Retrospective Study Evaluating Hypofractionated Radiotherapy Concomitantly with Weekly Boost for Early Breast Cancer Patients Treated with Conservative Breast Surgery

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Abstract:

Background: Breast cancer is the most life- threatening cancer, as it remains leading cause of women death among less developed countries, however in developed countries. Based on radiobiological models, it was evident that hypofractionated radiation schedules used as adjuvant treatment for breast cancer offer equivalent local control to standard conventional radiation therapy by giving larger doses per fraction in shorter period of time.

Patients & Methods: This retrospective study included 50 female patients with early stage (T1-2 N0-1 M0) breast cancer who underwent breast conservative surgery. All patients received adjuvant radiotherapy at the radiotherapy department of South Egypt Cancer Institute (SECI), Assiut University, Egypt, between 2013 and 2016. All patients received post-operative chemotherapy then adjuvant whole breast radiotherapy (42.5GY/16 fractions) with once weekly concomitant photon boost of 1 GY for 3 weeks (total boost dose 3GY) with whole radiotherapy schedule period of 16 days (3 weeks). The patients were followed up for 60 months.

Results: The 5 years disease free survival was 94% and the local recurrence 2%, distant metastasis 4%, and 5 years overall survival was 96%. Cosmetic outcome was Excellent or good in most of cases, with few poor and fair outcomes.

Conclusion: hypofractionation with integrated boost as adjuvant treatment for breast cancer is an acceptable option that provides excellent local control and low toxicity. Hypofractionated whole breast irradiation with concomitant weekly boost appears feasible and safe.

Key Words: Breast cancer, hypofractionation, Toxicity, Concurrent boost

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Introduction:

Breast cancer (BC) is globally prevalent and the leading cause of death due to cancer in females. Due to changes in risk factor profiles, improved cancer registration, and cancer detection, its incidence and death rates have risen over the past three decades [1].

In Egypt, breast cancer is the most common malignancy in women, accounting for 38.8% of cancers in this population and more than 22,000 new cases diagnosed each year [2]. It is estimated that the breast cancer mortality rate is around 11%, being the second cause of cancer-related mortality after liver cancer [3], and it represents 32% of cancer deaths in Egyptian women [2].

Adjuvant radiotherapy plays an important role in the breast cancer management paradigm. Results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis in patients undergoing breast conservation surgery showed that the use of adjuvant radiotherapy resulted in a 50 per cent relative reduction in the risk of a locoregional recurrence at 15 years [4].

Radiation therapy represents the standard adjuvant treatment after breast conserving surgery (BCS) as it is associated with a 70% reduction in the risk of recurrence and a 9-12% reduction in the risk of death [5].

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 [6].

Based on radiobiological models, it was evident that hypofractionated radiation schedules used as adjuvant

treatment for breast cancer offer equivalent local control to standard conventional radiation therapy by giving larger doses per fraction in shorter period of time [7].

Hypofractionation (HF) is a useful option for patients and healthcare providers. Potential advantages of HF are better patient's convenience, faster patients turnover at busy radiotherapy departments and lower health related costs. The timing of combining hypofractionated whole breast radiotherapy (HF-WBRT) and tumor bed boost has not been determined yet. One of these strategies is to give a daily simultaneous integrated boost with HF-WBRT in order to maintain the benefits of shortening the overall treatment time [8].

In our retrospective study, our aim was to evaluate the efficacy and the safety of a hypofractionated radiotherapy course with weekly concomitant boost for breast cancer patients treated with conservative breast surgery.

Patients and Methods:

This retrospective study included 50 female patients with early stage breast cancer (stage I -II) who underwent breast conservative surgery and received adjuvant radiotherapy at the radiotherapy department of South Egypt cancer institute (SECI), Assiut university, Egypt, between 2013 and 2016 and followed up over 5 years.

Patients with age of 18 years and above, with all histological types and grades of breast cancer, pathological T1-T2 tumors, N0-1 disease with negative surgical margins after breast conservative surgery were eligible. All patients received hypofractionated radiotherapy with weekly concomitant boost.

