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Ultrahypofractionation in Larger Breast size, a single institute feasibility study

Mona Salem
Assistant Lecturer, MSC, Clinical oncology department, Kasr Alainy School of Medicine, Cairo University, Egypt.
Corresponding author email: mona.m.salem@kasralainy.edu.eg

Ahmad S. Ali
Lecturer, MD, Clinical oncology department, Kasr Alainy School of Medicine, Cairo University, Egypt.
Email thedrahmadali@gmail.com

Hanaa Attia
Professor, MD, Clinical oncology department, Kasr Alainy School of Medicine, Cairo University, Egypt
Email: hana.attia@gmail.com

Shaimaa Lasheen
Associate Professor, MD, Clinical oncology department, Kasr Alainy School of Medicine, Cairo University, Egypt.
Email: shaimaa_lash@hotmail.com

***Abstract*---**Background: After the standardization of adjuvant moderately hypofractionated whole reast radiotherapy (HF-WBRT) over 15-16 fractions, with the favorable long-term results of the K-FAST trial and with the uncertainty about the safety in large breast sizes. We tested the easibility of using once-weekly HF-WBRT over 5-weeks in patients with larger breast sizes. Patients and Methods: In this prospective phase-II study, patients with early breast cancer with breast size>500cc, after breast conservative surgery (BCS), received radiotherapy at a dose of 28.5Gy in 5 once-weekly fractions. Patients were categorized according to the breast size to medium and large. The primary endpoints were assessment of acute skin-toxicity and patients` quality of life (QoL); secondary endpoints were late skin and subcutaneous-tissue toxicity and cosmetic score. Results: Twenty-nine patients were recruited. The median duration of follow-up was 24-months. The mean tumor size was 2.1cm and 96.5% were node negative. Following radiotherapy, 96.5% had G0-2 acute skin-toxicity, all patients had G0-1 late skin-toxicity. Regarding cosmesis 91.7% of patients had Excellent-Good cosmetic score. No significant correlation

was found between the breast size and the acute and late toxicities. The QoL was maintained during follow-up. Conclusion: The protocol showed acceptable toxicity profile regardless of the breast size.

***Keywords*---**Breast cancer, Radiotherapy, Hypofractionation, Once-weekly and large breast.

Introduction

The use of 2.0Gy fractions in breast cancer radiotherapy was based on the assumption that larger fraction sizes compromise the therapeutic ratio, causing higher late adverse events without much improvement in local tumor control [1]. However not all tumor types are the same, squamous cell carcinomas, with high α/β ratio (6Gy), are less sensitive to fraction size than adenocarcinomas of the breast and prostate with low α/β ratio (<6Gy) [2]. Another aspect to be noted is the irradiated total dose calculated in equivalent total doses in 2-Gy fractions (EQD2), when slightly lowered it will greatly decrease the normal tissue toxicity without much compromising local tumor control [3]. Hence, the rational of hypofractionation in breast adjuvant radiotherapy developed.

Assuming that the α/β ratio of the breast is 4-5Gy, the START pilot study followed by the Ontario, START A and B trials tested the use of modestly hypofractionated regimens with favorable toxicity profile and local tumor control, consequently making the 15-16 fractions regimens the standard of care in many countries starting with UK in 2009. [4],[5] Based on the results of these trials, assuming α/β ratio of the breast to be 3.0 and 4.0Gy, the UK FAST trial started single-weekly hypofractionated regimen using 5.7 and 6Gy per fraction, respectively compared with the standard fractionation. [6]

The early and late results published in 2011 and 2020, showed acceptable toxicity profile and cosmetic outcome in the 28.5Gy over 5 weeks arm (5.7Gy per fraction) without compromising the local tumor control. [6], [7] The safety of hypofractionated breast radiotherapy with big breast volume is a point of debate, some studies suggest that patients with a large breast size should receive biologically less intensive schedules. [8],[9],[10] The UK FAST trial didn`t put any restrictions regarding the breast size, but most of the recruited patients (more than 53%) had small breast size, less than 500cc, and only near 10% of the total population had large breast size. [6] So the safety of ultra-hypofractionation in large breast volume needs further evaluation. In Egypt and in the Middle East in general we are faced with high prevalence of overweight and obesity ranging from 74% to 86% among females [16]. This study aimed at investigating the feasibility of the UK FAST protocol in larger breast sizes.

