Phase 3 study comparing weekly concomitant boost for breast cancer patients treated with conservative breast surgery with sequential boost.

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Background: Radiation therapy after breast conserving surgery is a standard part of treatment for invasive breast cancer. Based on radiobiological models, it was found that shorter hypofractiontaed radiation schedules had equivalent local control to standard radiation therapy. Radiation boost to the tumor bed was evident to be associated with significant improvement in local control.
Methods: This study included 48 female patients with early breast cancer who underwent breast conservative surgery. There were two arm of radiation, hypofractionated radiotherapy with concomitant boost (group A) - hypofractionated radiotherapy with sequential boost (group B).
Results: after median follow up 43 months range (21-57). Four year over all survival rate for concomitant boost arm was (91.67%) and sequential boost arm was (87.50%), Four year disease free survival rate for concomitant boost arm was (87.5%) and sequential boost arm was (79.17 %). late skin toxicity, grade 0 was (72.73%) in concomitant boost arm and (54.55%) in sequential boost arm and grade 1 was (9.09%) in concomitant boost arm and (31.82%) in sequential boost arm and grade 2 was (18.19) in concomitant boost arm and (13.55%) in sequential boost arm, grade 3 late lung toxicity was (4.17%) in concomitant boost arm and (12.50%) in sequential boost arm, cardiac toxicity in concomitant boost arm (8.33%) and sequential boost arm (16.67%).The ipsilateral lymphedema after 24 months of follow up G2 (4.55%) in concomitant boost arm G3 (4.55%) in in sequential boost arm.
Conclusion: A shortened whole breast irradiation schedule with a weekly concomitant boost may be an alternative option with acceptable toxicity and excellent cosmesis.

Introduction

Breast-conserving therapy (BCT) for early stage result in survival rate equivalent to that of mastectomy, therefore BCT became the standard treatment of stage I– II breast cancer [1]. Radiation therapy represents the standard adjuvant treatment after breast conserving surgery (BCS) as it associated with a 70% reduction in the risk of recurrence [2] and a 9-12% reduction in the risk of death [3]. Conventional radiotherapy given in 6-7 weeks has economic and logistic load on radiotherapy departments as well as negative impact on patient's quality of life. Recent randomized trials have confirmed that hypofractioned whole-breast irradiation is equivalent to more conventional whole-breast irradiation with respect to local recurrence and cosmetic outcome [4]. In order to intensify treatment, a simultaneous boost dose, concomitant or integrated, has been introduced in clinics by using 3-D conformal radiotherapy [5]. Current study being prospective in nature to confirm the feasibility of weekly concomitant boost and comparability in term of local control, toxicity, survival to sequential boost.

Patients and Methods

This prospective study included 48 female patients with early breast cancer. Who received adjuvant radiotherapy in the radiotherapy department in Sohage University Hospital, Egypt, in period between March, 2014 and July, 2018 Patients

with age of 18 years and above, with all histological types and grades, pathological T1-T2 tumors,N0 and N1 disease with negative surgical margins after breast conservative surgery. Were eligible and written consent was taken from each patient then randomly Allocated into two groups.

A- The total whole breast radiation dose was 42.5 Gy in 16 fractions while the area of the lumpectomy cavity received additional 3Gy through once weekly 1 Gy concomitant boost.

B- The total whole breast radiation dose was 42.5 Gy in 16 fractions followed by sequential boost.

Radiation:

Patients treated in the supine position on a wedged board with both arm abducted and externally rotated. CT planning in CT simulation will patient in the same treatment position was used for the localization and determination of the target volumes, organ at risk, and the field arrangement. The CT scans were done in the supine position from the level of the larynx to the upper abdomen with both lungs were included and the scan thickness was 5 mm. The Whole Breast Clinical Target Volume (WB-CTV) included the glandular breast tissue. The Whole Breast Planning Target Volume (WB-PTV) was generated by the addition of a 5 mm margin around the WB-CTV. The Boost Clinical Target Volume (CB-CTV) was generated by adding at least a 10 mm margin around the lumpectomy cavity and the corresponding PTV (CB-PTV) created by adding a further 5 mm margin. The total whole breast radiation dose was 42.5 Gy in 16 fractions while the area of the lumpectomy cavity received additional 3Gy through once weekly 1 Gy concomitant photon boost in group A or received additional 10-16 Gy a sequential boost in group B.

Assessment and Follow up:

Clinical evaluations were performed weekly during treatment course for assessment of acute toxicity. A follow-up evaluation was performed every three months after treatment end for evaluation of the late radiation toxicity, disease free survival and local control. all patient evaluated by ECHO before radiotherapy and every 6 month after treatment to monitor change in left ventricular ejection fraction in comparison with base line assment. The RTOG scoring system for radiation reactions was used to score radiation toxicity.

