Outcome of short course hypofractionated radiation therapy with boost in early breast cancer: Local Control and Cosmesis

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Abstract:

Background: Hypo-fractioned whole breast irradiation with a subsequent boost is equivalent to conventional whole-breast irradiation and is well-tolerated in terms of local recurrence, toxicity and cosmetic outcome. The aim of the present study is to assess effect of HF-WBI followed by sequential boost over a total of 15 treatment days regarding to locoregional control and cosmesis in patients with early breast cancer.

Patient and Methods: Sixty early stage breast cancer patients were randomly allocated into 2 Arms (thirty patients in each arm), Arm A (standard hypofractionation arm, whole breast irradiation HF-WBI 40Gy/15fractions followed by boost 10Gy/5 fractions) and Arm B (short hypofractionated arm, HF-WBI 36.63Gy/11 followed by boost of 13.32Gy/4 fractions), with an equivalent dose to the regional nodes if indicated in both arms.

Results: There was encouraging locoregional control results in both arms. Ninety percent of patients in arm A and 76.67% of patients in arm B at our study had a good to excellent cosmetic outcome while 10% in arm A and 23.33% of patients in arm B had fair cosmetic outcome after finishing radiotherapy. There is improvement in cosmesis as after 12 months of follow up, there are 100% in arm A and 93.33% of patients in arm B good to excellent cosmesis.

Conclusion: A significant difference between the 2 protocols regarding cosmesis was noted as Arm A had better cosmetic outcome on follow up. However, both arms had encouraging local control results in follow-up after 12and 18 months. Thus, a shortened 3-week HF-WBI schedule is as safe, effective with excellent local control and non inferior cosmetic results as standard 4-weeks HF-WBI and may be a reasonable alternative following breast conservation surgery with time and cost benefit.

Keywords: Hypofractionated, Radiotherapy, breast cancer, cosmesis.

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Introduction:

Breast cancer is the most prevalent cancer among women and one of the leading causes of death among them [1]. In Egypt, the breast cancer mortality rate is about 11%, being the second cause of cancer-related mortality behind liver cancer [2]. Hypofractionation improves health-care access equity by reducing costs, time, patient visits to radiation departments, machine load, and waiting lists at RT facilities. There were no differences between the individuals receiving moderately hypofractionated irradiation and those receiving conventional radiation doses in terms of local recurrence, loco-regional recurrence, disease-free survival, or overall survival rates. [3].

Patients treated with breast-conserving surgery (BCS) followed by RT had improved outcome in clinical practice regarding local control, distant control and overall survival as compared to mastectomy alone [4]. WBRT alone lowers the 10-year risk of any first recurrence by 15% and the fifteen year risk of breast

cancer-related mortality by 4% [5]. Most patients who have unfavorable risk factors for local control, such as age 50 years, grade 3 tumours, the presence of lymphovascular invasion, hormone receptor negativity, or extensive intraductal component and non-radical tumour excision, should receive radiation boost, which results in a further 50% relative risk (RR) reduction [6].

A treatment is considered more effective if the same outcome can be achieved at a lower cost.

It is also useful for patients who have to travel a long way to the hospital because it reduces the amount of time needed for transportation. When it comes to saving time and money, hypofractionated radiotherapy is preferable than conventional radiotherapy. Hence, a lot of breast cancer patients favor hypofractionated RT. [7].

Hypo-fractioned whole breast irradiation with a subsequent boost is equivalent to conventional whole-breast irradiation and is well-tolerated in terms of local recurrence, toxicity and cosmetic result [8,9], hence, it is a practical choice for both patients and healthcare professionals [10].

The Ellis formula estimate of 45 Gy in 15 fractions is predicted to be equivalent to 54 Gy in 2.0 Gy fractions by the linear-quadratic model [11]. Hypofractionation has been supported by multiple trials.

There were no differences between the individuals receiving moderately hypofractionated irradiation and those receiving normal radiation doses in terms of local recurrence, loco-regional recurrence, disease-free survival, or overall survival rates [12].