Pretreatment evaluation:

Full history and physical examination were conducted at the time of initial presentation. Routine laboratory evaluation was done for all patients. Informed consent was signed by each patient. Chest X-ray and/or CT chest and Abdominopelvic ultrasonography were requested to all patients as a baseline study. Echocardiography was done to all patients with left sided breast tumors and those who was planned to receive anthracyclines.

Treatment:

The basic scheme of radiation treatment is the delivery of 42.5 Gy in 16 fractions 5 times a week to the whole breast plus a once weekly concomitant boost dose of 1 Gy to the lumpectomy area immediately after whole breast irradiation (WBI), thus a total boost dose of 3Gy in 3 fractions once a week). Doses were prescribed to international reference points. Total treatment time was 3 weeks plus 1 day.

Radiation Dose and energy:

The total whole breast radiation dose was 42.5 Gy in 16 fractions while the area of the lumpectomy cavity received 45,5 GY by the addition of the 1Gy once weekly. The energy used for the whole breast radiotherapy was 6 MV photon beam. The energy used to the concomitant boost was 6 MV photon beam also. All patients were treated by siemens linear accelerator.

Systemic Therapy:

Patients received adjuvant systemic therapy according to luminal status and staging, patients with tumor size more than 1 cm or with lymph node involvement received adjuvant anthracycline based chemotherapy followed by single agent taxane before starting Rth and those with positive estrogen and /or progesterone receptors received hormonal therapy with either estrogen receptor modulator like tamoxifen or aromatase enzyme inhibitors like letrozole according to patient menopausal state. Adjuvant trastuzumab was given to patients with positive Her2-neu expression.

Follow up:

Clinical examination was carried out daily through treatment; follow up for acute toxicity was arranged weekly during Rth and up to 3 months after that. Mammography was planned at 6 months after completion of treatment.

Statistical analysis:

Data were analyzed by SPSS 25.0. Descriptive statistics were done by number and percent as well as mean and SD. The paired samples t-test was used to compare the difference between two group means (patients at base line and at follow-up) in interval and ordinal variables. The Pearson's χ 2 test was used to compare qualitative variables. The McNemar's χ test assesses the difference between paired proportions. The McNemar-Bowher's test was used to test differences in categorical variable between baseline and follow-up visit. The level of statistical significance was set at a $P < 0.05$.

Results:

In our study, the mean age at diagnosis was 47.16 years with 34 patients (68.0%) <50years old. And 16 patients (32.0%) >50years old. 26 patients (52%) were Lt sided breast cancer, while 24 patients (48%) were Rt sided BC. Majority of cases 24 patients (48 %) had outer upper quadrant mass at diagnosis. The patient's characteristics are summarized in Table 1.

As regard pathological data of our patients are summarized in Table 2 the most common tumor grade (G) was grade II in 36 patients (72%) while GIII in only 14 patients (28%).

Only 3 cases had infiltrating lobular carcinoma (ILC) representing 6% of all patients, while 47 patients (94 %) were diagnosed with infiltrating ductal carcinoma (IDC).

Regarding the T stage, 40 patients (80 %) had T2 stage while only 10 patients (20 %) had T1, as for nodal stage (N) 39 patients (78 %) were nodal negative disease.

Table (1): Patient's characteristics:

Items	Descriptive
Age "years"	
mean± SE	47.16 ± 1.34
Median	45.0
<50yrs.	34(68.0%)
>50yrs.	16(32.0%)
Laterality side:	
Lt	26(52.0%)
Rt	24(48.0%)
Quadrant site:	
Central	4(8.0%)
Lower outer "LO"	10(20.0%)
Lower inner "LI"	6(12.0%)
Upper inner "UI"	6(12.0%)
Upper outer "UO"	24(48.0%)

Lt: left, Rt: right

According to the receptor status studied in this group:

35 patients (70%) were Estrogen and/or progesterone receptor positive, while 40 patients (80%) had HER2 negative disease. Only 10 patients (20%) had Her2 overexpression.