Patients and Methods

Eligibility criteria

This phase II feasibility study was conducted at Kasr AL-Aini Center of Clinical Oncology & Nuclear Medicine (NEMROCK). Fifty patients were screened between March 2018 and February 2020, 9 patients withdrew their consent, and 12

patients didn`t meet the specified dose constraints for organs at risk, subsequently 29 patients were included in the final analysis. Female patients≥18 years old with pathologically proven early breast invasive adenocarcinoma, having a breast size of more than 500cc, after breast conservative surgery were recruited to receive once-weekly adjuvant breast radiotherapy at a dose of 28.5Gy over 5 weeks (5.7Gy per fraction), regional lymphatic irradiation was allowed. No tumor bed boost was administered. Also, patients with bilateral synchronous or prior malignancy, prior radiotherapy to the thoracic region and contraindication to radiotherapy were excluded. Breast size was roughly categorized from the baseline into 2 grades (medium and large) corresponding to breast volumes 500–1000 and >1000 cc, respectively as calculated from the planning system.

Contouring and planning

Target volume delineation was done in concordance with ESTRO guidelines. Dosimetric constraints were extrapolated from the FAST-FORWARD trial published protocol. [17]

Ipsilateral lung:
V8.55 Gy < 15%

Heart:
V7.125 Gy < 5%
V 1.425 Gy <30%

During treatment set-up verification was done before each session using electronic portal image (EPI), the light field of the medial and lateral tanged fields and source skin distance (SSD) of both fields were checked.
Patients were followed up periodically by the treating physician using clinical examination, photographs and patient QoL questionnaires. Follow up visits were scheduled with every radiation session, 1 month after the end of treatment, 3 months, 6 months, 1 year and annually thereafter.
Reporting of acute toxicity was done using the RTOG scale (0 = no visible change; 1 = faint/dull erythema; 2 = tender/bright erythema ± dry desquamation; 3 = patchy moist desquamation; 4 = confluent moist desquamation, pitting edema). [12]
Late-occurring adverse tissue effects were assessed by physicians at the annual follow-up visits using the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. [13]
Change in cosmetic breast appearance compared with the post-surgical (pre-radiotherapy) baseline was scored using HARVARD/NSABP/RTOG Breast Cosmesis Grading Scale (Excellent, Good, Fair and Poor) compared to the contralateral breast. [14]

Statistical analysis

- Statistical analysis was performed using MedCalc Statistical Software for Windows Version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).
- Descriptive

  - Mean and standard deviation.
  - Median and interquartile range.
  - Number and percentages.
- Test for normal distribution: Shapiro-Wilk test. Comparison of abnormally distributed variable between more than 2 groups: Kruskal-Wallis test. Comparison of abnormally distributed variable between 2 groups: Mann-Whitney test. A p value <0.5 was considered significant.

Results

Patient's clinical characteristics:

The mean age of the included patients was 54.3 years (range 35-70 years), 45% pre-menopausal patients, and 55% were post-menopausal.
The mean weight was 84.2 kg (range 59-119 kg). The majority of cases (76.1%) had BMI ≥ 30 Kg/m2, and (28.5%) had BMI ≥ 35.
In our study 7 (24%) patients had large breast volume (more than 1000cc) while the majority of had a breast size ranging from 500-1000 cc: 22 patients (76%).
Fifteen patients received adjuvant chemotherapy with/without Trastuzumab.

Disease characteristics:

All patients recruited underwent BCS and axillary lymph node assessment before starting RT.

Table 1
Disease characteristics

Parameter	N (%)
(pT) staging	
T1	16 (55%)
T2	13 (45%)
(pN) staging	
N0	28 (96.5%)
N2	1 (3.5%)
Axillary surgery	
SLNB	17(59%)
ALND	12(41%)
Side	
Right	8 (27.6%)
Left	21 (72.4%)
Biological Sub-type	
luminal A	9 (31%)
luminal B1	16 (55.2%)
luminal B2	1 (3.4%)
Her-2 enriched	1 (3.4%)
TNBC	2 (6.9%)

Dosimetric data

All cases (29 patients) received hypofractionated radiotherapy with a dose of 28.5 Gy/5 Fr/5 weeks to the whole breast and one case received para-clavicular LN (PCLN) radiotherapy. No tumor bed boost irradiation was given.