The aim of the present study is to evaluate outcomes of HF-WBI followed by sequential boost over a total of 15 treatment days in patients with early breast cancer submitted to conservative breast surgery which leads to improving quality of life for patients and more sensible use of resources and time.

Methods:

Institutional Review Board (IRB) approval was obtained before starting this prospective clinical trial in clinical oncology and nuclear medicine department Zagazig University Hospitals, Egypt, from May 2020 to May 2022.

Patients who were confirmed histologically to have unilateral breast carcinoma, or ductal carcinoma in situ (DCIS) or invasive early breast carcinoma (Stages 0-IIB), and patients who had conservative breast surgery (lumpectomy/quadrantectomy), with negative surgical margins (no tumor on ink), who received no radiotherapy were included in this study. While patients who were diagnosed to have breast micro-calcifications before starting radiotherapy, or lobular carcinoma in situ alone or non-breast epithelium histology, multicentric disease, suspicious contralateral regional lymph nodes either clinically or radiographically unless confirmed tumor-negative, previous treatment for contralateral or synchronous breast cancer or if they had radiotherapy earlier to the current breast, synchronous second primary tumor, distant metastases, pregnancy, comorbid conditions: Paget's disease, Collagen vascular disease. Psychiatric or addictive disorder that precluded informed consent or lead to bad compliance and noncooperation were excluded from the study. Patients who had high-risk features such as lymphovascular invasion, close margins, young age, hormone receptor negativity, or extensive intraductal component were not excluded from study.

Sixty early stage breast cancer patients were randomly allocated into 2 Arms (thirty patients in each arm), Arm A (standard hypofractionation arm, whole breast irradiation HF-WBI 40Gy/15fractions followed by boost 10Gy/5 fractions) and Arm B (short hypofractionated arm, HF-WBI 36.63Gy/11 followed by boost of 13.32Gy/ 4 fractions), with an equivalent dose to the regional nodes if indicated in both arms. All doses prescribed to the ICRU reference point dose to whole breast (WB-PTV) using 3D conformal field arrangement of 2 wedged opposing tangential fields.

Patients were subjected to pre and post-radiotherapy assessment and data collected included age, breast laterality, histology, tumor size, AJCC pathological tumor &nodal status, receptors status (ER, PR, HER2Neu), radiation target volume (whole breast or whole breast +regional LN), systemic treatment (adjuvant chemotherapy, hormonal treatment).

Our primary end point was locoregional control; secondary end point was assessment of breast cosmesis. Cosmesis assessment was defined after 6,12 and 18 months using the Harvard criteria (4-point Likert scale): excellent, good, fair or poor, differentiating both the treated breast and the contralateral breast [13,14].

The statistical analysis was performed with computer program (SPSS Statistics V22). Categorical data were represented by number and percentage; Continuous data was represented by mean, standard deviation, median and range. P-value <0.05 was considered statistically significant.

Radiation treatment planning and techniques

Computed tomography (CT)-based treatment planning was done (14-63 days after last surgery or last cycle of chemotherapy), whole-breast tangential fields were used while dose to non-breast structures was kept within acceptable limits.

The dose within the clinical treatment volume (CTV) was prescribed to be within 95% to 105% of treatment dose. We permitted therapy of local lymph nodes utilizing the same treatment schedule with a supraclavicular field and/or posterior axillary boost if necessary. Nodal volumes were contoured and tested for coverage (3D conformal radiotherapy). The patient got an electron beam boost to a volume that included a 2-cm margin on the lumpectomy scar if the cavity could not be seen. The prescription for Boost pointed to an isodose line that covered the volume entirely.

Fields and wedges: Wedges and field in field were allowed, to achieve dose homogeneity.

Results:

Sixty female patients were included in this study from May, 2020 to May, 2022, they were equally and

randomly divided into 2 groups. The treatment protocol was completed by all participants.

Demographic and tumor characteristics

They are shown in Table (1). Median age was slightly higher in Arm A, 46 years with a range of 27 to 70, in comparison to 45 years with a range of 30 to 65 in Arm B. Postmenopausal status predominated in both arms, with 56.67% in Arm B. A substantial portion of higher-risk patients were included in both groups, Arm A had 15 patients (50%) while arm B had 13 patients (43.33%) with pathologically positive nodes who required RNI.