Table (2): Pathology and Receptor status data in study group:

Items	Descriptive
Tumor grade:	
GII	36(72.0%)
GIII	14(28.0%)
Pathology:	
IDC	47(94.0%)
ILC	3(6.0%)
T stage:	
T1	10(20.0%)
T2	40(80.0%)
Node stage:	
No	39(78.0%)
N1	11(22.0%)
ER and/or PR:	
-ve	15(30.0%)
+ve	35(70.0%)
HER2:	
-ve	40(80.0%)
+ve	10(20.0%)

IDC: infiltrating ductal carcinoma, ILC: infiltrating ductal carcinoma

Outcome (Table 3, Fig. 1 & 2):

After follow up for 5 years, only one case (2%) developed local recurrence (LR) at 15 months, while distant metastases (DM) occurred in 2 patients (4%), one developed bone metastasis at 18 months, and the other developed liver metastasis at 20 months. Two patients died during the follow up period (4%), the first at 13 months of follow up due to age related events (patient was 70 years old with comorbid uncontrolled hypertension), and the other died after 20 months due to development of liver metastases (cancer related).

Table (3): Outcome in study group:

Items	Descriptive
Locoregional relapse:	
Local recurrence	1(2.0%)
Negative	49(98.0%)
Distant metastasis:	
Bone Mets.	1(2.0%)
Liver Mets.	1(2.0%)
Negative	48(96.0%)
State:	
Live	48(96.0%)
Died	2(4.0%)

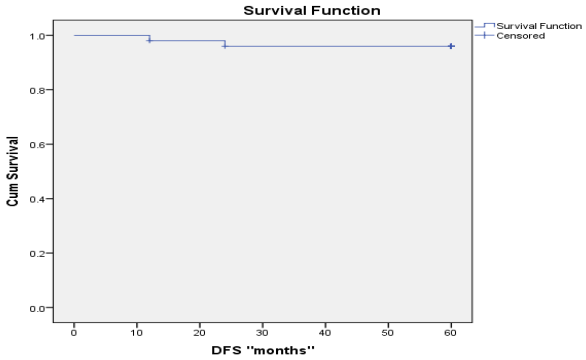

Fig (1): DFS in study group

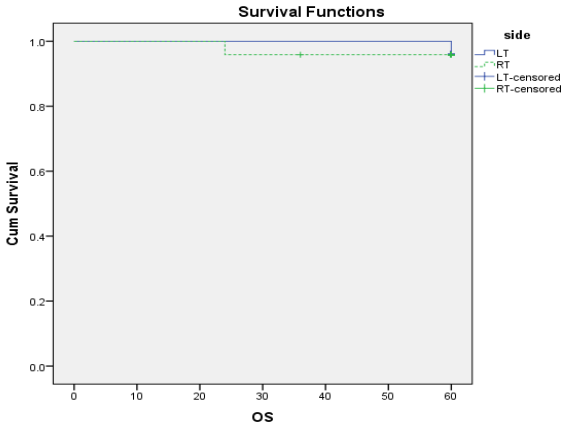

Fig (2): OS in study group

Toxicity

As shown in table 4, the incidence and grading of acute and late toxicities were assessed at the end of treatment and at 12, 24,36,48,60 months after finishing the treatment.

As regard acute skin toxicity, 19 patients (38 %) had G1 toxicity at the end of treatment and 6 patients (12%) had G2, there was significant improvement of skin toxicity from baseline to after the follow up period ($p < 0.001$). Our initial results of late effects appear promising as no grade III-IV toxicity were reported. The frequency of telangiectasia in our study was observed at 12 months where 10 patients (20%) had G1 and 6 patients (12%) had G2. At 24 months there was no reported cases of G2 observed, and only 9 patients (18%) had G1 skin telangiectasia at the end of the follow up period (60 months). As regarding skin hyperpigmentation, it was only reported at 12 and 24 months with only 4 patients (8%) had G 1 skin hyperpigmentation, and 1 patient (2%) had G2 at 12 months. Along the follow up period there was a significant improvement, 100% of patients had G0 skin hyperpigmentation. ($p < 0.04$). Subcutaneous fibrosis was G0 in 78% of cases, while G1 and G2 representing 18 % and 4 % of cases respectively at 12 months, while at the end of follow up period (60months) only 9 patients (18%) had G1 fibrosis.

As regarding arm lymphedema, a significant improvement was observed among the studied group along follow up period; at the 12 month 7 cases (14%) had G1 lymphedema, while 4 cases (8%) had G2. At the end of follow up period 100% of cases had G0 lymphedema. Cardiac events were observed in only 2 patients (4%). Acute lung complications G1 and G2 were observed in 8% and 4% of cases respectively, while chronic lung complications G1 was seen in 3 patients (6%) and only one patient (2%) had G2 toxicity.