Table 2
Dosimetric data

Dosimetric data for breast coverage	
Parameter	Mean (SD)
Breast PTV	
D 98 %	90.9±2.4 (Gy)
D 95 %	93.9±1.04 (Gy)
D 50%	100.3±1.09 (Gy)
Homogeneity index	0.149±0.029
Conformity index	1.39±0.13
Dosimetric data for OAR	
Parameter	Mean (SD)
Ipsilateral lung	
V 8.55	12.9 ± 3.27 (%)
CLD	2.34 ± 0.23 (cm)
Heart	
V 7.125	2.08 ± 1.7 (%)
V 1.425	10.7 ± 8.5 (%)
MHD	1.09 ± 0.9 (cm)
Contralateral Breast	
Mean Dose	0.37 ± 0.1 (Gy)

OAR: organ at risk, MHD: mean heart dose, CLD: central lung distance.

Toxicity Profile

Patients were followed up for a median duration of 24 months, toxicity and QoL were assessed and documented.

RTOG Acute Skin Toxicity:
During RT:

Week 5 showed the maximum grade of acute toxicity during RT; with most of the patient (58.6%) having grade 2 toxicity. Patients were then followed up at 1 month and 3 months

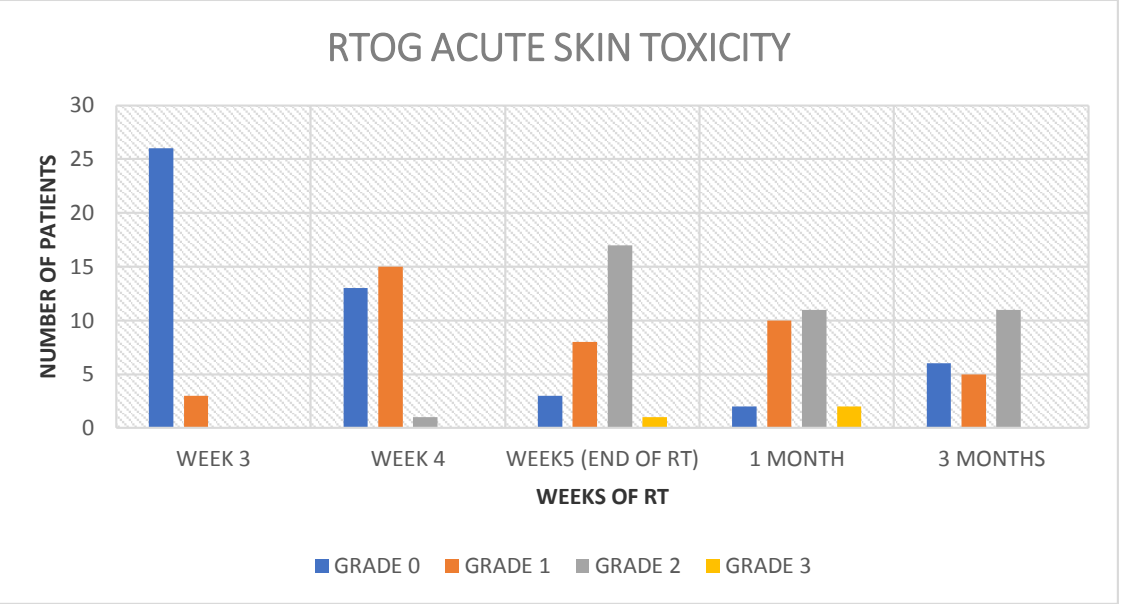

Figure 1: *Acute Skin toxicity.*

Late toxicity using RTOG/EORTC Late Radiation Morbidity Scoring Scheme:

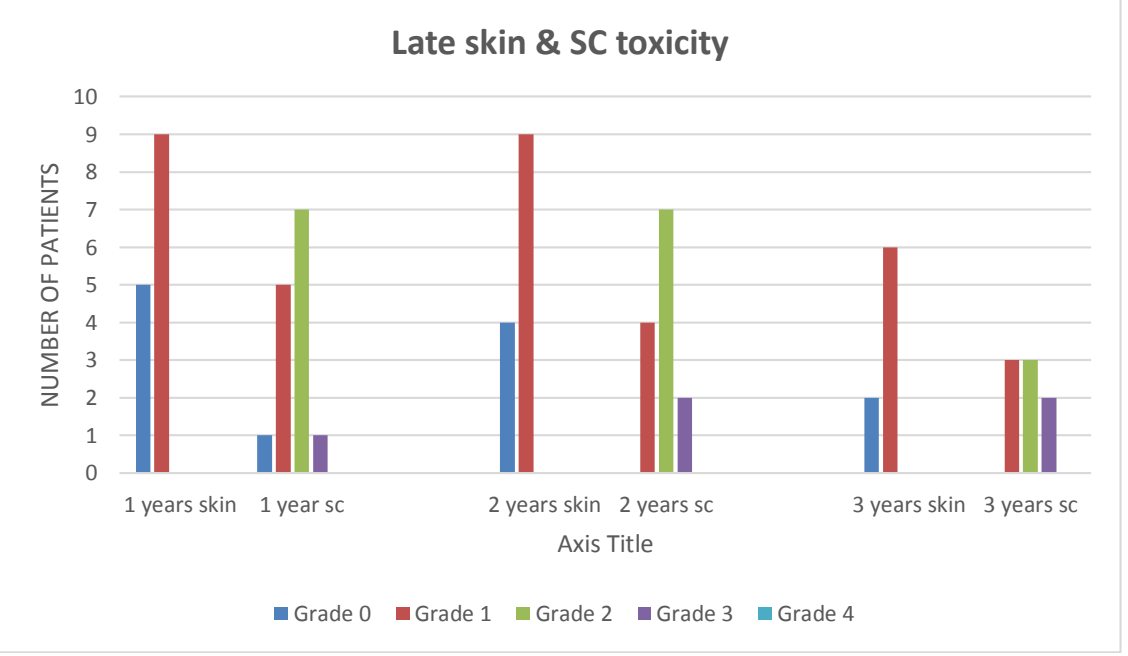

Figure 2: *Late Skin &Subcutaneous tissue toxicity.*

Cosmetic outcome using HARVARD/NSABP/RTOG Breast Cosmesis Grading Scale

Cosmetic breast evaluation using HARVAD cosmesis scale was conducted at baseline (before RT), at the end of RT, at 1 month after RT, at 3 months after RT and at 6 months then annually thereafter. The number of patients with ***Excellent*** cosmetic outcome was 9 (31%), 6 (20.6%), 6 (23%), 4 (17.4%), 3 (16.6%), 3 (21.4%), 3 (25%) and 2 (28.5%) at baseline, end of RT, 1 month, 3 months, 6 months, 1 year, 2 years and 3 years, respectively.

Regarding patients with ***Good*** scores the number was 20 (69%), 23 (79.4%), 18 (69.2%), 17 (74%), 12 (66.6%), 10 (71.4%), 8 (66.6%) and 4 (57.5%) at baseline, end of RT, 1 month, 3 months, 6 months, 1 year, 2 years and 3 years, respectively. In our study no patients had ***Fair*** cosmetic score at baseline before starting RT and by the end of RT this escalated to 2 (7.6%), 2 (8.6%), 3 (16.6%), 1 (7%), 1 (8.3%) and 1 (14.2%) patients at 1 month, 3 months, 6 months, 1 year, 2 years and 3 years, respectively. No patients had ***Poor*** cosmetic outcome at any time of assessment.