UOQ lesions predominated in both groups (56.67 vs 66.67%), with majority of cases having IDC histology (86.67% vs 93.33%), however, no statistical significance was detected. Most lesions were in the right breast (66.67% in arm A and 80% in arm B). Most of the cases were ER+, PR+, Her-2 negative The majority of patients received adjuvant hormonal treatment (86.66% and 83.33%). Only Three patients in arm A and 5 patients in arm B received trastuzumab.

Locoregional control

There was an excellent locoregional control in both arms (Table 2). In both arms, CA15-3 as a tumor marker showed normal levels during follow up. Chest X-ray, Pelvi-abdomen Ultrasound and Echocardiography detected no abnormalities during follow up period. Median follow-up was 12 months.

Cosmesis

Ninety percent of patients in arm A and 76.67% of patients in arm B at our study had a good to excellent cosmetic outcome while 10% in arm A and 23.33% of patients in arm B had fair cosmetic outcome after finishing radiotherapy. Breast cosmesis documented by the patients during all the follow-up intervals showed improvement in cosmesis as after 12 months of follow up, there are 100%in arm A and 93.33% of patients in arm B good to excellent control (Table 3) (Fig. 1).

Discussion:

We delivered a whole-breast dose of 36.63Gy in 11 fractions of 3.33Gy delivered 5 days per week, 1 fraction per day (equivalent dose for 2Gy fractions [EQD2] Z 45Gy, using linear quadratic formalism and an a/b ratio of 4). Patients received a mandatory lumpectomy bed boost delivered in 4 fractions of3.33Gy, delivered once daily (EQD2 Z 15Gy) in comparison with standard HF-WBI, delivering 40Gy in 15 fractions then boost 10 in 5 fractions over a total of 20 treatment days.

Hypofractionation decreases the length of the RT facilities' waiting lists, the workload on the machines, the number of patients who attend the radiation departments, and the associated medical costs, improving access to healthcare. No differences were seen between the groups receiving moderately hypofractionated irradiation and conventional radiation doses in terms of local recurrence, loco-regional recurrence, disease-free survival, or overall survival rates. Acute and late side effects as well as cosmesis are comparable or often less severe following substantially hypofractionated irradiation than after conventional radiation doses. The rate of severe side effects was low in both groups; acute and late side effects and cosmesis are comparable or often less sever after moderately hypofractionated irradiation compared to conventional radiation doses [12].

The median age at our study was 46 years in arm A and 45 years in arm B. Postmenopausal status predominated in both arms with 16(53.33%) in arm A and 17(56.67%) in arm B. Gupta et al.[15]reported the median age was 54 years (range, 33-82), this study delivered a whole breast dose of 36.63Gy in 11 fractions of 3.33Gy, with an equivalent dose to the regional nodes if indicated, followed by a tumor bed boost of 13.32Gy in 4 fractions of 3.33Gy over a total of 15 treatment days (the same dose of arm B in our study).

In our study, Grade 2 tumors were most frequently found, 20 patients in arm A and 18 patients in arm B. Ciammella et al. [16] as well, recorded that grade 2 tumors are common 118 (56%). START Trialists' Group A (50Gy/25, 39Gy/13 versus 41.6Gy/13 fractions) recorded 28% grade 3 tumors, while slightly down to 23% with START Trialists' Group B (50Gy/25 versus 40Gy/15 fractions) [17,18].

In our study, T2 tumors showed predominance, 20 patients (66.67%) in Arm A and 17 patients (56.67%) in Arm B. N1 tumors showed 50% in arm A and 53.33% in arm B. The majority of patients in our study showed absence of perineural and lymphovascular invasion. Most of our cases were ER+, PR+, Her-2 negative. Ki-67 expression was high in only 6 patients (20%) in arm A and 3 patients (10%) in arm B. Ciammella et al. [16] reported 159 (75%) of patients HR+, while only 18 (8%) HER-2. Gupta et al. [17] recorded the triple negative disease was 11%.