As regarding cosmesis in the study group (Table 5), the results were good in most of cases (46%), excellent in 32% of cases, fair in 16 % of cases and poor in 6% of cases.

The 5 year disease free survival (DFS) in our cases was 94 % and the overall survival was 96% as shown in Figs (1 & 2).

At 5 years follow up and as shown in Table 13, only the age of patients was shown to affect the OS, it was 100% in patients < 50 years old and 96 % in patients > 50 years old. ($P < 0.04$).

Discussion:

In our current study we evaluated a hypofractionated dose of 42.5 Gy in 16 fractions used as adjuvant treatment for the whole breast after conservative surgery in early stage 1-2 with a 3D photon concomitant boost of 1 Gy once weekly for a total boost dose 3 Gy to the tumor bed.

In present study the mean age at diagnosis was 47.16 years with (68.0%) of patients <50yrs and (32.0%) of patients >50years. This agrees with Eldesoky et al. who reported Median age of 48 years with a range of 33–68 years [8].

Regarding locoregional relapse in present study there was one patient who developed local recurrence at 15 months. Distant metastases occurred in 2 patients (4%), one developed bone metastasis at 18 months, and the other developed liver metastasis at 20 months. The 5-year DFS and OS for all study patients were 98.0% and 96.0% respectively. Our results were similar to those of Eldesoky et al who reported in their study a local control rate of 100%. Two patients had 2 failure events: One of them developed distant bone metastases, the other developed contralateral breast cancer. The estimated 3- year DFS and OS was 95 % and 97.5 % respectively [8]. Formenti et al. reported 1 recurrence among 91 breast cancer women who received IMRT with simultaneous integrated boost (SIB) [9].

Another study Bantema-Joppe et al. reported consecutive series of 752 consecutive female invasive breast cancer patients (stages I-III) the 5-year loco-regional control was 98.9% [10]. Cante et al. used a dose of 45 Gy/20 fractions to the whole breast and a daily SIB dose 0.25 Gy to the tumor bed to a total dose of 50 Gy [11]. With a median follow up of 60 months, OS was 97.6%; cancer-specific survival was 99.4%; DFS was 96.6%; and local control was 100%, which is comparable to the median DFS rate at our study. [12].

In present study acute skin toxicity was GII at end of RTH in (12.0%) of cases, which is comparable to other studies [12-14] where Grade II toxicity was reported in 9%, 12%, 15%, and 10.5% respectively. Our initial results of late effects appear promising as no grade III-IV toxicities were reported which is similar to that reported by (Guenzi et al., Scorsetti et al., Ciammella et al. [14-16].

Hyperpigmentation in present study was reported as Grade II at 12 months in 2 patients (4.0%). These results agree with Guenzi et al. [14], while Sayed et al. [13] and El-Hadaad et al. [17] reported higher toxicities 11.8% and 8.3% respectively due to use of higher total doses.

In present study, Telangiectasia was reported as Grade II in 8% at 12 months of follow up which was comparable to that reported by El-Hadaad et al. [17] (13.9%). Moreover, Raza et al. [18] with a median follow-up of 61 months recorded Grade 3 telangiectasia only in one patient.

Regarding subcutaneous fibrosis, grade 2 was reported in 4% of patients at 12 months of follow up and no cases at 24 months of follow up that is similar to 3% reported by Guenzi et al. [14].

Regarding late toxicity, in present study there were no GII & GIII toxicities in each of telangiectasia, hyperpigmentation, subcutaneous fibrosis and lymphedema after 24months up to 60ms. These agree with that reported by Chadha et al. [19] showing no late toxicity >Grade II in terms of fibrosis or deterioration of cosmetics with a median follow-up of 24 months and similarly Cante et al. [20] reported no late skin and subcutaneous toxicities >Grade II with a follow-up of 60 months.

