SKIN TOXICITY IN RANDOMIZED CLINICAL TRIAL COMPARING TWO ADJUVANT HYPOFRACTIONATION RADIOTHERAPY SCHEDULES IN THE TREATMENT OF POST MASTECTOMY BREAST CANCER PATIENTS

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Abstract

Background and Purpose: Comparable outcomes between conventional fractionation and moderate hypofractionation (MHF) had been established. The UK FAST and Fast-Forward trials proved the non-inferiority of ultra-hypofractionation (UHF) after conservative breast surgery. This study is a non-inferiority phase III randomized control trial to evaluate UHF compared to the MHF regimen in mastectomy patients (NCT04550910).

Material and methods: Female patients above 18 years were randomized to receive chest wall and nodal irradiation with either a weekly UHF regimen (28.5 Gy/5fx/5 weeks) or MHF (40 Gy/15fx/3 weeks). Conformal 3-D or forward intensity-modulated radiotherapy planning was done. The primary endpoints were acute and late toxicity. Patient-reported outcomes (PROMs) were assessed to evaluate shoulder function and brachial plexopathy. Secondary endpoints were loco-regional recurrence (LRR), overall survival (OS), and disease-free survival (DFS).

Results: From November 2019 to June 2021, 176 eligible patients were recruited. The median follow-up was 26.73 ± 5.98 months. Only 1.1 % reported G3 acute skin toxicity in both arms. Severe late skin reaction, telangiectasia or fibrosis were not reported.

Conclusion: Once weekly UHF regimen is tolerable and non-inferior to MHF regarding toxicity. Large-scale multi-institutional studies and longer follow up are needed for the evaluation of treatment toxicities and survival benefits.

Keywords: chest wall, radiotherapy, breast cancer, hypofractionation

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1. BACKGROUND AND REVIEW

According to World Health Organization (WHO), Breast cancer was the most common cancer globally in 2021, accounting for 12% of all new annual cancer cases worldwide **(WHO.2021).** Breast cancer mortality (BCM) rates have been decreasing since the 1970s due to is due to improvements in screening and adjuvant treatment **(De Gelder R, et al. 2015).** According to the American cancer society, the estimated number of new breast cancer cases in the US is 290.560 cases in 2022 representing the most diagnosed cancer while the estimated mortality cases are 43.780 and coming fourth after lung, colorectal, and pancreas, respectively.

In Egypt, female breast cancer cases represent 16.4 % (22.000 patients) of new cancer cases and are the second most common cancer after liver cancer. However, breast cancer was the most common female cancer representing about 32.2% of newly diagnosed female cancer.

Multiple randomized controlled trials (RCT) have shown that postmastectomy radiotherapy (PMRT), either conventional or hypofractionation, has a survival benefit for high-risk patients, including those with clinical stage III, pathological stage III, and residual nodes following neoadjuvant chemotherapy (NACT) **(Pham YD & Tendulkar RD. 2018).**

Prostate and breast cancer are two cancers that are particularly sensitive to fraction size because they have low alpha/beta ratios. Research into hypofractionation for breast irradiation has gained interest because of the low average for breast cancer /ratio (2.88; 5.01 Gy) **(Qi XS, et al. 2011).**

Between 1999 and 2002, two UK RCT Standardization of Breast Radiotherapy (START) trials included female patients with pT1-T3 N0-1. START A: approximately 2.200 patients who had a mastectomy (15%) or CBS (85%) were randomly

assigned to receive 50 Gy/25 fx over 5 weeks as opposed to the two MHF arms of 41.6 Gy (3.2 Gy/fx) or 39 Gy in 13 fx QOD over 5 weeks. 15% of patients used regional nodal irradiation (RNI). There was no difference in the 10-year locoregional recurrence rate (LRR) between 41.6 Gy and 50 Gy or between 39 Gy and 50 Gy at the median follow-up (MFU) of 9.3 years. START B: The 50 Gy/25 fx/5 weeks and the 40 Gy/15 fx/3 weeks were the randomization arms. No difference in 10-yr LRR between 40 Gy and 50 Gy at MFU of 9.9 years. With 40 Gy compared to 50 Gy, breast shrinkage, telangiectasia, and edema were much less frequent for the MHF arm. The current standard of care in the UK is 40 Gy/15 fx based on START-B **(Haviland JS, et al. 2013).**

