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The Impact of Radiotherapy Boost Dose Delivery in Breast Cancer Treatment on Acute Skin Reactions and Cosmetic Outcome: A Randomized Trial of Sequential and Concomitant Schedules Boost

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Abstract

Background: Minimizing the overall treatment time is an issue of great importance in cancer management. Concomitant boost is a way of decreasing the overall treatment time in breast cancer. The present prospective randomized study aimed to evaluate the feasibility and toxicity and cosmetic outcome of concomitant weekly boost in patients with breast cancer.

Method: Patients with breast cancer who underwent breast conservation surgery and were referred to our Radiation Oncology department from 2018 to 2019 were included in this randomized clinical trial. They were randomized to two groups both of which received conventional (50 Gy in 25 fraction, 5 days a week) whole breast irradiation (WBI) with 10 Gy boost dose to lumpectomy cavity. The boost dose in one group (n = 40) was delivered concomitantly on the 6th day of each week. The other group (n = 42) received the boost dose sequentially after completion of conventional WBI. Skin toxicity and cosmetic outcome was compared between the two groups according to CTCAE-4 skin complications and Harvard criteria.

Results: We did not observe any significant differences between the sequential and concomitant groups in terms of acute skin reaction within and one month after completion of radiotherapy. After one year of follow-up, no significant differences were seen concerning the cosmetic outcome between the two groups. No local recurrence was observed after 22 months of follow-up.

Conclusion: Accelerated radiotherapy with weekly concomitant boost in breast cancer patients was found to be feasible with an acceptable toxicity profile and cosmetic outcome during one year of follow-up.

Keywords: Breast neoplasms, Radiotherapy, Concomitant boost, Toxicity, Cosmetic outcome

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Introduction

Radiotherapy is an important non-surgical treatment for breast cancer. Effective radiotherapy treatment depends extensively on the patient's compliance and willingness to complete a course of treatment that typically extends over six weeks.[1,2] In addition, the boost dose has been suggested to decrease the rate of local failure, without having an impact on survival.[3,4] Thus, decreasing the overall treatment time might increase patients' compliance to complete the treatment course, resulting in a greater utilization of post-operative radiotherapy with economic and logistic advantages for radiotherapy departments. In this regard, a concomitant boost might be used to reduce the overall treatment time down to five weeks instead of six weeks in sequential boost dose delivery.[4]

On the other hand, skin reaction is the most prevalent side-effect of radiotherapy, with as many as 95% of patients experiencing a certain degree of this kind of reaction.[1-5] The degree might be affected by several factors, such as chemotherapy, hormone therapy, high body mass index (BMI), as well as radiotherapy-related factors, including dose, overall treatment time, treated volume, and radiotherapy technique.[6,7]

Skin reaction due to radiotherapy is an unpleasant phenomenon, which could significantly decrease the quality of life in breast cancer patients and in severe cases, it may even lead to treatment discontinuation.[8,9]

In order to minimize the overall treatment time, we aimed to evaluate the feasibility and side-effects of concomitant boost compared to conventional sequential boost in breast cancer patients.

Material and Methods

In this randomized clinical trial, the patients diagnosed with breast cancer who underwent breast conservation surgeries (BCS) were enrolled. Randomization was done with permuted block method. We conducted this trial in the Radiation Oncology Department of Cancer Institute, Tehran University of Medical Sciences, from December 2018 to December 2019. The enrolled patients were randomly divided into two groups of concomitant boost and sequential boost. The trial protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences (Trial No: IR.TUMS.IKHC.REC.1398.02) under the IRCT registration code of IRCT20220 221054089N1. All the participants provided written informed consent.

All the patients received a complete course of whole breast radiotherapy (with or without nodal irradiation), from Saturday to Wednesday (50 Gy in 25 fractions). WBI was performed with 3D conformal technique and two tangential fields. In the concomitant boost group, 10 Gy boost dose was delivered in five fractions, each of which carried out on the 6th day of the week. Meanwhile, in the sequential group, the same dose was delivered in five subsequent fractions, after completion of the whole breast radiotherapy. Tumor bed was defined through sonography, and according to the depth of tumor bed, the boost dose was delivered via electron beams with 9-12 MeV energy. 2-cm margin was added to the tumor bed to define the boost target volume.

