Evaluation of Safety and Efficacy of 1 week versus 3 weeks hypofractionation radiotherapy for breast cancer patients: Phase III trial

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Abstract:

Background: The current gold standard for adjuvant radiotherapy for breast cancer nowadays is hypofractionated radiotherapy. Measures for balancing both infectious and oncologic risk among patients and healthcare professionals must be carefully considered in the context of expected resource shortages and worldwide widespread community SARS-CoV-2 infection during the COVID-19 pandemic. Here, we document the early and late skin toxicity and efficacy outcome of a prospective institutional phase III trial comparing a 1-week course of adjuvant breast radiotherapy to a 3-week regimen after surgical treatment for early breast cancer.

Methods: A phase III, randomized controlled trial is described here. Patients who underwent breast conserving surgery or a mastectomy and had invasive ductal or lobular breast cancer (pathological stagingT1-3, pN0-1, M0) were eligible if they were at least 18 years old. Sequential tumor bed boost radiotherapy (dose of 10 Gy/ 4 fractions and 5.2 Gy/ 1 fractions, respectively) is permitted in patients who have undergone breast conservative surgery and are younger than 50 years old and those of older age with high grade tumor or lymphovascular invasion. Patients were randomly assigned to receive 40 Gy/15 fractions (F)/3 weeks or 26 Gy/5 fractions (1 week). First endpoint evaluation of immediate and delayed effects on normal tissue and cosmetic results, Clinicians evaluated the impact on normal tissue using pictures, secondary endpoint estimation of two years LRR free survival, and two years disease free survival

Results: At six weeks after the end of treatment, 65 patients in the control arm and 63 patients in the test arm were assessed for the most severe acute breast skin reactions. Grade 2 reactions, which were graded using CTCAE criteria (V4.03), were present in 47.7% of the control arm patients and 27% of the test arm patients, respectively.

Our study's assessment of the late effects on normal tissue after a median follow-up of 25 months, a range of 21 to 30 months, revealed that radiotherapy-related fibrosis, Telangiectasia, and hyperpigmentation were similar between the two groups ($p>0.05$), with fibrosis within the tumour bed being the most prevalent moderate or marked effect at 2 years, as occurred in 2 patients (3.1%) of 65 patients who received 40 Gy and 4 patients (6.3%) of 63 patients. Ultrahypofractionation resulted in incidence of excellent or good cosmesis over fair or poor cosmesis of 87.3% versus 12.7%, and the control arm resulted in a rate of 87.7% versus 12.3%, which is statistically insignificant ($p=0.9$). Two-year LRR-free survival was 96.9% in the control group and 98.4% in the ultrahypofractionation group, both of which were statistically insignificant. Of the two patients with LRR (3.1%) in the control arm and one (1.6%) patient in the ultrahypofractioation group, respectively, the disease-free survival rate was 95.3% in the control arm and 95.2% in the ultrahypofractioation arm.

Conclusion: 26 Gy in 5.2 Gy per fraction daily over 1 week is equal to 40.05 Gy in 2.67 Gy per fraction daily over 3 weeks for patients received adjuvant radiotherapy after surgical resection for early-stage breast cancer as regard normal tissue effects up to 2 years and for local tumor control and to confirm study result need longer follow up.

Keywords: Breast cancer, Ultrahypofractionation, Radiotherapy.

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Introduction:

In less developed nations, breast carcinoma continues to be the major cause of death for women. In industrialized nations, it is the second greatest cause of death for women from cancer after lung cancer. Breast cancer accounts for 29% of all cancer cases in the United States [1]. In Egypt, 32% of women who die from cancer had breast cancer. [2]. Adjuvant breast radiotherapy improve the 10-year loco regional recurrence rates (LRR) from 35 to 19.6%. This improves breast cancer patients survival (25.2% versus 21.4%) at 15 years in patients undergoing breast conservative surgery [3]. The same value was seen in patients who have treat by mastectomy [4]. Adjuvant radiation treatment for the breast employing a total dosage of 45 to 50 Gy (Gray) over 5 weeks with an additional 1–2 weeks in the event of treatment boost. A lengthy treatment plan has the drawbacks of being inconvenient for patients and adding to the workload of radiation departments, where treating many patients will take longer and have an impact on the upkeep and turnover of radiation machines. Breast cancer differs from other types of cancer in that it has a higher fraction sensitivity, which allows for the use of a high dose per fraction but is linked to shorter cell survival. Breast cancer's "healing exponent" was quite similar to that of healthy skin, rendering lengthy fractionation ineffectual in these tumors [5]. A randomized experiment assessing two regimens of adjuvant radiotherapy, either 13 or 16 fractions (39 Gy and 42.40 Gy, respectively), versus the usual treatment of 50 Gy in 25 fractions developed from the previously mentioned radiobiological feature of breast cancer was completed at the Royal Marsden Hospital and Gloucestershire Oncology Center in 1998. The findings of this research were utilized to calculate the alpha/beta ratio for both tumour control (4.1 Gy) [6] and late normal tissue reactions (ranging between 3 and 4 Gy) [7]. Later on, the combination of the results of the Canadian hypofractionation trial [8] and the two START trials [9], it became obvious that estimate for the alpha/beta ratio of tumour control was about 3.5 Gy [9]. Hypo fractionated regimens for whole breast irradiation have produced encouraging results in prospective randomized clinical trials [7],[10],[11]. Delivering a hypo-fractionated dose schedule that is biologically equal to the conventional radiation fractionation dosage of 50 Gy in 25 fractions of 2 Gy was the aim of each of these research. Similar in-breast local control has been shown in these trials' 5–10 year follow-up periods between the hypofractionated and conventional fractionated arms. Also the shortage in total time in adjuvant radiotherapy of breast cancer to only 3 weeks was great advance and of great value for both health care facilities and patients, this not considered the extreme radiobiological limit and further hypofractionation is radiobiologically possible based on the higher fraction sensitivity of breast cancer, The FAST randomised control study compares two 5 fractions weekly hypofractionated breast radiation regimens (28.5 Gy or 30 Gy) to the usual 50 Gy arm [12]. The first acute skin toxicity result, as well as the photographic assessment of breast appearance, demonstrated that the 28.5 Gy regimen was similar to 30 Gy. Both arms had the same locoregional control, with no significant differences in cosmesis or late toxicity profile. Additional research into the safety and efficacy of a once-weekly regimen has yielded similar results. [13, 14]. The FAST Forward randomized control trial was created to compare two schedules of 5 fraction radiation therapy delivered in one week to the United Kingdom standard arm of 15 fractions delivered in three weeks based on the promising results of the FAST trial and the possibility of a reduction in overall treatment time with good tumor control. According to the results of the fast forward trial's acute skin toxicity substudy, grade 3 RTOG toxicity for 26 Gy delivered in 5 fractions is 5.8%, compared to 13.6% for 40 Gy delivered in 15 fractions [15]. In both arms, none of the patients experienced CTCAE grade 3 toxicity. [15]. Additionally, according to findings from a fast-forward experiment, a 15-fraction treatment after primary surgery for early breast cancer is just as effective and safe as 26 Gy given in five fractions. In terms of patient comfort and affordability, as well as for global health services, the 1-week plan has considerable advantages over the 3-week or 5-week timetables. The aim of our study is to evaluate Acute and late Skin Toxicity of 1 week versus 3weeks hypofractionation radiotherapy for breast cancer patients and evaluation of disease outcomes.

Patients and Methods:

Study design

This Randomized prospective phase III study received institutional ethical committee approval at the South Egypt cancer institute, Assiut University, Egypt in December 2020 under approval No.518, comparing the safety and effectiveness of five-fraction adjuvant radiation therapy schedules to the UK standard 15-fraction 3-week schedule for the chest wall or entire breast when administered in one week and this trial considered rapid ultrahypofractionation deployment for postoperative breast radiotherapy therapy at the time of a huge worldwide health crisis in the COVID-19 pandemic.