So, studies of ultra-hypofractionation (UHF) schedules were conducted considering the positive outcomes and safety from MHF, which are crucial for older patients because of comorbidities, social support, and transportation issues **(El Awadly M, et al. 2022).**

A multicenter, phase 3, randomized, non-inferiority trial is carried out in the UK Fast-Forward trial. Patients over the age of 18 who underwent CBS (94%) or a mastectomy (7%) and had invasive breast cancer (pT1-3, pN0-1, M0) were included. Patients were randomized to either an MHF regimen (40 Gy /15 fx/3 weeks) or two UHF regimens (27 Gy /5 fx/1 week, or 26 Gy /5 fx/1 week). The estimated risk of ipsilateral breast relapse at 5 years was 2.1% for the MHF, 1.7% for 27 Gy, and 1.4% for 26 Gy after an MFU of 6 years. Acute skin toxicity of grade 3+ was documented in 14% (0% in the second sub-study) of MHF, 10% (2.4% in the second sub-study) for 27 Gy, and 6% (0% in the second sub-study) for 26 Gy **(Brunt AM, et al. 2020).**

The landmark RCT UK FAST study compared two once-weekly UHF regimens with the CF regimen. About 900 patients were randomly assigned to one of the two experimental arms, which were 30 Gy or 28.5 Gy in five once-weekly fractions of 6 Gy or 5.7 Gy, respectively. Patients with tumors larger than 3 cm in diameter, mastectomy, nodal irradiation, tumour bed enhancement, and chemotherapy (CTH) were excluded. Photographic breast appearance was worse in the 30 Gy arm compared to 50 Gy after 2 and 5 years, but there was no statistically significant difference between 28.5 Gy and 50 Gy at MFU of 9.9 years. LRR is very low without significant difference between randomized arms (0.7 % for CF, 1.4 % for 30 Gy, and 1.7% for 28.5 Gy) **(Brunt AM, et al. 2020).**

Despite the efficiency of such UHF regimens after CBS, no well-randomized data was done to assess the safety and efficiency of these schedules for mastectomy patients.

2. PATIENTS AND METHODS

This is a phase III RCT comparing post-mastectomy hypofractionation schedules (40 Gy/15 fx / 3 weeks, 5 days per week VS 28.5 Gy delivered in 5 once-weekly fractions of 5.7 Gy each week) as adjuvant radiotherapy in female patients with breast cancer after mastectomy. The study was submitted to the institutional review board (IRB) with national clinical trial (NCT) registration (NCT04550910).

1. Inclusion criteria

- Female patients >18 years.
- Invasive carcinoma of the breast.
- WHO performance status (PS): 0-2.
- Able to provide documented informed consent and follow-up.

2. Exclusion criteria

- Patients with collagen vascular disease, specifically systemic lupus, or scleroderma.
- Patients didn't match the inclusion criteria.
- Pregnancy or breastfeeding.
- Prior RT to the breast or thoracic area or who had other malignancies.

3. Objectives

3.1. Primary Objectives

Acute and late toxicity regarding skin, heart, lung,

3.2. Secondary Objective

- **Locoregional recurrence (LRR)**
- **Distant-metastasis-free survival (DMFS)**
- **Overall survival (OS)**

4. Statistical analysis and randomization

Data were analyzed using IBM SPSS statistics version 22. Quantitative data will be presented as mean, standard deviation (SD,) or median and range as appropriate. Qualitative data will be presented as numbers and percentages. Numeric data will be explored for normality using Kolmogrove- Smirnove and Shapiro-Wilk Test. Comparison between the 2 groups for normally distributed numeric variables will be done using a student test and for non-inferiority normally distributed numeric variables, comparison between 2 groups will be by the Whitney test. Comparison of categorical variables will be done by the chi-square square test. P-value gets significant at 0.05 levels. All tests will be tailed. A computerized randomization table will be the method of randomization of the study.