The overall treatment time was five and six weeks for the concomitant and sequential boost dose schedules, respectively (Figure 1).

The inclusion criteria were the age of over 18 years, pathologically-proven breast tumor (pT1-3pN0-2M0), surgery with a negative margin, and distance from the midline to the mid-axilla line (separation) of below 25 cm (in order not to lose the homogeneity of the dose in the tissue). The exclusion criteria included a history of

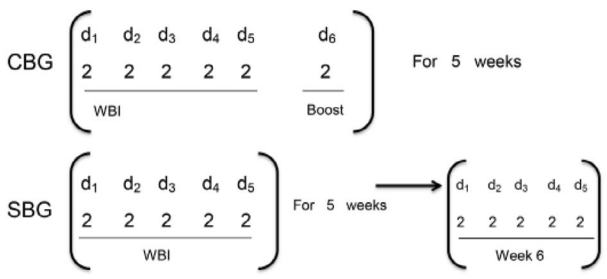

Figure 1. This figure shows the treatment schedules in the two groups (CBG and SBG).
CBG: Concurrent boost group; SBG: simultaneous boost group; WBI: Whole breast irradiation; 2: Two Gy

Table 1. The frequency of the patients and disease charectristic

Items	Sequential boost group	Concomitant boost group
Age		
20-40	4 (9.52%)	3 (7.5%)
40-50	10 (23.8%)	12 (30%)
50-60	21 (50%)	18 (45%)
Over 60	7(16.6%)	7 (17.5%)
Tumor grade		
Grade 1	4 (9.5%)	3 (7.5%)
Grade 2	27 (64.2%)	20 (50%)
Grade 3	11 (26.19%)	17 (42.5%)
Others		
Estrogen - Progesterone	34 (80.95%)	33 (82.5%)
Her2+	11 (26.19%)	14 (35%)
Tumor stage		
T1-T2 N0	8 (19%)	11(27.5%)
T1-T2 N1-2	32 (76.19%)	27 (67.5%)
T3N0	1 (2.4%)	0
T3N1	1 (2.4%)	2 (5%)

Her2: Human epidermal growth factor-2

radiotherapy in the contralateral breast, the presence of multifocal disease, critical non-malignant disease (cardiovascular or pulmonary), a history of connective tissue disease and invasive breast cancer, hormone therapy during radiotherapy, and positive surgical margin.

The initial condition of the patients' breast cosmetics was scored based on Harvard criteria, consisting of the surgical scar, the difference in the size of the two breasts, the condition of the nipple, the retraction of the nipple, and the condition of the areola (acceptable = 0, significant difference = 1). Based on the total score, the patients were divided into four groups of excellent (1-0), good (2), relatively good (3), and weak (4-5) conditions.

Skin toxicities were recorded based on version 4 of the Common Terminology Criteria for Adverse Events (CTCAE). In both groups, we assessed skin toxicity on a weekly basis during radiotherapy and one month after completion of radiotherapy. The cosmetic results were scored six and 12 months after the treatment according to Harvard criteria. In order to obviate the inter-observer bias, the same specialist, who was blinded to the treatment arms, performed all the pretreatment and post-treatment scorings.

Data collection was performed using the breast cancer radiotherapy skin registration form employing two methods, namely concomitant boost and sequential boost. In this form, some factors, such as age, history of chemotherapy or hormone therapy, type of radiotherapy, the patient's cosmetics score at the time of the treatment initiation, as well as skin complications during radiotherapy were recorded 1, 6, and 12 months after the treatment.

The statistical analysis was done via SPSS version 24. T-test was conducted to compare the means of cosmetic score in the two groups. We used Kendall's test to examine the toxicity grade of the patients during radiotherapy. *P* value <0.05 was the critical criterion for statistical significance. Moreover, the sample size was calculated with G*Power software version 3, considering the power of the study, reaching 0.8 and $\alpha = 0.05$.

