

Concurrent Boost with Adjuvant Breast Hypofractionated Radiotherapy and Toxicity Assessment

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Abstract

Background: The use of shorter radiotherapy schedules has an economic and logistic advantage for radiotherapy departments, as well as a high degree of patient convenience. The aim of this study is to assess the acute and short-term late toxicities of a hypofractionated radiotherapy schedule with a concomitant boost.

Methods: We enrolled 57 eligible patients as group A. These patients received 42.5 Gy in 16 fractions of 2.66 Gy each to the whole breast over 3.2 weeks. A concomitant electron boost of 12 Gy in 16 fractions was also administered which gave an additional 0.75 Gy daily to the lumpectomy area for a total radiation dose of 54.5 Gy. Toxicity was recorded at three weeks and at three months for this group as well as for a control group (group B). The control group comprised 76 eligible patients treated conventionally with 50 Gy to the whole breast over five weeks followed by a sequential electron boost of 12 Gy in 2 Gy per fraction.

Results: There were no statistically significant differences observed in the incidence of acute skin toxicity, breast pain, and edema recorded at three weeks or pigmentation and fibrosis recorded at three months between the two groups ($P < 0.05$). Acceptable toxicity occurred in both groups with no grade 3 or higher complications. Chest wall separation was highly correlated with toxicity in both groups ($P < 0.001$) while age showed no correlation ($P > 0.05$).

Conclusion: The results of this study suggest there are no increased acute and short-term late toxicities affiliated with the hypofractionated schedule plus a concomitant boost as prescribed compared to the conventional fractionation of adjuvant breast radiotherapy. Large randomized trials and long-term follow-up are needed to confirm these favorable findings.

Keywords: Concomitant boost, Hypofractionated irradiation, Toxicity, Breast cancer

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Introduction

Breast cancer is the most common cancer among females worldwide.

Although high in industrialized countries, its incidence is markedly increasing in low and middle income

countries.¹ Breast-conserving therapy (BCT) has become firmly established as a standard therapeutic approach for eligible women with early stage breast cancer over the past two decades.² Multiple prospective randomized trials have evaluated the benefit of radiation following conservative surgery.³⁻⁹ In these studies, postoperative radiotherapy resulted in a highly significant reduction in local recurrence compared to surgery alone. A pooled analysis of 15 randomized trials demonstrated a small significant increase in survival with the addition of radiotherapy.¹⁰ In addition, randomized trials have noted that a boost after whole-breast irradiation further improved local control compared to no boost.^{11,12} Despite this clinical evidence, there is lower use of radiotherapy and compliance with BCT.¹³ A possible explanation is the protracted six- to seven-week duration of treatment, which is an economic and logistic load on radiotherapy departments as well as a negative impact to the patient's quality of life.¹⁴ 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. This may suggest a therapeutic benefit from accelerated schedules using a larger dose/fraction.¹⁵⁻¹⁸

Therefore, an interest in evaluating hypofractionated schedules for breast cancer irradiation exists. Published results from phase III randomized trials comparing accelerated and standard fractionated courses of whole-breast radiotherapy have reported equivalent results in patients with early breast cancer.¹⁹⁻²¹ These trials, however, did not routinely include a boost. In trials where a boost was planned, it was administered sequentially after whole-breast radiation, which increased the overall treatment time. In the present study we reported the incidence of acute and short-term late toxicity of an accelerated dose fractionation schedule that employed a daily concurrent boost compared with the toxicity observed in patients treated with conventional fractionation.

Patients and Methods

This prospective study compared Group A, which consisted of the first 57 eligible patients who received post-operative breast irradiation in South Egypt Cancer Institute. Patients were treated according to an Institutional Review Board-approved protocol using an accelerated schedule with a concomitant boost and Group B (control) which included 76 eligible patients treated conventionally during approximately the same time period. The eligibility criteria for the two groups included patients with pathological stages T1 and T2 tumors that were N0 and N1. Patients aged 18 years and above with all histological types were eligible. Anti-estrogen therapy was given after completion of radiotherapy. Patients treated with chemotherapy were allowed to participate after two weeks from cessation of treatment. We excluded patients with positive histological margins.

On the accelerated schedule, the whole breast received 42.5 Gy in 16 fractions of 2.66 Gy; the lumpectomy site received a 12 Gy electron boost divided in 16 fractions of 0.75 Gy each over 3.2 weeks. Patients treated on the conventional schedule received 50 Gy to the whole breast over 5 weeks followed by a 12 Gy electron boost to the lumpectomy site in 2 Gy fractions.