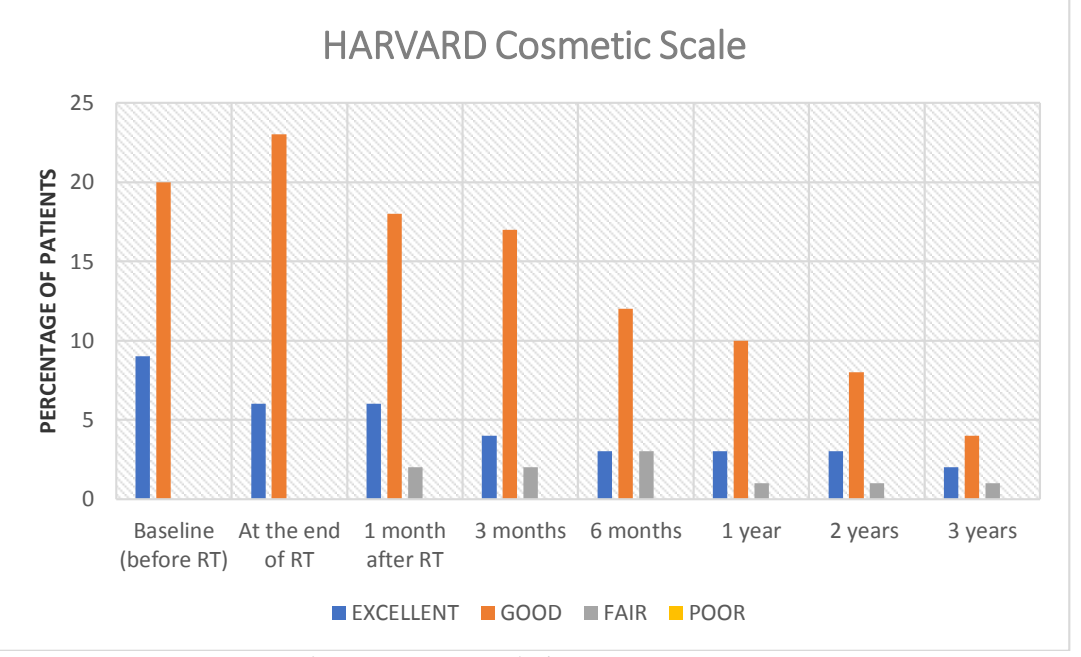

Figure 3: *Cosmetic breast appearance*

The rate of "significant cosmetic change" from baseline to last follow up (dropping from excellent or good to fair or poor) was 13.7%.

When subclassified according to the breast size:
Patients with large breast size; 83.4%, 100%, 80% and 75% had Excellent to Good cosmetic breast appearance by 6 months, 1 year, 2 years and 3 years, respectively, and none had Poor cosmetic outcome and only one patient had significant change in cosmetic breast appearance from baseline to last follow up.

As regarding medium breast size, 90.9%, 89%, 100% and 100% had Excellent to Good cosmetic breast appearance by 6 months, 1 year, 2 years and 3 years, respectively, and none had Poor cosmetic outcome and 3 patients (13.6%) had significant change in cosmetic breast appearance from baseline to last follow up.

Table 3
Toxicity profile according to the breast size

RTOG acute skin toxicity	Breast size	
	Medium (%)	Large (%)
0 = no visible change	3 ((13.6)	0
1 = faint/dull erythema	7 (31.8)	1 (14.3)
2 = tender/bright erythema ± dry desquamation	11 (50)	6 (85.7)
3 = patchy moist desquamation	1 (4.5)	0
4 = confluent moist desquamation, pitting edema	0	0
RTOG late skin toxicity	Breast size	
	Medium (%)	Large (%)
At 1 year:		
Grade 0	4 (44)	1 (20)
Grade 1	5 (56)	4 (80)
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
At 2 years:		
Grade 0	3 (37.5)	1 (20)
Grade 1	5 (62.5)	4 (80)
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
At 3 years:		
Grade 0	2 (50)	0
Grade 1	2 (50)	4 (100)
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
RTOG late sc toxicity	Breast size	
	Medium (%)	Large (%)
At 1 year:		
Grade 0	1 (11)	0
Grade 1	3 (33)	2 (40)
Grade 2	4 (44)	3 (60)
Grade 3	1 (11)	0
Grade 4	0	0
At 2 years:		

Grade 0	0	0
Grade 1	2 (25)	2 (40)
Grade 2	5 (62.5)	2 (40)
Grade 3	1 (12.5)	1 (20)
Grade 4	0	0
At 3 years:		
Grade 0	0	0
Grade 1	2 (50)	1 (25)
Grade 2	1 (25)	2 (50)
Grade 3	1 (25)	1 (25)
Grade 4	0	0
HARVARD Breast Cosmesis Grading Scale	Breast size	
	Medium (%)	Large (%)
At 6 months:		
Excellent	2 (18.18)	1 (16.6)
Good	8 (72.7)	4 (66.6)
Fair	1 (9.1)	1 (16.6)
Poor	0	0
At 1 year:		
Excellent	1 (11)	2 (40)
Good	7 (77.7)	3 (60)
Fair	1 (11)	0
Poor	0	0
At 2 years:		
Excellent	1 (14.3)	2 (40)
Good	6 (85.7)	2 (40)
Fair	0	1 (20)
Poor	0	0
At 3 years:		
Excellent	1 (33.3)	1 (25)
Good	2 (66.7)	2 (50)
Fair	0	1 (25)
Poor	0	0

Quality of life:

Using FACT-B QoL questionnaire:

FACT-B QoL questionnaire was filled by the patients at baseline, at the end of RT, 1 month after RT, 3 months after RT and at 6 months.

