21] An inverse-plan IMRT technique was used to deliver the simultaneous integrated boost. In their experience, a concomitant inverse-planned IMRT boost added to a non-IMRT base plan for the whole-breast tangent fields was preferred. The authors found that this dosimetric plan spared radiation exposure to nonbreast tissue superiorly and inferiorly and also did not require fluence editing to eliminate high-dose areas as required in IMRT plans with simultaneous integrated boost. This plan also helped in reducing the volume of high-dose regions and maximum dose in the target.

There is limited evidence that inverse-plan IMRT technique renders more conformal plans; however there are limitations for its application when delivering a simultaneous integrated boost.[21,28] Our preferred approach for modulating dose to the breast and boost targets was to use a field-in-field technique for the larger whole-breast volume and a 3-dimensional conformal plan for the boost, delivering a small fraction of the dose to a smaller volume of target. Using this combination of technique in treatment planning provided flexibility for achieving dose optimization and individualizing RT plans for a wide range of variance in patient anatomy. Incorporating this straightforward approach for treatment planning is practical and permits wide applicability. With this combination for RT plans we were consistently able to achieve optimal target coverage and dose homogeneity with negligible hot spots. This dosimetry technique does not include the complexity and time involved in treatment planning and delivery using inverse-plan IMRT. Furthermore

there is limited application of breast IMRT because it is not widely accepted in the treatment of breast cancer.

Conclusion

The goal of this study was to evaluate acute toxicity of accelerated whole-breast RT with a concomitant boost. Our review of this preliminary group of patients suggests that the toxicity profile of the accelerated schedule as prescribed is acceptable. Within the constraints of a comparative group that may not be perfectly matched in all clinical variables as perhaps would be true in a randomized controlled trial, the data presented suggest no evidence of higher acute toxicity among patients receiving accelerated RT when compared with those receiving a conventional RT schedule. Longer follow-up is needed for evaluating late toxicity, cosmetic outcome, and local control.

Clinical Practice Points

- Published results from phase III randomized trials comparing accelerated and standard fractionated courses of whole-breast RT have reported the therapeutic efficacy of the shorter RT schedule among patients with early-stage breast cancer. There are additional ongoing trials worldwide to further establish the optimal dose fractionation schedule.
- The dose fraction schedules in the randomized trials already published did not routinely prescribe a boost, and when a boost dose was planned, it was administered sequentially after whole-breast irradiation. In the US, a randomized trial has just been opened (RTOG 1005) that will compare whole-breast irradiation and a concurrent boost with conventional RT. Our study provides single-institution experience with a similar study concept.
- The observations of this study add to the body of data on the feasibility and tolerability of accelerated whole-breast treatment with a concomitant boost. There is an expectation that more and more radiation oncologists will be using the shorter RT schedule in the foreseeable future and having the clinical outcomes as reported in our study will be helpful.

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