5. Intervention in detail

- One hundred and sixty-seven patients of breast cancer patients after mastectomy were randomized into **two hypofractionation arms:**
  - **•MHF arm: Arm A (89 patients): 40 Gy /15 fx / 3 weeks, 5 days per week.**
  - **•UHF arm: Arm B (87 patients): 28.5 Gy delivered in 5 once-weekly fractions of 5.7 Gy each**

6. Toxicity assessment scale

Acute and late toxicity reactions were assessed using (RTOG) toxicity scoring scales using clinical and photographic assessment.

7. Radiotherapy verification and treatment

- **Before first treatment:** Baseline and weekly Electronic portal images (EPI) or Cone beam CT (CBCT) were done for all patients and approved by a physician.

7. Follow up

- Weekly follow-up was done to assess acute toxicity.
- History and physical exam, including assessment of RT adverse effects were performed every 3 months in the first 2 years after the end of RT.
- **Annual mammogram.**

3. RESULTS

From November 2019 to June 2021, 176 postmastectomy female patients who fulfilled the eligibility criteria of the study were recruited and analyzed at the Radiation Oncology Department of NCI, Cairo University.

I. Characteristics of the patients

The patients' criteria of both study arms were broadly comparable **Table (1).**

Table (1): The patients' criteria of both arms

	Arm A	Arm B	Total	P-value
	No = 89 (%)	No = 87 (%)	No = 176 (%)	
Age				
Mean +/-SD	50.55 ± 10.82	54.39 ± 10.49	52.16 ± 11.47	0.01
Range	27-71	29-71	27-71	
Age Groups				
≤40	12 (13.48%)	9 (10.34%)	21(12%)	0.10
41 to 49	39 (43.82%)	27 (31.03%)	66 (37%)	
≥50	38 (42.69%)	51(58.62%)	89 (51%)	
Yes	17 (19.1%)	17 (19.54%)	34 (19.32%)	
Cardiac				
No	83 (93.26%)	80 (91.95%)	163 (92.61%)	0.96
Yes	6 (6.74%)	7 (8.05%)	13 (7.39%)	
Menstrual status				
Post-menopausal	82 (92.13%)	83 (95.4%)	165 (93.75%)	0.55
Pre- menopausal	7 (7.87%)	4 (4.6%)	11 (6.25%)	

II. Clinical criteria

- Early-stage clinical T stages (T1-2) constituted 72 % of the whole study cohort while advanced clinical T stages (T3-4) constituted 28% **Figure (1).**