At simulation all patients underwent computed tomography (CT) to generate a 3D plan. The planning target volume (PTV) included the extent of the breast volume as identified on CT, excluding a 0.5 cm skin thickness. The boost PTV was identified using the lumpectomy cavity seroma and/or surgical clips. If the tumor bed seroma was not easily palpated and surgical clips were not found, a 3-4 cm margin was placed parallel to the surgical scar with a 1 cm margin at the ends of the scar to define the boost PTV. The heart and lung were also contoured. Two tangential wedged fields for the whole breast were used and a matched supraclavicular field when indicated. An en face electron field for the boost volume prescribed at the 90% isodose line was given to all patients.

The radiation therapy plan was evaluated using a dose-volume histogram. V95 and V107 were

Table 1. Patients' characteristics.

Variable	Group A N=57	Group B N=76	P-value
Patients (N)			
Median age (years; range)	45 (21-68)	49 (22-70)	0.057
Laterality			
Right	26	32	
Left	31	44	0.686
Hormones received			
Tamoxifen	30	33	
Aromatase inhibitor	17	31	
None	10	12	0.421
Median separation of tangents at central axis (range)	21.5 (17-28)	21 (17-29)	0.938

defined as the volumes that received 95% and 107% of the prescribed dose, respectively. The chest wall separation along the central axis of the tangents was recorded as an indicator for body shape and breast size.

The period for toxicity recording included the period of therapy with weekly follow-up for the first three months post-treatment, in which radiation side effects were scored according to the National Cancer Institute Common Toxicity Criteria version 3 toxicity scale.²² Toxicity was assessed at three weeks (acute toxicity as the primary end point) and three months (short term late toxicity as the secondary end point) post-radiation.

Statistical analysis

Data was analyzed using Graphpad Prism version 5. Univariate factors were analyzed using the chi-square test for categorical variables and continuous variables with the t-test. All tests were 2-tailed and differences were considered statistically significant at $P < 0.05$.

Results

Table 1 summarizes relevant treatment factors. The groups were closely matched in terms of age, tumor side, hormone treatment received immediately after radiotherapy, and the median separation of tangents at the center. There was no significant difference noted for these factors, although age showed a trend toward significance which was due to the variability in ages that

acquired this disease.

Acute toxicity was assessed in terms of skin changes, edema and pain at three weeks and short-term late toxicity by pigmentation and fibrosis at three months. Table 2 shows the incidence of the development of each radiation side effect in the two groups. No grade 3 or higher complication occurred in either group. No cases of skin ulceration, fibrosis or telangiectasia were seen. The incidence of early and late complications was similar in the two groups with no statistically significant differences found due to the different radiation schedules.

Correlation was performed between age and chest wall separation, and the incidence of occurrence of early and late effects. The development of both acute and late complications were not related to patients' ages in both groups. However, chest wall separation was correlated with the acquisition of both early and late effects as assessed in both groups. Table 3 shows the correlation between age and chest wall separation with skin toxicity, edema, pigmentation and the development of complications for group A. Table 4 shows these correlations for Group B.

Discussion

Hypofractionation is highly beneficial both for patient convenience and economically for radiation departments due to the frequency of breast cancer. It is proposed to have sound radiobiological basis in breast cancer because of an estimated α/β ratio of 3 to 4 for these tumors.¹⁵⁻¹⁸

Table 2. Toxicity.

	Toxicity	Grade	Group A (n=57) N (%)	Group B (n=76) N (%)	P-value
Three weeks	Skin toxicity	0	16 (28.1)	21 (27.6)	0.114
		1	36 (63.1)	47 (65.8)	
		2	5 (8.8)	8 (10.5)	
	Edema	0	44 (77.2)	57 (75.0)	0.086
		1	13 (22.8)	19 (25.0)	
	Pain	0	37 (64.9)	53 (69.7)	0.210
		1	20 (35.1)	23 (30.3)	
Three months	Pigmentation	0	26 (45.6)	32 (42.1)	0.916
		1	25 (43.9)	35 (46.1)	
		2	6 (10.5)	9 (11.8)	
	Fibrosis	0	53 (93.0)	70 (92.1)	0.850
		1	4 (7.0)	6 (7.90)	

Hypofractionated schedules have been established as an alternative in numerous trials, hence hypofractionation for adjuvant breast irradiation in early breast cancer has been adopted by institutes such as the UK National Institute for Health and Clinical Excellence (NICE) as the standard of care.²³ However, boost fractionation is not as standardized. In order to maximize the benefit of the shortened overall time in the schedules using fewer fractions, a concurrent boost is an appealing alternative to sequential boost. There is limited data experience with accelerated whole-breast radiotherapy and a concomitant boost, mostly from single institution studies.²⁴

The present study was undertaken to evaluate the toxicity of a 12 Gy electron daily boost in 16 fractions which gave a 0.75 Gy electron boost to the lumpectomy area administered concurrently with the hypofractionated schedule of 42.5 Gy in 16 fractions for a total of 2.66 Gy daily to the whole breast over 3.2 weeks. We compared this irradiation schedule with the conventional 50 Gy over 5 weeks schedule followed by a 14 Gy boost administered as 2 Gy per fraction for an additional 1.5 weeks. In these preliminary results, no statistically significant difference was observed in the incidence of occurrence of skin toxicity, edema, or pain in the two groups at 3 weeks or at 3 months. Comparable acceptable toxicity was achieved in the two groups.