Table (4): Acute and late toxicities reported at our study group:

Items	Descriptive				P-value
	G0	G I	G II	GIII	
Skin toxicity:					
Acute					**P<0.001****
At end of RT	25(50.0%)	19(38.0%)	6(12.0%	0(0%)	
At 6 weeks	41 (82.0%)	9(18%)	0(0%)	0(0%)	
Telangiectasia					
12ms	36(72.0%)	10(20.0%)	4(8.0%)	0(0%)	
24ms	39(81.25%)	9(18.75%)	0 (0%)	0(0%)	
36ms	39(81.25%)	9(18.75%)	0(0%)	0(0%)	**P=0.728n.s**
48ms	39 (81.25%)	9(18.75%)	0(0%)	0(0%)	
60ms	39 (81.25%)	9(18.75%)	0 (0%)	0(0%)	
Hyperpigmentation					
12ms	45(90.0%)	4(8.0%)	1(2.0%)	0(0%)	
24ms	45 (93.75%)	3(6.25%)	0(0%)	0(0%)	**P<0.04***
36ms	48(100%)	0 (0%)	0(0%)	0(0%)	
48ms	48(100%)	0(0%)	0(0%)	0(0%)	
60ms	48 (100%)	0(0%)	0(0%)	0(0%)	
Subcutaneous fibrosis					
12ms	39(78.0%)	9(18.0%)	2(4.0%)	0(0%)	
24ms	39 (81.25%)	9(18.75%)	0(0%)	0 (0%)	**P=0.438n.s**
36ms	39 (81.25%)	9 (18.75%)	0(0%)	0(0%)	
48ms	39 (81.25%)	9(18.75%)	0(0%)	0(0%)	
60ms	39 (81.25%)	9(18.75%)	0(0%)	0(0%)	
Lymphedema:					
Before Rth	45(90.0%)	5(10.0%)	0(0%)	0(0%)	
3ms	41(82.0%)	6(12.0%)	3(6.0%)	0(0%)	
12ms	39(78.0%)	7(14.0%)	4(8.0%)	0(0%)	**P=0.249n.s**
24ms	38(79.16%)	9(18.75%)	1(2.08%)	0(0%)	
36ms	44(91.6%)	4(8.3%)	0(0%)	0(0%)	
48ms	46(95.8%)	2(4.16%)	0(0%)	0(0%)	
60ms	48(100%)	0(0%)	0(0%)	0(0%)	
Cardiac toxicity:					
Negative	48(96.0%)	--	--	--	
Positive	2(4.0%)				
Pulmonary complications:					
G0	40(80.0%)				
Acute GI	4(8.0%)				
Chronic GI	3(6.0%)	--	--	--	
Acute GII	2(4.0%)				
Chronic GII	1(2.0%)				

Table (5): Cosmesis:

	Excellent	Good	Fair	Poor
Frequency	16(32%)	23(46%)	8(16%)	3(6%)

Table (6): Prognostic factors that may affect DFS:

Item	DFS	P-value
Age at diagnosis:		
<50yrs.	58.59 ± 8.23	P=0.181n.s
>50yrs.	52.50 ± 16.32	
Laterality:		
Rt. Side	58.62 ± 7.06	P=0.456n.s
Lt side	54.5 ± 15.04	
T stage:		
T1	60.0 ± 0.00	P=0.312n.s
T2	55.8 ± 12.9	
Nodal stage:		
N0	56.62 ± 11.98	P=0.978n.s
N1	56.73 ± 10.85	
Hormonal therapy:		
-ve	57.00 ± 10.78	P=0.666n.s
+ve	55.20 ± 15.17	

Table (7): Prognostic factors that may affect OS:

Item	OS (months)	P-value
Age at diagnosis:		
<50yrs.	60.00 ± 0.00	**p<0.04***
>50yrs.	56.25 ± 4.65	
Laterality:		
Rt. Side	60.00 ± 0.00	P=0.147n.s
Lt side	57.5 ± 8.65	
T stage:		
T1	60.00 ± 0.00	P=0.497n.s
T2	58.50 ± 6.76	
Nodal stage:		
N0	58.46 ± 6.84	P=0.463n.s
N1	60.00 ± 0.00	
Hormonal therapy:		
-ve	59.40 ± 3.79	P=0.290n.s
+ve	56.40 ± 11.38	

In fact, acute toxicity had shown to be related to late toxicity in terms of subcutaneous fibrosis and telangiectasia [21].