Patients:

Women with invasive ductal or lobular carcinoma of the breast (pathological staging T1-3, pN0-1, M0) and who had undergone mastectomy or complete microscopic excision (conservative surgery) of the primary tumor were potential candidates. Breast cancer history, absence of epithelial carcinoma, metacentric breast cancer disease, nodal involvement with extracapsular extension, bilateral breast cancer, cosmetic breast augmentation, history of collagen or vascular disease, pregnancy, or nursing were all grounds for exclusion from the study. Nodal radiation was not allowed; all patients underwent axillary surgery (axillary dissection or sentinel node biopsy). Patients were randomly assigned (1:1) to receive either 40.05 Gy in 15 fractions of 2.67 Gy over 3weeks or 26 Gy in five

fractions of 5.2 Gy over 1 week. It was permitted to provide successive tumor bed radiation (dosage of 10 Gy/ 4 fractions in the control arm and 5.2 Gy/ 1 fractions in the test arm) to the conserved breast in patients who were younger than 50 years old those of older age with high grade tumor or lymph vascular invasion. The randomization was carried out over the phone from the radiation oncology department of the South Egypt Cancer Institute (SECI), Assiut University, Egypt. Treatment allocation was not concealed from either doctors or patients. Every patient signed a written informed consent form.

Radiotherapy technique:

The complete breast clinical target volume, which consists of the soft tissues from 5 mm below the skin's surface to the deep fascia, was contoured. The chest wall clinical target volume involves post-surgical skin flaps and underlying soft tissues to the deep fascia, and surgeons were strongly advised to mark the tumor cavity walls with surgical radiopaque clips at the time of conservation surgery in order to facilitate delineation of the tumor bed in women treated with mastectomy. To produce a planning target volume, a standard margin of 10 mm was included around the breast or chest wall clinical target volume to accommodate for set-up error, breast swelling, and breathing (PTV). A comprehensive 3D CT set of outlines including the entire breast and organs at risk was acquired for all patients, with a slice separation of up to 5 mm, and organs at risk were delineated prospectively. A tangential opposed pair field plan uses the entire PTV of the breast or the chest wall, minimizing exposure of the ipsilateral heart and lungs. In order to achieve the following PTV dose distribution, the radiotherapy treatment planning was optimized with 3D planning: more than 95% of the PTV received 95% of the prescribed dose, less than 5% of the PTV received 105% or more, less than 2% of the PTV received 107% or more, and the overall dose maximum was less than 110%. The ipsilateral lung volume getting 12 Gy less than 15%, the volume of the heart receiving 2 Gy less than 30%, and the heart receiving 10 Gy less than 5% were the dose restrictions for the control group. The following were the dose restrictions for the five-fraction schedules: Less than 15% of the ipsilateral lung's volume receiving 8 Gy, less than 30% of the heart's volume receiving 1.5 Gy, and less than 5% of the heart's volume receiving 7 Gy. 6 MV or 10 MV X-ray beam intensities were used for treatment. Either electrons or photons were used to offer the tumor bed boost. Kilo voltage x-rays were used for electronic portal imaging during the verification process. Verification of the control group treatment was required once per week with a tolerance of 5 mm for the first week for at least three fractions, with correction for any systematic mistake. The ultrahypofractionation schedules call for recommendations to stabilize every measured shift and verification imaging for each fraction.

Assessment and Follow-up:

Using common CTCAE criteria [16], acute skin responses on the treated breast were graded (v4.03) (Appendix 1). A healthcare professional performed toxicity evaluations. The assessments were planned to be done every week during treatment and for six weeks after radiotherapy ended.

At annual visits, patients were evaluated by a physician for late normal tissue effects. impact on the ipsilateral breast or chest wall's late normal tissue (breast fibrosis, telangiectasia, and hyperpigmentation) were assessed using modified late effects on normal tissues scoring methods beginning one year after the trial's commencement. (Appendix 2) taken to mean none, mild, moderate, or marked and assessment for ipsilateral loco regional relapse, Photographs of the cosmetic result were taken prior to the initiation of radiotherapy and two years after the course of radiotherapy was completed. On a Harvard scale for assessing cosmosis, after surgery and before radiation, changes in photographic breast appearance compared to baseline were graded. (Appendix 3), The cosmetic outcomes were classified into four categories: excellent, good, fair, and poor. Photographs were assessed and scored by two physicians who were not aware of the patient's name or treatment allocation.

Statistical analysis:

The statistical package for the social sciences (SPSS) version 20 was used to analyze the data. There were descriptive statistics used, including median, mean, number, and percentage. The Log-rank test was performed to evaluate whether there were statistically significant differences between the variables, and the Kaplan-Meier test [17] was used for the survival analysis. The Chi-square test was used to evaluate the relationship between variables and treatment response. P value of 0.05 was regarded as significant.