Results

Herein, we recruited 82 patients diagnosed with breast cancer, with 42 in the sequential boost group and 40 in the concomitant boost group. The majority of the subjects were in the age group of between 50 and 60 years old. The mean age in each group was almost the same. According to table 1, there are no significant differences in terms of age distribution, tumor stages, and hormone receptor status between these two groups. The most frequent disease stage in both groups was T2N1 (40% in the concomitant boost group and 28.6% in the sequential boost group). Based

Table 2. Acute skin reaction due to radiotherapy

Time	Concomitant boost group					Sequential boost group				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Week 2	90% (36)	7.5% (3)	2.5% (1)	0	0	97.7% (41)	2.3% (1)	0	0	0
Week 3	65% (26)	35% (14)	0	0	0	78.5% (33)	21.5% (9)	0	0	0
Week 4	20% (8)	67.5% (27)	12.5% (5)	0	0	38 % (16)	57.1% (24)	4.7 % (2)	0	0
The last week	0	65% (26)	22.5% (9)	12.5% (5)	0	11.9% (5)	69% (29)	14.9% (6)	4.7% (2)	0
Month 1	52.5% (21)	47.5% (19)	0	0	0	57.1% (24)	42.8% (18)	0	0	0

on Harvard criteria, all the patients enrolled in this study had excellent and good initial cosmetic score and there were no significant differences between the two groups with regard to primary cosmetic condition. Out of the total of 82 patients, 74 were followed for 6 months, while 65 were followed for 12 months. 35 subjects (47.2%) in the concomitant boost group and 39 (52.8%) in the sequential boost group had a 6-month follow-up. After 1 year, 34 patients (52.3%) in the sequential boost group and 31 (47.6%) in the concomitant boost group were reachable to be assessed for cosmetic outcome. There was no local recurrence in the concomitant or the sequential groups following 22 months of follow-up.

Kendall's test was used to examine the toxicity grade of the patients during radiotherapy. No significant skin reactions were observed in the second week of radiotherapy. However, in the third week, mostly grade 1 skin reaction was observed. In the concomitant boost group, the frequency of grade zero toxicity decreased from 65% in the third week to 20% in the fourth week. Nonetheless, grade 1 side-effects increased from 35% to 67.5% in the fourth week. In the sequential boost group, the frequency of grade zero toxicity dropped from 78.5% in the third week to 38% in the fourth week, while the frequency of grade 1 increased from 21.5% in the third week to 57.1% in the fourth week.

In the fourth week, as shown in table 2 (K2 statistical test), the frequency of grade1-2 toxicity was 80% in the concomitant boost group and 61.8% in the sequential boost group but the difference was not statistically significant ($P > 0.05$). In the last week of radiotherapy, all the patients in the concomitant boost group had some degree of skin reaction of mostly grade 1 (65%); whereas in the sequential boost group, five (11.9%) cases did not have any skin reactions and 69% had grade 1 skin toxicity ($P > 0.5$). One month after the completion of radiotherapy, no skin reaction was observed in 25% of the patients in the concomitant boost group and 28.57% of them in the sequential boost group. Overall, there were no differences in terms of the grade of skin toxicity between the two groups after one month.

The average planning target volume (PTV) was 1115.65 cm^3 and 945.08 cm^3 in the concomitant and sequential boost groups, respectively. In both groups, the analysis failed to show any significant associations between PTV and the frequency of acute complication ($P > 0.05$).

To evaluate the cosmetic outcome, the patients were visited by the same physician 6 and 12 months after the treatment. As shown in table 3, after 6 months, the frequency of excellent and good results in the concomitant boost group was 71.4% and 28.6%, respectively. In the sequential boost group, the frequency of excellent and good results after 6 month was 74.3% and 25.64%, respectively. The differences in the two groups were not statistically significant ($P > 0.05$). Following 12 months, the frequency of excellent and good results in the concomitant boost group was 62.96% and 33.33%, respectively. In the sequential boost group, the frequency of excellent and good results after 12 month was 65.51% and 34.48%, respectively. The differences between the two groups were not statistically significant ($P > 0.05$).