Results

Variable	Concomitant boost N=24	Sequential boost N=24	P value
Age/years			
Mean ± SD	45.92±7.37	50.17±10.82	0.12
Median (range)	46 (27-60)	51 (33-65)	
Site			
Right	13 (54.17%)	7 (29.17%)	0.08
Left	11 (45.83%)	17 (70.83%)	
Quadrant			
Lower inner	4 (16.67%)	2 (8.33%)	
Lower outer	2 (8.33%)	7 (29.17%)	
Supra areolar	3 (12.50%)	1 (4.17%)	0.14
Upper inner	1 (4.17%)	4 (16.67%)	
Upper outer	14 (58.33%)	10 (41.67%)	
Pathology			
IDCA	24 (100%)	24 (100%)	1.00
Tumor grade			
2	22 (91.67%)	23 (95.83%)	1.00
3	2 (8.33%)	1 (4.17%)	
Tumor size			
Mean ± SD	2.70±0.77	2.66±0.79	0.85
Median (range)	2.75 (1.5-4)	2.5 (1-4)	
Number of positive LN			
Mean ± SD	1 ±1.28	1.25 ±1.26	0.47
Median (range)	0 (0-3)	1 (0-3)	
Number of removed LN			
Mean ± SD	22.08±6.20	16.29±5.66	0.003
Median (range)	22 (12-39)	14 (6-25)	
Estrogen receptors			
Negative	5 (20.83%)	8 (33.33%)	0.33
Positive	19 (79.17%)	16 (66.67%)	
Progesterone receptors			
Negative	7 (29.17%)	8 (33.33%)	
Positive	17 (70.83%)	16 (66.67%)	0.76
HER2			
Negative	17 (70.83%)	17 (70.83%)	1.00
Positive	7 (29.17%)	7 (29.17%)	

Table (1) Patients characteristic in concomitant and sequential boost groups

Variable	Concomitant boost N=24	Sequential boost N=24	P value
Acute skin toxicity			
G0	8 (33.33%)	4 (16.67%)	
G1 dry desquamation	10 (41.67%)	6 (25.00%)	
G1 mild erythema	3 (12.50%)	3 (12.50%)	0.18
G2 tender erythema	2 (8.33%)	4 (16.67%)	
G3 moist desquamation	1 (4.17%)	6 (25.00%)	
G4 ulceration	0	1 (4.17%)	
Late skin toxicity 12ms			
G0	8 (33.33%)	5 (20.83%)	
G1	5 (20.83%)	3 (12.50%)	
G2	10 (41.66%)	16(66.67%)	0.19
G3	1 (4.17%)	0	
Late skin toxicity 24ms	N=22	N=22	
G0	16 (72.73%)	14 (54.55%)	
G1	2 (9.09%)	7 (31.82%)	0.24
G2	4 (18.19%)	3 (13.64%)	

Table (2) skin toxicity in concomitant and sequential radiotherapy boost groups

Variable	Concomitant boost N=24	Sequential boost N=24	P value
Acute lung toxicity			
G0	23 (95.83%)	23 (95.83%)	1.00
G2 cough dyspnea	1 (4.17%)	1 (4.17%)	
Late lung toxicity			
G0	23 (95.83%)	21 (87.50%)	0.30
G3 dense radiograph	1 (4.17%)	3 (12.50%)	
Heart toxicity			
No	22 (91.67%)	20 (83.33%)	0.38
Yes	2 (8.33%)	4 (16.67%)	

Table (3) lung and heart toxicity in concomitant and sequential radiotherapy boost groups

Variable	Concomitant boost N=24	Sequential boost N=24	P value
Arm lymphedema before RT			
G0	22 (91.67%)	24 (100%)	
G1 mild lymphedema	2 (8.33%)	0	0.15
Arm lymphedema after12 ms of RT	19 (79.17%)	22 (91.67%)	
G0	2 (8.33%)	1 (4.17%)	0.24
G1 mild lymphedema	3 (12.50%)	1 (4.17%)	
G2 moderate lymphedema			
Arm lymphedema after24 ms of RT	N=22	N=22	
G0	21 (95.45%)	21 (95.45%)	
G2 moderate lymphedema	1 (4.55%)	0	0.37
G3 severe lymphedema	0	1 (4.55%)	