Results:

Patient's characteristics were reported in Table 1, as regard test arm Median age was 54 years, 47.6% < 50 years old,54% right sided breast cancer patients, 68.3% had T2, 96.8% N0,3.2% N1, 49.2% G2, 76.2% had positive Estrogen receptors (ER) receptor and negative Her2neu as regard control arm median age 50 years old,55.4% left sided breast cancer patient, 63.1% had T2,80% N0,20%N1,50.8% with grade 2and 78.5% had positive ER receptor and negative Her2neu.

Treatment characteristics reported in Table 2, 87.3% underwent BCS. Regarding chemotherapy, 41.3% received Adriamicin/cyclophosphamide with taxanes and (46%) not received chemotherapy at all.. Regarding Hormonal therapy, 66.7% received aromatase inhibitors and regarding target therapy 11.1% received trastuzumab and 61.9% received tumor bed boost radiotherapy in test arm and as regard control arm 87.7% underwent breast conservative surgery (BCS). Regarding chemotherapy, 35.4% received Adriamicin/cyclophosphamide with taxanes and (41.5%) not received chemotherapy at all. Regarding

Hormonal therapy, 56.9% received aromatase inhibitors and regarding target therapy 10.8% received trastuzumab and 70.8% received tumor bed boost radiotherapy.

Early toxicity assessment 6 weeks after finish radiotherapy show in test arm 61.9% with grade 1 dermatitis according to CTCAE, 27% with grade 2 and only 11.1% not reported any skin toxicity and in control arm 50.8% with grade 1, 47.7% grade 2 and 1.5% not reported any toxicity and no any patient report grade 3 toxicity in both arms as shown in table 3.

After median follow up 25 months ranged from 21 to 30 months, the late toxicity assessment listed in table 4,5,6 & 7 show 15.9 % with mild fibrosis ,6.3% with moderate and marked fibrosis in test arm and 15.4% mild fibrosis and 3.1% with moderate and marked fibrosis in control arm. As regard telangiectasia 9.5% with mild degree, 3.2% with moderate and marked telangiectasia in test arm and 7.7% mild telangiectasia and 3.1% with moderate and marked telangiectasia in control arm . As regard hyperpigmentation 6.3% with mild hyperpigmentation, 6.3% with moderate and marked hyperpigmentation and 6.2% mild hyperpigmentation and 1.5% with moderate and marked hyperpigmentation in control arm with insignificant difference between 2 arms in all assessed late toxicity.

Table 8 show incidence of Changes in photographic breast look in BCS patients after 2 years from the end of radiation only (55 patient) that show excellent & good cosmesis versus fair &poor cosmesis was 87.3% versus 12.7% for ultrahypofractionation and 87.7% versus 12.3% which is statistically non-significant (p=0.9).

Mean follow up period after radiotherapy 25 months ranged from 21 to 30 months

2 years LRR free survival was 96.9% in control group and 98.4 % in ultrahypofractionation group which statistically insignificant and there were 2 patients who had LRR (3.1%) in control group and 1 (1.6%) patient in ultrahypofractionation group mostly LRR occur in patient with high grade tumor G3 and triple –ve .and also distant metastasis DM occur in 1 case in control arm after 11 months follow up and occur in 2 cases in ultrahypofractionation arm after 16 and 17 months follow up

Age, T stage, N stage, tumor grade, and hormone receptor status were determined to not substantially affect survival rates (P-value > 0.05) in accordance with the prognostic factors that may affect the LRR free survival, as indicated in table 9. Statistically negligible, disease-free survival rates were 95.3% in the control group and 95.2% in the ultrahypofractionation group. Age, T stage, N stage, tumor grade, and hormone receptor status were found to have little effects on survival rates when considering prognostic factors that may affect disease-free survival, as indicated in table 10.