The mean score was 99.9 at baseline and 96.2, 101.6, 98.5 and 106 at the end of RT, 1 month, 3 months and 6 months after RT, respectively.

Using FACIT-PS-TS QoL questionnaire:

FACIT-PS-TS QoL questionnaire was filled by the patients at the end of RT, 1 month, 3 months and at 6 months after RT.

The mean score was 65.6 at the end of RT and 74.4, 71.9 and 74.37 at 1 month, 3 months and 6 months after RT, respectively. [18]

Correlation analysis:
Correlation between breast volume and Harvard scale at 2 years

There was no statistically significant correlation between the breast volume of the breast and Harvard score at 2 years form the end of RT (p=0.88).

Correlation between breast volume and acute toxicity at the end of radiotherapy from the end of RT & late skin toxicity at 2 years

There was no statistically significant correlation between the breast volume of the breast and acute skin toxicity at the end of radiotherapy (p=0.3) or late skin toxicity at 2 years (p=0.14).

Discussion

The three weeks radiation regimen, for early breast cancer, was adopted as the standard of care in many countries following the 10 years follow up results of the main four randomized controlled trials that compared hypofractionation with conventional radiotherapy for whole breast irradiation (Canadian, UK pilot, START A, and START B) with achievement of a local control similar to the standard fractionation, without increasing the long-term side effects. [4],[5]

Based on the convenience and good long-term outcomes of the modestly hypofractionated protocols, further reduction in the number of fractions was questioned starting with the UK FAST trial with acceptable long-term outcomes using single weekly schedule over 5 weeks compared to standard fractionated whole breast radiotherapy [6]. Furthermore, based on the 3-years results of the UK FAST trial in 2011, the FAST-FORWARD trail started recruitment using the 5 fractions schedule over 1 week and compared it to 3-weeks schedule and the 5-years outcome was non-inferior in the 26 Gy arm [11]. However, the majority of the patients in the UK-FAST trial had small breast size which is not the situation in many patients in Egypt where we are faced with high prevalence of overweight and obesity that ranges from 74% to 86% among females [16].

Accordingly, this prospective phase II study was conducted to test the feasibility of ultra-hypofractionation in larger breast sizes. A total of 29 eligible patients received adjuvant radiotherapy sessions on weekly basis with a dose of 28.5 Gy over 5 fractions in 5 weeks following BCS. The results were reported at a median follow-up period of 24 months ranging from 24 to 40 months.

Patients with breast size more than 500cc were included. The mean breast size was 913 cv (range, 600-1442 cc), this was further divided to 2 main categories: with 76% and 24% having breast size 500-1000cc and more than 1000cc, respectively. These results are different than the comparable arm (28.5 Gy arm) in the UK FAST trial which reported a percentage of 53.4%, 30.5% and 7.9% having breast size less than 500cc, 500-1000cc and more than 1000cc, respectively. [6]
Another difference between the included patients and the UK FAST trial was that this study allowed higher risk patients; in the current study the mean tumor size was 2.1 cm (range, 1-4.5 cm), while in the UK FAST trial the mean tumor size was 1.3 cm (range, 1-3 cm) this is explained by the fact that they only recruited

patients with tumor size less than 3 cm [6]. Also, node positive patients were allowed in this study unlike the UK FAST trial [6]. Furthermore, 48.4% of the patients received adjuvant chemotherapy, those patients were excluded in the UK-FAST trial. [6]

The guidance for the dosimetric constraints were extrapolated from the FAST-FORWARD protocol [17]. Regarding the target coverage, the mean dose received by ***95%*** of the planned target volume was ***93.9%***. As for the organs at risk: in the lung the mean ***V8.55 Gy*** was ***12.9%*** and the heart we used ***V7.125 Gy*** and ***V1.425 Gy*** the mean was ***2.08%*** and ***10.7%***, respectively**.** In order to meet the dose constraints for the heart one patient needed to use Deep Inspiratory Breath Hold technique to decrease the heart dose.