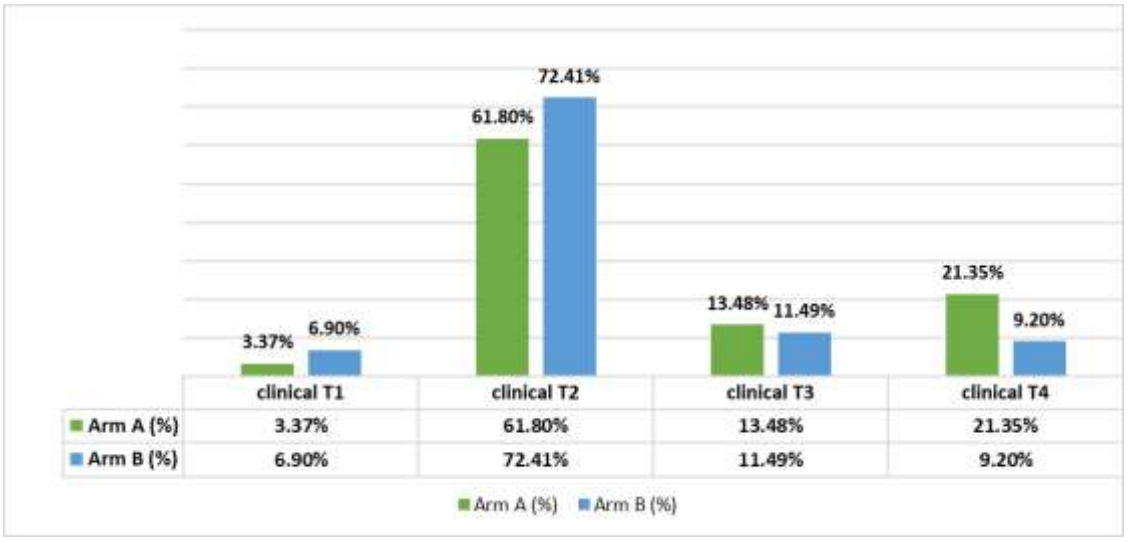

Figure (1): Clinical T stage in both study groups.

- Clinical axillary node (N1) was reported for 132 patients (75%) followed by clinical N0 (18%) then clinical N2 (7%) **Figure (2).**

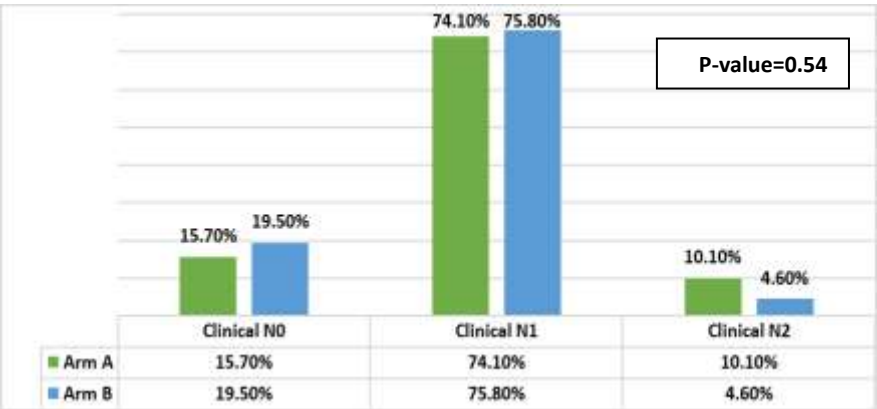

Figure (2): Clinical N stage in both study groups.

III. Tumour and pathological criteria of the study groups

The tumor and pathological criteria of both study arms were nearly comparable Table(2).

Table (2): Pathological criteria in both study arms

	Arm A No=89 (%)	**Arm B No=87(%)**	**Total No=176(%)**	**P value**
Tumor longest diameter (in cm)				
Mean ± SD	2.51 ± 2.46	3.24 ± 1.97	2.87 ± 2.26	**0.03**
Path type				
Invasive ductal carcinoma (IDC)	80 (89.89%)	77 (88.51%)	157 (89.2%)	0.93
Invasive lobular carcinoma (ILC)	4 (4.49%)	4 (4.6%)	8 (4.55%)	
Mixed	5 (5.62%)	6 (6.9%)	11 (6.25%)	
Grade				
1	1(1.12%)	3 (3.45%)	4 (2.27%)	0.50
2	75(84.27%)	74 (85.06%)	149 (84.66%)	
3	13(14.61%)	10 (11.49%)	23 (13.07%)	
LN				
1	58 (65.17%)	54 (62.07%)	112 (63.64%)	0.56
2	15 (16.85%)	20 (22.99%)	35 (19.89%)	
3	16 (17.98%)	13 (14.94%)	29 (16.48%)	

- **Stage grouping (AJCC)**

According to the 8th edition of the AJCC staging, stage III represented 41.4% of the whole cohort followed by stage I (33%) then stage II (26%) with the statistical difference (p=0.03) Figure(3)