Discussion

In this study, we evaluated the feasibility and toxicity of accelerated radiotherapy with weekly concomitant boost dose compared to conventional

Table 3. Cosmetic outcome due to radiotherapy

	Concomitant boost group				Sequential boost group			
	Excellent	Good	Fair	Poor	Excellent	Good	Fair	Poor
Initial condition	80% (32)	20% (8)	-	-	80/9% (34)	19/04% (8)	-	-
After 6 months	71/4% (25)	28/6% (10)	-	-	74/35% (29)	25/64% (10)	-	-
After 12 months	61/2% (19)	35/4% (11)	3/2% (1)		64/7% (22)	35/2% (12)	-	-

fractionated radiotherapy with sequential boost dose in breast cancer patients. The obtained results suggested that concomitant boost dose is feasible with similar acute skin toxicity and final cosmetic results compared to sequential boost dose.

To the best of our knowledge, no other studies have investigated the toxicity and feasibility of weekly concomitant boost in conventional whole breast radiation (50 Gy in 25 fraction). On the other hand, there are investigations evaluating the feasibility of weekly concomitant boost in hypo fractionated regimen.[10] Our findings are in line with those of Ghannam et al. who evaluated cosmetic outcome and skin toxicity of concomitant boost radiotherapy in hypo fractionated regimen. They reported 74% skin toxicity of grade 0-1 at the end of the treatment with an acceptable cosmetic result after 31 months of follow-up. The authors concluded that concomitant boost was feasible with good therapeutic results in hypo fractionated regimen. In another study in Genoa University, in patients in the early stages of breast cancer submitted to hypo fractionated radiotherapy and concomitant weekly boost, after 24 months of follow-up, late toxicity was G0 in 92%, G1 in 7%, and G2 in 1% of the patients. Additionally, the cosmetic was excellent or good in 95% of them. They did not report any local recurrence after 33 months of follow-up.[11]

Cante et al. indicated the effectiveness and acceptable skin toxicity of concomitant boost radiotherapy in hypo fractionated regimen as well. According to them, acute skin toxicity was seen in 57% of the patients and the cosmetic results were excellent or good in 96% of them, with no local recurrences after 60 months of follow-up.[12] In the present study, we did not observe any kinds of locoregional recurrence after 22 months of follow-up.

The severity of skin reaction has been linked to different factors, including history of smoking, stage of the disease, dose of radiation and energy of the beam used for boost delivery, race, skin type and color, and breast size and volume.[13-15] Among the aforementioned factors, the dose of radiation and boost energy has been reported to be the most predictive factor to induce severe skin reactions.[16-18] Herein, the boost dose was 10 Gy in both groups and the electron energy was 9-12 MEV; thus, the comparable skin reaction and cosmetic outcome in the two groups could be explained.

In a study by Hannan et al., although with an increase in the breast size, the maximum dose to the skin would rise, the overall skin toxicity did not significantly change due to breast size.[19] In our paper, no relationship was identified between PTV and the severity of skin reaction.

The results of this study revealed that accelerated radiotherapy with concomitant weekly boost would not increase acute skin toxicity compared to conventional sequential boost. After 1 year of follow-up, the cosmetic outcome was also comparable in the two types of boost regimen. Even though several guidelines, like UK national Institute for Health and clinical Excellence (NICE),[20] consider hypo fractioned regimen as the preferred schedule for early-stage breast cancer, the results of the present study are still beneficial for the patients who need a supraclavicular field and are candidate for conventional whole breast irradiation.[21]

To the best of our knowledge, this research is the only one in which the effect of concomitant radiation boost was assessed in conventional radiotherapy of breast cancer. Regarding the limitation of the study, we could mention the small sample size and the fact that some of the patients were lost to follow-up for long-term toxicity assessment.

Conclusion

In conclusion, the results of this study shed light on the fact that the boost dose delivery schedule might not be a significant factor for acute skin toxicity and cosmetic outcome in radiotherapy of breast cancer. With confirmation of the results after a longer follow-up, accelerated radiotherapy with concomitant boost might be safely used to reduce the overall treatment time from 6 weeks to 5, which would be conducive to increasing patients' convenience, while decreasing the workload in radiation oncology departments. This result might be beneficial in developing countries suffering from shortage of radiotherapy facilities.

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Conflict of Interest

None declared.

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