Lymphedema in present study occurred as grade 1 in 14% and as grade 2 in 8% at 12 months. While at 24 months of follow up grade 1 reported in 18% and grade 2 in 2% only. These agree with review and meta-analysis by Disipio et al. [22] 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% which increased up to 2 years after diagnosis or surgery of breast cancer.

Regarding pulmonary toxicity in present study the acute radiation induced was reported as grade 2 in 4% of cases while the chronic toxicity reported as grade 2 in 2% of cases. These results also are comparable to those reported by Shahid et al. [23] with 5% of patients developed acute lung toxicity.

Van Parijs et al. [24] reported on 69 women who were randomized between conventional radiotherapy 50 Gy/25 fractions, and sequential boost 16 Gy/8 fractions if BCS versus experimental HF tomotherapy 42 Gy/15 fractions and SIB of 0.6 Gy if BCS (cumulative dose 51 Gy/15 fractions). Change in forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLco) were reported. Lung function tests showed a significant reduction in HF arm based on changes of DLco, but not on changes of FEV1. At 2 years, 5 patients (22%) in the experimental arm had ≥ grade 1 lung toxicity.

In present study there was (4.0%) of patients have cardiac toxicity which was evaluated by LVEF using Echocardiography. This agrees with Eldesoky et al. [8] reported (2.5%) of patients have cardiac toxicity in G1-G2.

Regarding cosmoses, Good to excellent cosmoses was present in 78.0%, which is very similar to that reported by Hernandez et al. [25] showing excellent cosmoses as well as the results from studies that have involved HF and concomitant boost [11-26].

In study by Eldesoky et al. reported cosmetic outcome (CO) as 95% and 5% of their study participants had a good or excellent, and fair or poor cosmoses respectively. Cante et al. reported good/excellent CO in 91 % and fair/poor in 9 % of patients. Cosmoses were good to excellent in all the patients included in a study by Mondal et al. Our lower cosmetic outcomes may be due to subjective variations in assessment of cosmoses or surgical bad outcomes [8,11,27].

Conclusion:

The results of the present study demonstrate that hypofractionation with integrated boost is an acceptable option that provides excellent local control and low toxicity. Hypofractionated whole breast irradiation with concomitant weekly boost appears feasible and safe.

References:

1- Kerketta ZH, Kujur A, Kumari N, et al. A Cross Sectional Study on the Epidemiology of Newly Diagnosed Breast Cancer Patients Attending Tertiary Care Hospitals in a Tribal Preponderant State of India: Regression Analysis. Cureus. 2023 Jun 15;15(6):e40489..

2- Ibrahim AS, Khaled HM, Mikhail NN, et al. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.

3- International Cancer Control Partnership. WHO Cancer Country Profiles. March 9, 2020.

4- Chakraborty S, Chatterjee S. Adjuvant radiation therapy in breast cancer: Recent advances & Indian data. Indian J Med Res. 2021 Aug;154(2):189-198.

5- Elkalla HMHR, Morad DHZ, Elsergany et al. Comparison between the risk of ipsilateral breast tumor recurrence after breast-conserving surgery in early breast cancer cases treated by whole breast irradiation with and without boost in patients ≥ 50 years old. International Journal of Cancer and Biomedical Research. 2022;6(1):57-66.

6- Abd-Elbadee O, Abd Elkareem S, El Sayed M, et al. (2016): Evaluation of the efficacy and the safety of a hypofractionated radiotherapy course with weekly concomitant boost for breast cancer patients treated with conservative breast surgery. SECI Oncology. 2016; 4(2):28-34.

7- Untch M, Gerber B, Harbeck N, et al. 13th st. Gallen international breast cancer conference 2013: primary therapy of early breast cancer evidence, controversies, consensus-opinion of a German team of experts (Zurich 2013). Breast Care (Basel). 2013 Jun;8(3):221-9.

8- Eldesoky AR, Elshahat A, Eskander M et al. Hypofractionated Whole Breast Radiotherapy with Simultaneous Integrated Boost Following Breast Conservative Surgery for Early Breast Cancer. Benha Medical Journal 2020;37(1):259-270.

9- Formenti SC, Gidea-Addeo D, Goldberg JD, et al. Phase I-II trial of prone accelerated intensity modulated radiation therapy to the breast to optimally spare normal tissue. J Clin Oncol. 2007 Jun 1;25(16):2236-42.