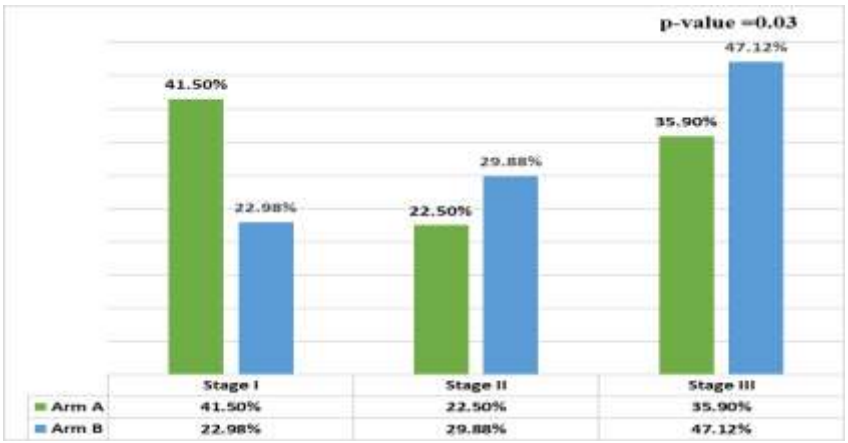

Figure (3): AJCC staging in both study groups.

IV. Acute skin toxicity

G 0-2 acute skin reaction was reported for 174 patients (98.9%) while G3 was reported for only 2 patients (1.1%) with no statistical difference (p=0.17). No G4 acute skin reaction was recorded Figure(4).

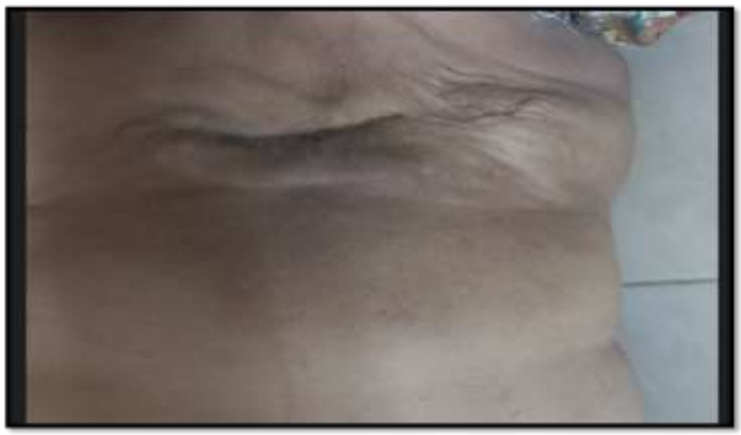

Figure (4): Acute chest wall skin reaction,63 years old, pT2N3, 4th week of the treatment (UHF arm).

V. Late skin toxicity

The median duration of follow-up is 26 +/- 5.7 months. The most common late skin reaction was G 0-1, and it was recorded in 158 patients (89.9%) while G2 was reported for 18 patients (10.2%) with no statistical difference (p=.43). No documented severe late skin reaction (G3-4) or telangiectasia or fibrosis in both study arms Figure (5).

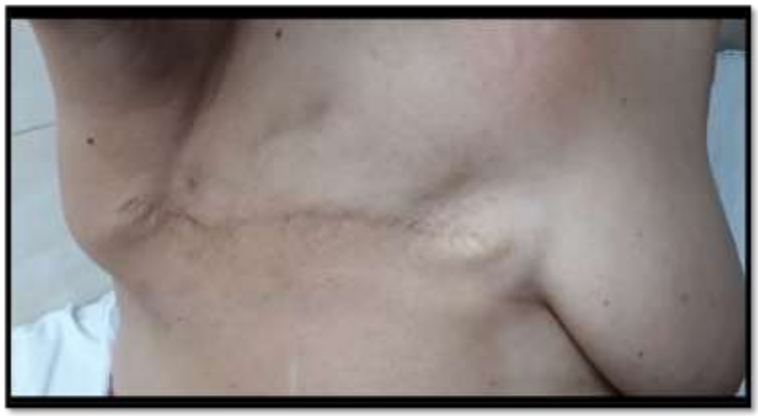

Figure (5): Late chest wall skin effect :66 years old, pT2N1, 24 months after RT (UHF arm).