In the current study, there was grade 0 acute

skin toxicity observed in 16 patients (28.1%), grade 1 in 36 patients (63.1%), and grade 2 in 5 patients (8.8%) in those who received concomitant boost. These results were similar to those reported by Freedman et al.,²⁵ who treated 75 patients with a whole breast dose of 2.25 Gy per day for 20 fractions for a total of 45 Gy over 4 weeks by IMRT. An incorporated tumor bed boost was given simultaneously to the tumor bed of 2.8 Gy per fraction for a total of 56 Gy. The acute skin toxicity by the end of treatment was grade 0 in 9 patients (12%), grade 1 in 49 patients (65%), and grade 2 in 17 (23%). There was no grade 3 or higher skin toxicity, as in our study. Of note, in this trial grade 2 toxicity was slightly higher than the results of the current study. This might be attributed to the fact that results were assessed at the end of treatment by Freedman et al.²⁵ who reported that all grade 2 skin toxicities resolved at 6 weeks, whereas we reported acute toxicity at 3 weeks. Thus some of our cases of skin toxicity had resolved.

Formenti et al.²⁶ reported a clinical trial of IMRT, hypofractionation, and a concomitant boost that shortened treatment length to 3 weeks. They treated 91 patients with a whole-breast dose of 40.5 Gy delivered in 15 fractions with a concomitant boost of 0.5 Gy per day for a total tumor bed dose of 48 Gy. There were 2 acute grade 3 toxicities. Late soft tissue fibrosis was grade 1 in 48% and grade 2 in 3% of cases. This was higher than the fibrosis we reported. In the

Table 3. Correlation between age, chest wall separation and toxicity for Group A.

Complication	Age (<i>P</i> -value)	Chest wall separation (<i>P</i> -value)
Skin toxicity	0.84	<0.0001
Edema	0.37	<0.0001
Pain	0.84	=0.014
Pigmentation	0.45	<0.0001
Fibrosis	0.71	=0.012

current study, there were 4 patients (7%) who developed grade 1 fibrosis and no grade 2. A possible explanation was that we used electrons for the boost, whereas Formenti et al.²⁶ used photons. In a multivariate analyses performed in the EORTC 'boost versus no boost' trial, it was noted that a boost with photons instead of electrons made a statistically significant difference in the prediction of a higher degree of fibrosis.²⁷ Also, we assessed the patients at 3 months because our aim was acute, short-term late toxicity as a feasibility study for this hypofractionated regimen with a concurrent boost. Formenti et al. assessed patients at a median of 12 months which allowed more time for fibrosis to develop.

Chada et al.²⁴ reported acute toxicity in the first 50 patients enrolled in a prospective trial compared to a control group treated conventionally. The whole breast dose was 2.7 Gy per fraction in 15 fractions to a total dose of 40.5 Gy with a concomitant boost dose of 0.3 Gy per fraction to a total dose of 45 Gy. Both 3D-CRT and IMRT were used in the reported study. There was a lower incidence of grade 2 skin toxicity with the concurrent boost (4% versus 24%, $P=0.0015$) and a lower incidence of breast pain ($P=0.045$), which the authors attributed as secondary to skin toxicity. No difference was noted on the incidence of breast edema. The authors attributed the decrease in skin toxicity in the group treated with

hypofractionation to the lower total dose of radiation and the majority of patients on the concurrent schedule received IMRT and integrated photon boost instead of an electron boost, which might have improved the acute skin toxicity. There were no acute grade 3 or 4 toxicities.

Conclusion

The toxicity profile of the accelerated schedule, as prescribed, is acceptable with no higher acute and short-term late toxicity when compared to conventional radiation. These promising results need longer follow-up to evaluate late toxicity, cosmetic outcome, and local control.

Conflict of Interest:

No conflict of interest is declared.

Authors' contributions:

Mona M. Sayed participated in patient diagnosis, management, and manuscript writing. Mohamed I. El-sayed participated in patient diagnosis, management, statistical analysis, manuscript writing and final revision of the manuscript. Alia M. Attia participated in patient diagnosis and management. Mostafa E. Abdel-Wanis participated in patient diagnosis and management. All authors approved the final manuscript.

Table 4. Correlation between age, chest wall separation and toxicity for Group B.

Complication	Age (<i>P</i> -value)	Chest Wall Separation (<i>P</i> -value)
Skin toxicity	0.20	<0.0001
Edema	0.69	<0.0001
Pain	0.46	<0.0001
Pigmentation	0.53	<0.0001
Fibrosis	0.31	=0.029

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