One of the challenges in this study was the unavailability of a model for gap calculation particularly in the weekly radiotherapy regimens. One of our patients developed cellulites after week 2 and required 1 week rest, 3 other patients had a delay of 2 days due to machine breakdown. In these cases, we aimed to keep the overall treatment time, the number of fractions and the dose per fraction constant by giving more than one fraction per week, which may be acceptable now after the results of the FAST-FORWARD trial results where patients received ultra-hypofractionated radiotherapy on daily basis. [11]

The acute toxicity profile in our schedule was generally tolerable. The rate of acute skin toxicity according to the RTOG scale at the end of the treatment was 10.3%, 27.5%, 58.6% and 3.4% for grade 0, 1, 2 and 3, respectively. No grade 4 toxicity was reported during radiotherapy. On the other hand, the UK FAST trial in the 28.5 Gy arm reported 39.6%, 50%, 8.5%, and 1.9% for grade 0, 1, 2 and 3, respectively. Also, with no grade 4 toxicity reported during radiotherapy [6]. This is probably attributed to the difference in breast sizes as some studies showed increase in acute skin toxicity with increasing the breast size [19],

However, this improved by the end of 1 month following radiotherapy, with improvement of grade 2 in about 14% of the patients. The reported acute toxicity was 8%, 40%, 44% and 8% for grade 0, 1, 2 and 3, respectively. With no patients reaching grade 4 toxicity. Toxicity kept improving, with no reported grade 3 toxicity by the end of 3 months follow up only grade 0,1 and 2 in 27.3%, 22.7% and 50%, respectively. The WHBI US trial reported the maximum observed acute toxicity during the period between completion of treatment and 6 weeks after therapy [15]. The acute toxicity profile was comparable across all groups. No significant correlation could be found between breast size and the development of acute skin toxicity.

Late normal tissue effect was assessed at 1 year, 2 years and 3 years using RTOG/EORTC Late Radiation Morbidity Scoring Scheme. All patients had grade 0-1 skin toxicity on long term follow up. Regarding the subcutaneous tissue toxicity, at 1 year, 92.8% had grade 0-2 subcutaneous tissue toxicity and only one patient with medium sized breast developed grade 3 toxicity. Grade 0-2 toxicities were reported in 84.6% and 71.4% of the patients at 2 and 3 years, respectively. The rest had grade 3 toxicity with no grade 4 reported. There was no

correlation found between the breast size the reported late skin and subcutaneous tissues toxicity.

The cosmetic outcome was evaluated using HARVARD cosmesis scale at baseline and on follow up. At baseline after surgery 20 patients (69%) had ***Good*** cosmetic outcome before starting radiotherapy and the rest had ***Excellent*** outcome. On longer follow up; 92.8%, 91.6% and 85.7% had Excellent to Good cosmesis on 1 ,2 and 3 years follow up, respectively. And the rest had Fair cosmesis with no Poor outcome reported. This was in contrary to the UK FAST trial that reported 2 years change in photographic breast appearance in the 28.5 Gy arm; 76%, 22% and 3.7% having no change, mild change and marked change in the appearance [6]. This is probably related to the worse baseline cosmesis, related to the surgical cosmetic outcome and the HARVARD scale we used was comparing the treated breast to the contralateral breast not the baseline breast cosmesis. Therefore, we looked at the rate of "significant cosmetic change" from baseline to last follow up (dropping from excellent or good to fair or poor) in that regard it was 13.7% in our study compared to 11.6% in the WHBI US trial [15]. The rate was 13.6% and 14.2% in medium and large breast sizes, respectively.

Conclusion

At median follow up of 24 months, 28.5Gy in 5 once-weekly fractions showed acceptable toxicity profile regarding acute skin toxicity and on longer follow up favorable cosmesis and late skin and subcutaneous toxicities regardless of the breast size. Patients` QoL was maintained. Longer follow up is warranted for better evaluation of long-term toxicity and relapse.

Funding: None.

Conflict of Interest: The authors declare that there are no conflicts of interest to disclose.

Data availability: The data that supports the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to the containing information could compromise the privacy of research participants.

Ethical considerations: The research protocol was presented and accepted by the research ethics committee and the scientific research committee of the department of clinical oncology, Faculty of Medicine, Cairo University. And accepted by the Faculty of Medicine research Ethics Committee with approval number of I-031018.
The trial was registered on ClinicalTrials.gov, the ClinicalTrials.gov Identifier is NCT04580784.

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