4. DISCUSSION

PMRT is classically indicated for high-risk patients **(Pham YD & Tendulkar RD. 2018).** Hypofractionation schedules have been developed to reduce the number of sessions and to increase cost-effectiveness. Comparable outcomes between conventional and MHF regarding LRR, and chronic toxicity had been established **(Shaitelman SF, et al. 2015).** The UK FAST and Fast-Forward trials proved the non-inferiority of UHF after CBS.

The main 4 key trials comparing MHF with conventional fractionation are START A, START B, RMH/GOC, and Canadian OCOG-93. In START A/B trials, mastectomy patients constituted only 15% and 8 %, respectively.

In other two studies, MHF regimens (40Gy/15fx/3 weeks and /or 45 Gy/17fx/3.3 weeks) were compared with CF regimen (50Gy/25fx/5 weeks) in mastectomy patients **(Wang SL, et al. 2019 & El deep H, et al. 2012).** The main limitations of these two studies were that the 2D-RT technique was used in almost all patients (98 % in Wang's study and all patients in El deep H' study). To note, the Egyptian study was not true RCT, it was a pilot comparative study.

In the UK Fast-Forward trial, a more condensed UHF of a one-week treatment schedule was used. In this RCT, 4096 patients with less favorable criteria were included: more younger patients, positive nodes, mastectomy patients (7%), and patients who received CTH **(Brunt AM, et al. 2016).**

In previous RCT in NCI, 152 patients with early-stage breast cancer after CBS were randomized to either once weekly UHF regimens (30 Gy/ 5fx and 28.5/ 5 fx) or standard MHF schedule (40Gy/15 fx/3 weeks) **(El awadly M, et al. 2022).**

The most common challenge in the fore-mentioned trials is the limited number of mastectomy patients who need RNI. So, this trial was conducted to compare the efficiency of once weekly UHF regimen (28.5 Gy/5 fx/ 5 weeks) with the standard MHF regimen (40Gy/15fx/ 3 weeks) in the post-mastectomy setting.

Acute skin reaction

Most patients (88 %) in this study had G 0/1 skin reaction, 14.5 % and 9 % developed G2/3 reaction in MHF and UHF regimens, respectively (p-value= 0.17)

This is comparable to START B trials in which 0.7 % and 1.2 % reported marked acute skin reactions in both arms (50 Gy and 40 Gy).

Our figures also are comparable with Fast-Forward trial in which G3 RTOG toxicity was 13.6% in the 40 Gy arm, 9.8% in the 27 Gy arm, and 5.8% in the 26 Gy arm.

This is close to Chinese data in which 87% and 89 % of both study arms reported G1-2 reaction.

This is in contrast to El deep H' study, where 68 % had G1 reaction in CF compared to 58 % and 66 % in both MHF groups (40 Gy and 45 Gy, respectively) with a statistically significant difference.

Late skin effect

In this study, the most common late skin reaction is G 0/1 (89.9%), and no reported G3 reaction (p-value = 0.43). No documented fibrosis or telangiectasia. The excellent reported late-grade skin reaction may be due to short MFU, so we need a longer follow-up to confirm the safety of such UHF on the chest wall.

This is similar to Wang SL' study, where only <1% reported G3 skin toxicity.

This contrasts with El deep H' study where more telangiectasia and fibrosis were reported in the MHF arms (45 Gy/17 fx and 40 Gy/15 fx). GII–III was noticed in 17% of group 50 Gy, 33% in 40 Gy, and 37% in the 45 Gy group with a statistical significance difference.

In the Fast-Forward trial, the published results of late skin reactions with MFU of 48 months. So, it is too early to compare late adverse effects in UHF arms with their results.

5. CONCLUSION AND RECOMMENDATION

Once weekly UHF regimen is tolerable and non-inferior to MHF regarding toxicity. Large-scale multi-institutional studies and longer follow up are needed for the evaluation of treatment toxicities and survival benefits.

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