The 2018 guidelines recommend a boost in patients under 50 or between 51 and 70 with high-grade disease, and suggest omitting a boost in patients over 70 with hormone-receptor positive and low-to intermediate grade tumors.[19], who make up 0% of our study. This is in contrast to our HF WBI regimen, in which we mandated a lumpectomy boost. The use of HF-WBI and tumour bed boost is further supported by the absence of relapses seen in our study.

It's interesting to note that when adjuvant radiation therapy is administered, the local recurrence rate (LRR) rates among diverse populations of breast cancer patients are impressively and uniformly low. No local recurrence was reported at follow-up in this 12- to 18-month study, favorably comparable to the HF arms of the START A trial (3-year study) at 94.8% and 96.5% (39Gy/13 versus 41.6Gy/13 fractions), as well as the HF arm's local control rate of 97.8% (40Gy/15 fractions) in the START B trial.

Table (1): Demographic and Tumor characteristics and treatment details.

Variables	Arm A *n=30 (%)*	Arm B *n=30 (%)*	P-value
Age *(years)*			
Mean±SD	47.5±9.7	45±8.6	0.29
Median (Range)	46 (27-70)	45 (30-65)	
Menopausal status			
Premenopausal	14 (46.67%)	13 (43.33%)	0.80
Postmenopausal	16 (53.33%)	17 (56.67%)	
Tumor location			
UOQ	17(56.67%)	20(66.67%)	0.464
UIQ	3(10%)	5(16.67%)	
LOQ	7(23.33%)	4(13.33%)	
LIQ	3(10%)	1(3.33%)	
Histology			
IDC	26(86.66%)	28(93.34%)	0.690
ILC	2(6.67%)	1(3.33%)	
Mixed (ductal and lobular)	2(6.67%)	1(3.33%)	
Laterality			
Right	20 (66.67%)	24 (80%)	0.24
Left	10(33.33%)	6(20%)	
Tumour size			
T1	10 (33.33%)	13 (43.33%)	0.425
T1a	0(0%)	0(0%)	
T1b	0(0%)	0(0%)	
T1c	10(33.33%)	13(43.33%)	
T2	20(66.67%)	17 (56.67%)	
Nodal status			
N0	15(50%)	14(46.67%)	0.80
N1	15(50%)	16(53.33%)	
ER status			
Negative	4(13.33%)	5(16.67%)	0.72
Positive	26(86.67%)	25(83.33%)	
PR status			
Negative	7(23.33%)	8(26.67%)	0.765
Positive	23(76.67%)	22(73.33%)	
Her-2 status			
Negative	20(66.67%)	22(73.33%)	0.333
Equivocal	7(23.33%)	3(10%)	
Positive	3(10%)	5(16.67%)	
Radiation Target Volume			
Whole Rt breast	10(33.33%)	13 (43.33%)	0.607
Whole Lt breast	5(16.67%)	4 (13.33%)	
Whole Rt+Supraclav LN	10(33.33%)	11(36.67%)	
Whole Lt+Supraclav LN	5(16.67%)	2(6.67%)	
Hormonal treatment			
None	4(13.33%)	5(16.67%)	0.960
Anstrazol	6(20%)	7(23.33%)	
Letrazol	6(20%)	5(16.67%)	
Tamoxifen	5(16.67%)	6(20%)	
Tamoxifen/Zoladex	9(30%)	7(23.33%)	
Trastuzumab			
No	27(90%)	25(83.33%)	0.45
Yes	3(10%)	5(16.67%)	

Table (2): Locoregional control

Variables	Arm A	Arm B	P-value
	n=30 (%)	*n=30 (%)*	
Locoregional control after 12 months	30(100%)	30(100%)	1.00
Locoregional control after 18 months	30(100%)	30(100%)	

Table (3): Patient cosmesis regarding Harvard/NSABP/RTOG Breast Cosmesis Grading Scale over time.