10- Bantema-Joppe EJ, Vredeveld EJ, de Bock GH, et al. Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. Radiother Oncol. 2013 Aug;108(2):269-72.

11- Cante D, Franco P, Sciacero P, et al. Five-year results of a prospective case series of accelerated hypofractionated whole breast radiation with concomitant boost to the surgical bed after conserving surgery for early breast cancer. Med Oncol. 2013 Jun;30(2):518.

12- Corvò R, Ricchetti F, Doino D, et al. Adjuvant hypofractionated radiotherapy with weekly concomitant boost for women with early breast cancer: the clinical experience at Genoa university. Anticancer Res. 2010 Nov;30(11):4749-53.

13- Sayed MM, El-Sayed MI, Attia AM et al.

Concurrent boost with adjuvant breast hypofractionated radiotherapy and toxicity assessment. Middle East Journal of Cancer 2015; 6(1):21-27.

14- Guenzi M, Vagge S, Azinwi NC, et al. A biologically competitive 21 days hypofractionation scheme with weekly concomitant boost in breast cancer radiotherapy feasibility acute sub-acute and short term late effects. Radiat Oncol. 2010 Nov 22;5:111.

15- Scorsetti M, Alongi F, Fogliata A, et al. Phase I-II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: a report of feasibility and early toxicity results in the first 50 treatments. Radiat Oncol. 2012 Aug 28;7:145.

16- Ciammella P, Podgornii A, Galeandro M, et al. Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors. Radiat Oncol. 2014 Apr 24;9:97.

17- El-Hadaad HA, Wahba HA, Elnahas W et al. Concomitant Boost Radiotherapy after Conservative Breast Surgery in Early Breast Cancer. Advances in Breast Cancer Research. 2016;5(3):97-102.

18- Raza S, Lymberis SC, Ciervide R, et al. Comparison of acute and late toxicity of two regimens of 3-and 5-week concomitant boost prone IMRT to standard 6-week breast radiotherapy. Front Oncol. 2012 May 8;2:44.

19- Chadha M, Woode R, Sillanpaa J, et al. Results using 3-week accelerated whole-breast (WB) radiation therapy (RT) and concomitant boost for early-stage node negative breast cancer. Int J Radiat Oncol Biol Phys. 2009;75(3):S77.

20- Cante D, Rosa La Porta M, Casanova-Borca V, et al. Accelerated hypofractionated adjuvant whole breast radiotherapy with concomitant photon boost after conserving surgery for early stage breast cancer: a prospective evaluation on 463 patients. Breast J. 2011 Nov-Dec;17(6):586-93.

21- Ippolito E, Rinaldi CG, Silipigni S, et al. Hypofractionated radiotherapy with concomitant boost for breast cancer: a dose escalation study. Br J Radiol. 2019 Mar;92(1095):20180169.

22- DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013 May;14(6):500-15.

23- Tunio MA, Rafi M. Post mastectomy adjuvant radiotherapy in breast cancer: a comparison of three hypofractionated protocols. J Pak Med Assoc. 2009 Sep;59(9):656-7;

24- Van Parijs H, Miedema G, Vinh-Hung V, et al. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. Radiat Oncol. 2012 Jun 1;7:80.

25- Bautista Hernandez MY, Lujan Castilla PJ, Quézada Bautista AA. Hypofractionation with concomitant boost using intensity-modulated radiation therapy in early-stage breast cancer in Mexico. Rep Pract Oncol Radiother. 2018 Jul-Aug;23(4):276-283.

26- Tsang Y, Ciurlionis L, Kirby AM, et al. IMPORT Trial Management Group. Clinical impact of IMPORT HIGH trial (CRUK/06/003) on breast radiotherapy practices in the United Kingdom. Br J Radiol. 2015;88(1056):20150453.

27- Mondal D, Julka PK, Sharma DN, et al. Accelerated hypofractionated adjuvant whole breast radiation with simultaneous integrated boost using volumetric modulated arc therapy for early breast cancer: A phase I/II dosimetric and clinical feasibility study from a tertiary cancer care centre of India. J Egypt Natl Canc Inst. 2017 Mar;29(1):39-45.