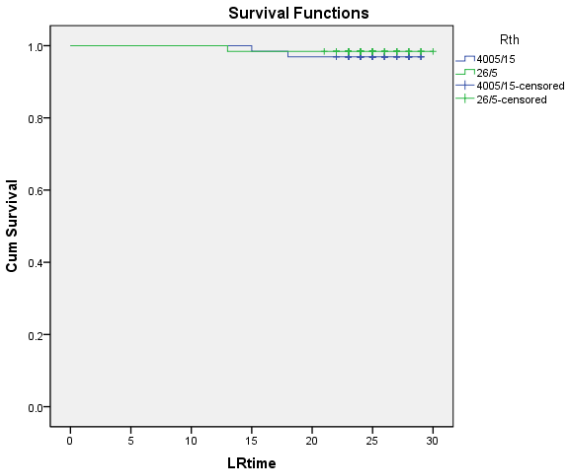

Fig 1: Locoregional recurrence free survival

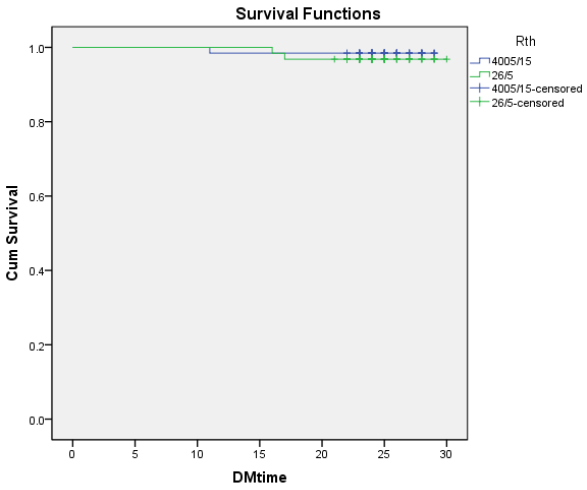

Fig 2: Distant metastasis free survival

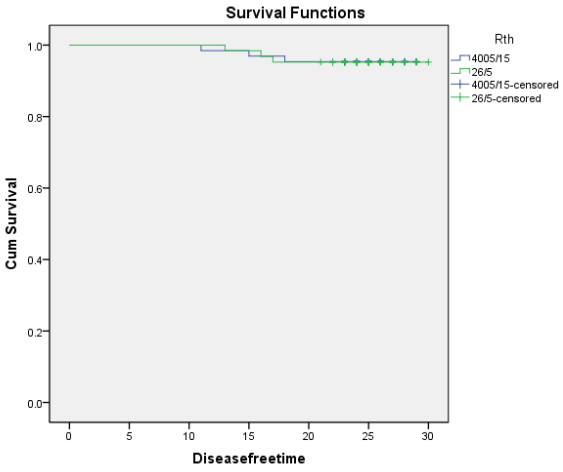

Fig 3: Disease free survival

Table 1: Patient's characteristics

Variable	26Gy/5fractions N=63	40Gy/15fractions N=65
1.Age at time of diagnosis:		
<50 years	30(47.6%)	31(47.7%)
≥50 years	33(52.4%)	34(52.3%)
Median	54	50
Range	32:72	30:72
2.Tumor grade		
Grade 1	14(22.2%)	15(23.1%)
Grade 2	31(49.2%)	33(50.8%)
Grade 3	18(28.6%)	17(26.2%)
3.Side		
Right	34(54%)	29(44.6%)
Left	29(46%)	36(55.4%)
4.T stage:		
T1	19(30.2%)	18(27.7%)
T2	43(68.3%)	41(63.1%)
T3	1(1.6%)	6(9.2%)
5.Node stage:		
N0	61(96.8%)	52(80%)
N1	2(3.2%)	13(20%)
6.Hormonal receptors:		
Positive ER& Positive Her2neu	5(7.9%)	5(7.7%)
Positive ER & Negative Her2neu	48(76.2%)	51(78.5%)
Negative ER & Positive Her2neu	2(3.2%)	2(3.1%)
Triple Negative	8(12.7%)	7(10.8%)