Variables	Arm A	Arm B	P-value
	n=30 (%)	*n=30 (%)*	
Assessment after finishing radiotherapy			
Excellent	12(40%)	7(23.33%)	0.229
Good	15(50%)	16(53.34%)	
Fair	3(10%)	7(23.33%)	
Poor	0(0%)	0(0%)	
Assessment after 3 months			
Excellent	13(43.34%)	5(16.67%)	**0.010***
Good	16(53.33%)	17(56.67%)	
Fair	1(3.33%)	8(26.66%)	
Poor	0(0%)	0(0%)	
Assessment after 6 months			
Excellent	16(53.33%)	7(23.33%)	**0.02***
Good	14(46.67%)	20(66.67%)	
Fair	0(0%)	3(10%)	
Poor	0(0%)	0(0%)	
Assessment after 12 months			
Excellent	18(60%)	7(23.33%)	**<0.01****
Good	12(40%)	21(70%)	
Fair	0(0%)	2(6.67%)	
Poor	0(0%)	0(0%)	

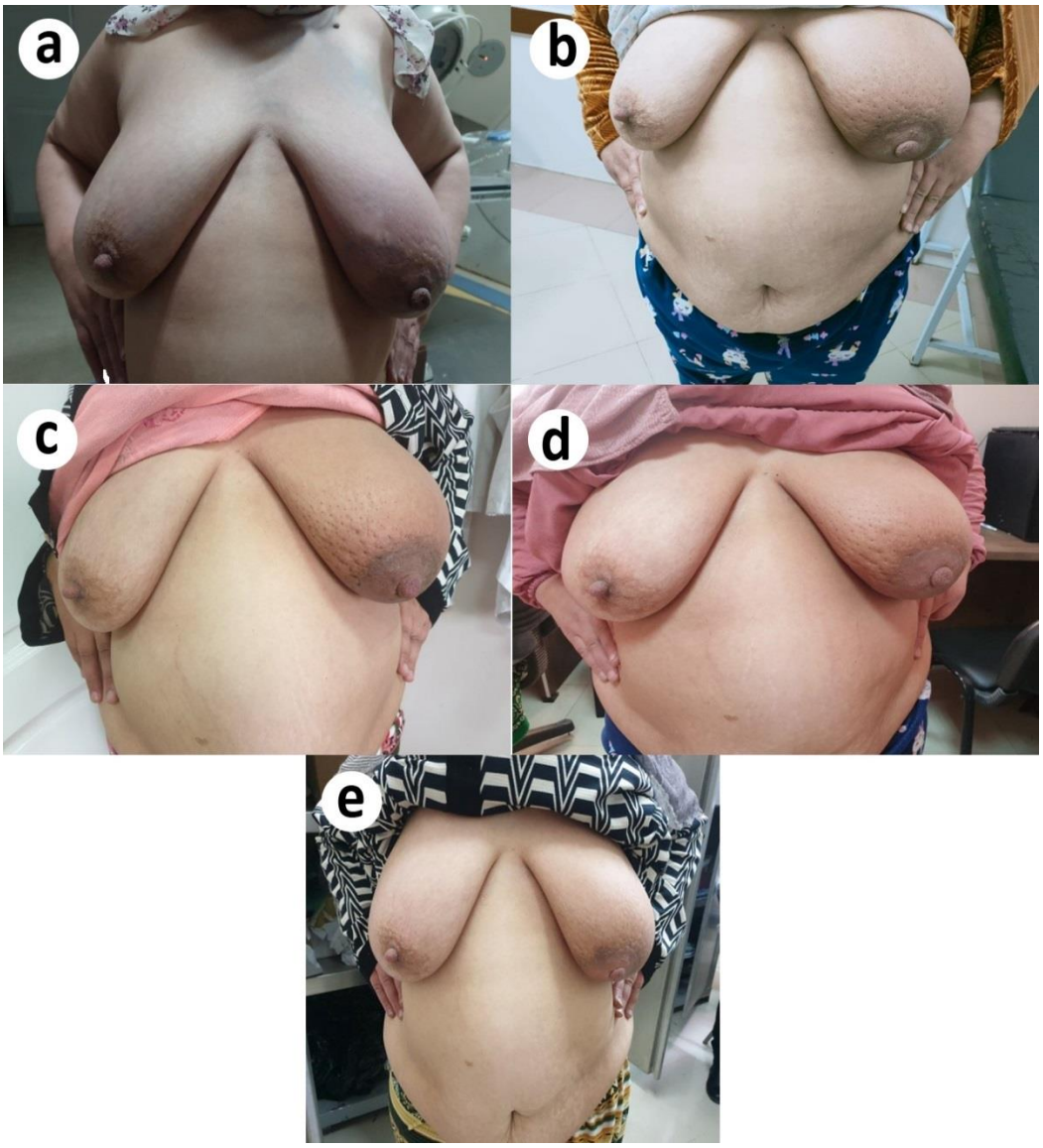

Fig. (1): Arm B (short hypofractionation), case 2, Lt breast cancer(a) Before starting radiotherapy. (b) After finishing radiotherapy "dull erythema& sever edema" (c) After 3 months"dull erythema & sever edema". (d) After 6 months "Slight atrophy & Pigmentation change". (e) After 12 months "mild pigmentation".

In the OCOG study, local control in the HF arm (42.7Gy/15 fractions) was 93.8%. [17,20]. Most of the results showed good local control due to early selection of cases and non-exceeded N1 status. We believed we could adopt a common statistical goal of local-regional control for all of the patients in our trial because large meta-analyses showed comparable disease control rates following RT throughout the risk spectrum.

Coinciding with our results, Cante et al. [21] demonstrated that no local recurrence had been seen following median follow-up of 60 months (range 36-88). Keeping with that, Chadha et al. [22] analysis of a 3.5-year median follow-up period revealed local control of 99%. Similar results were reported by Hou et al. [23] after a median follow-up of 27 months a local control was 100%. However, at follow up of RHM/GOC trial, local relapse was 12.1% in the 50Gy arm, 9.6% in the 42.9Gy arm, and 14.8% in the 39Gy arm. At OCOG trial, local relapse was 7.5% in the 50Gy arm and 7.4% in the 42.56Gy arm, which were not significantly different. At follow up of START A trial, local relapse was 6.7% in the 50Gy arm, 5.6% in the 41.6Gy arm, and 8.1% in the 39Gy arm; neither HF-WBI arm was significantly different from the control CF-WBI arm. Similarly, distant relapse and overall survival did not significantly differ between either of the HF-WBI