Table (4) Arm lymphedema in concomitant and sequential radiotherapy boost groups

Variable	Concomitant boost N=24	Sequential boost N=24	P value
Time from diagnosis to death/end of study			
Mean ± SD	3.65±0.82	3.45±0.82	0.42
Median (range)	3.70 (2.04-4.86)	3.50 (1.76-4.69)	
Death			
No	22 (91.67%)	21 (87.50%)	1.00
Yes	2 (8.33%)	3 (12.50%)	
Time from surgery to recurrence/end of study			
Mean ± SD	3.47±1.03	3.19±1.08	0.36
Median (range)	3.68 (1.20-4.80)	3.42 (1.05-4.69)	
Recurrence			
All	3 (12.50%)	5 (20.83%)	0.44
Local	0	0	1.00
Distance	3 (12.50%)	4 (16.67%)	1.00
Nodal	0	1 (4.17%)	1.00

Table (5) Follow up and fate in concomitant and sequential radiotherapy boost groups

Discussion

In our study follow up schedule from time of diagnosis till end of study or death, time of surgery till end of study or recurrence showed no statistically significant difference Table (5**)** with median follow up 43 months range (21-57). Four year OS rate for group A was (91.67%) and group B was (87.50%) with no statistically significant difference P value=1.00, Four year disease free survival rate for group A was (87.5%) and group B was (79.17 %) with no statistically significant difference P value=0.44 while Corvo et al [7] median follow-up 33 months, range: 24-41 months, Two year disease free survival rate (94.6%).

Regarding the treatment outcomes incidence of death for group A was (8.33%) and for group B was (12.50%) with no statistically significant difference P value=1.00.

disease relapse occurred only in 8 patients (33.34%), Distance recurrence for group A was 3 (12.50%) and group B was 4 (16.67%), one patient in group B (4.17%) developed nodal recurrence, with no statistically significant difference P value=0, 44, while Corvo et al [7] disease relapse was 5.4%.

Acute skin complication in our study were assessed during the treatment and up to 12 weeks, The incidence of grade 1 (dry desquamation) was (41.67%) in group A and (25.00%) in group B and grade 2 was (8.33%) in group A and (16.67%) in group B. but acute skin toxicity reported at Guenze et al [6] where grade 1(39%) grade 2 was 9 %. While Corvo et al [7] reported12 % of patients developed grade 2 acute skin toxicity so our results are comparable to that shown in the reported studies.

In our study late skin toxicity 24 ms, the incidence of grade 0 was (72.73%) in group A and (54.55%) in group B and grade 1 was (9.09%) in group A and (31.82%) in group B and grade 2 was (18.19) in group A and (13.55%) in group B, but late skin toxicity

reported at Guenze et al [6]. where G0 (52%) G1 (45%) G2 (3%) while late skin toxicity reported at Corvo et al[7] where G0 in 92%, G1 in 7% and G2 in 1% of patients, so our results are comparable to that shown in the reported studies as regard incidence of grade 1 late skin toxicity in group A .

In our study, the acute radiation induced pnumonitis was reported as grade 2 was (4.17%) in both groups, while the chronic toxicity reported as grade 3 late lung toxicity was (4.17%) in group A and (12.50%) in group B. These results also are comparable to those reported by Shahid et al [8], where 5% of patients developed acute pulmonary radiation toxicity and El-Hadaad et al [9] grade 1 late lung toxicity was 5.5%.

In our study, the cardiac toxicity was evaluated by measuring the left ventricular ejection fraction at base line and every 6 months after radiotherapy. In our study we had only two patients in group A (8.33%) and four patients in group B (16.67%) who showed drop more than 10% below the base line left ventricular ejection fraction (LVEF). while Shahid et al[8] reported that cardiac toxicity occurred in 5% to 6% of patients between the three hypo fractionated schedules so our patients showed more toxicity as most of patients received anthracyclin combined with taxan based chemotherapy and tamoxifen as hormonal treatment and some patients received trastuzomab contaning regmin

Regarding the ipsilateral lymphedema, in our study 12 at months of follow up G1 lymphedema (8.33%) in group A, (4.17%) in group B, G2 moderate lymphedema (12.50%) in group A (4.17%) in groupB. After 24 months of follow up G2 moderate lymphedema (4.55%) in group A G3 severe lymphedema (4.55%) in groupB while Shahid et al[8]reported that G2 and G3 lymphedoema was 21%, 22% and 27% between the three hypo fractionated schedules. recently published systematic review and meta-analysis on the incidence of unilateral lymphedema after breast cancer where a pooled estimate of lymphedema in the 72 studies showed an incidence of edema of 16.6% as reported by Disipio et al [10].Our lower rates of lymphedema toxicity may be due to avoid using axillary radiation in separate fields in node positive patients.

Conclusion

We suggest that this radiation schedule may provide an alternative option to conventional WBI with acceptable acute and late toxicity, good compliance and excellent cosmesis.

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