regimens and CF-WBI regimen. At follow up of START B trial, local relapse was 5.2% in the 50Gy arm and 3.8% in the 40Gy arm, which were not significantly different. Interestingly, distant relapse (16.0% vs. 12.3%, p=0.014) and overall mortality (19.2% vs. 15.9%, p=0.042) were significantly higher in the CF-WBI arm compared to the HF-WBI arm (Gupta et al., 2018).In agreement with our results, at Five –year follow up, Gupta et al documented locoregional and distant control were 97.7% and 97.9% respectively[15].After a median follow-up of 40 months in a study by Ahlawat et al.[24], only 2 cases of isolated ipsilateral breast tumor recurrence occurred. Three-year estimated local recurrence-free survival was95.9%. The 3-year estimated distant recurrence-free survival was 97.3% [24].

Another approach is testing extremely hypofractionated regimens. The randomized phase 3 United Kingdom (UK) FAST trial tested 30Gy or 28.5Gy in 5 once-weekly fractions against 50Gy in25 fractions in postmenopausal women>50 years of age after BCS with early-stage, had tumour 3cm or less, node-negative tumours;10-year results were recently reported, showing low rates of local recurrence in all arms and similar late toxicity between the 28.5Gy and 50Gy arms but increased toxicity in the 30Gy arm (worse breast appearance outcomes compared to those with 28.5 and 50Gy).With a median follow-up of 37.3 months, there were 2 local relapses and 23 deaths[25].In addition, there are several ongoing or completed large randomized trials investigating HF-WBI. The UK FAST-Forward trial aims to assess shortening this fractionations schedule even more, building on the UK FAST trial. The control arm of the trial is 40Gy in 15 fractions. The experimental arms include 27Gy in 5 daily fractions of 5.4Gy and 26Gy in 5 daily fractions of 5.2Gyin a higher-risk population including younger, postmastectomy and node-positive women. A10- or 16-Gy boost maybe added to the surgical scar or lumpectomy site. RNI was permitted. Follow-up continues for endpoint of tumor control [25]. The UK-HF trials have demonstrated excellent local control and cosmetic outcomes with HF WBI treatment compared to standard treatment [17,26] and that is favorably consistent with our study.

Ninety percent of patients in arm A and 76.67% of patients in arm B at our study had a good to excellent cosmetic outcome while 10% in arm A and 23.33% of patients in arm B had fair cosmetic outcome after the end of radiotherapy. Breast cosmesis documented by the patients during all the follow-up intervals showed improvement in cosmesis as after 12 months of follow up, there are 100% in arm A and 93.33% of patients in arm B good to excellent control. As the majority of patients underwent lumpectomy rather than quadrantectomy, Ciammella et al. [16] recorded subjective and objective good or excellent cosmetic outcome in 93% and 92% of the women, respectively. In the same setting, Cante et al. documented excellent cosmetic results in 69% of patients, good results in 22%, fair results in 5%, and poor results in 4%.[21]. Cante et al. [21] found results of excellent/good in 87.8% of patients and fair/poor in 12.2% of patients in 2017, demonstrating improved cosmesis after longer follow-up periods.

In the RMH/GOC study, the 42.9Gy arm and the 39Gy arm, respectively, had freedom from notable change in photographic breast appearance of 84.4% and 93.4%, respectively (p 0.001). Moreover, there were notable disparities in the clinical evaluation of breast cosmesis, with the 39Gy arm generally performing better and the 42.9Gy arm generally performing worse. At the time of the OCOG trial's follow-up, there was no difference in the cosmetic result, with 69.8% of patients in the HF-WBI arms reporting a good or excellent cosmetic result [27]. Our results compare favorably with the outcomes of both the START B (5 years study) and OCOG studies, despite variances in the grading scales employed for cosmesis [18,20].

In the study by Linares et al. [28], 91% of patients had good or excellent cosmetic results and the study by Gupta et al. [15], physicians rated the breast cosmesis of 95% of the patients as good or excellent. Ninety percent of the cosmesis reported by Ahlawat et al..[24] was good or excellent. In comparison to normal fractionation, Reddy et al.'s.[29] documentation of enhanced cosmetic results with hypofractionation was comparable to conventional fractionation. According to Charfare et al. [30] the percentage of breast volume removed can affect the cosmetic outcome; removal of a larger percentage volume results in a poor cosmetic outcome, while removal of a smaller percentage volume results in an excellent/good cosmetic outcome. For example, 45-65% of patients with an estimated breast volume removed of less than 10% had good to excellent cosmetic outcomes, compared to 35-50% of patients with an excised breast volume of more than 10% who had good to excellent outcomes.

Our trial has several limitations, including small number of patients, short time of follow up, data bias and not all patients commit the precautions during treatment, which limits comparative analyses with other HF-WBI regimens. Furthermore, although points of strength are that the study is prospective, its inclusion of high-risk women such as young age and negative hormone receptors, 50% and 43.33% of patients in arm A and B respectively received regional nodal irradiation with encouraging results, the heterogeneity of the study cohort combined with very good local control relapses limits subgroup analysis. In order to achieve maximal benefit from the 3-week hypofractionated schedule included sequential boost, patients must be told to abide to the pre-radiotherapy precautions. Further studies are required to standardize this protocol, especially in the old age patients, which are an area of debate. Larger multi-centric studies may be beneficial due to incorporation of larger number of patients with a liability to longer follow-up period.

Conclusion:

A significant difference between the 2 protocols regarding cosmesis was noted as Arm A had better cosmetic outcome on follow up. However, both arms

had encouraging local control results in follow-up after 12and 18 months. Thus, a shortened 3-week HF-WBI schedule is as safe, effective with excellent local control and non inferior cosmetic results as standard 4-weeks HF-WBI and may be a reasonable alternative following breast conservation surgery with time and cost benefit.

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