Table 2: Treatment characteristics

Variable	26Gy/5fractions N=63	40Gy/15fractions N=65
1.Surgery:		
Breast conservative surgery	55(87.3%)	57(87.7%)
Modified radical mastectomy	8(12.7%)	8(12.3%)
2.Chemotherapy:		
No chemotherapy	29(46%)	27(41.5%)
Adriamicin/cyclophosphamide with taxanes	26(41.3%)	23(35.4%)
Fourouracil/Epirubcin/Cyclophosphamide	8(12.7%)	15(23.1%)
3.Trastuzumab		
No	56(88.9%)	58(89.2%)
Yes	7(11.1%)	7(10.8%)
4.Hormonal therapy		
Not received hormonal therapy	10(15.9%)	9(13.8%)
Tamoxifen (TAM)	11(17.5%)	15(23.1%)
Aromatase inhibitors (AI)	42(66.7%)	37(56.9%)
Switched from TAM to AI	0	4(6.2%)
5.Boost		
No	24(38.1%)	19(29.2%)
Yes	39(61.9%)	46(70.8%)

Table 3. Worst acute skin toxicity according to CTCAE Score

Grades	26Gy/5fractions N=63	40Gy/15fractions N=65
Grade 0	7(11.1%)	1(1.5%)
Grade 1	39(61.9%)	33(50.8%)
Grade 2	17(27%)	31(47.7%)
Grade 3	0	0

Table 4: Late Effect Fibrosis

	26Gy/5fractions N=63	40Gy/15fractions N=65	P value
None	49(77.8%)	53(81.5%)	
Mild	10(15.9%)	10(15.4%)	
Moderate	3(4.8%)	2(3.1%)	0.723
Marked	1(1.6%)	0	

Table 5: Late Effect Telangiectasia

	26Gy/5fractions N=63	40Gy/15fractions N=65	P value
None	55(87.3%)	58(89.2%)	
Mild	6(9.5%)	5(7.7%)	
Moderate	2(3.2%)	2(3.1%)	0.933
Marked	0	0	

Table 6: Late Effect Hyperpigmentation

	26Gy/5fractions N=63	40Gy/15fractions N=65	P value
None	55(87.3%)	60(92.3%)	
Mild	4(6.3%)	4(6.2%)	
Moderate	3(4.8%)	1(1.5%)	0.535
Marked	1(1.6%)	0	

Table 7: Incidence of moderate / marked Late toxicity

Moderate/Marked Event	26Gy/5fractions N=63	40Gy/15fractions N=65	P value
Fibrosis	4(6.3%)	2(3.1%)	0.381
Telangectasia	2(3.2%)	2(3.1%)	0.975
Hyperpigmentation	4(6.3%)	1(1.5%)	0.160

Table 8: Change in photographic breast appearance at 2year (BCS Patients)

	26Gy/5fractions N=55	40Gy/15fractions N=57	P value
Excellent	20(36.4%)	22(38.6%)	
Good	28(50.9%)	28(49.1%)	
Fair	5(9.1%)	6(10.5%)	0.975
Poor	2(3.6%)	1(1.8%)	

Table 9: Univariate analysis of 2 years Locoregional recurrence free survival in both arm

Variable		26Gy/5fractions			40Gy/15fractions		
		No. of patient	2 year LRR %	P value	No. of patient	2 year LRR %	P value
Age at diagnosis	**<50 yrs**	1/30	96.7%		1/31	96.8%	
	≥50 yrs	0/33	100%	0.290	1/34	97%	0.947
T stage	**T1**	0/19	100%		0/18	100%	
	T2	1/43	97.7%	0.790	2/41	95.1%	0.547
	T3	0/1	100%		0/6	100%	
Nodal stage	**N0**	1/61	98.4%		2/52	96.2%	
	N1	0/2	100%	0.855	0/13	100%	0.473
Hormonal status	**ER+Her+**	0/5	100%		1/5	80%	
	ER+Her-	0/48	100%		1/51	98%	
	ER-Her+	0/2	100%	0.072	0/2	100%	0.151
	Triple -ve	1/8	87.5%		0/7	100%	
Grade	**G1**	0/14	100%		0/15	100%	
	G2	0/31	100%	0.281	0/33	100%	0.054
	G3	1/18	94.4%		2/17	88.2%	

Table 10: Univariate analysis of 2 years disease free survival in both arm

Variable		26Gy/5fractions			40Gy/15fractions		
		No. of patient	2 year DFS %	P value	No. of patient	2 year DFS %	P value
Age at diagnosis	**<50 yrs**	2/30	93.4%		2/31	93.5%	0.50
	≥50 yrs	1/33	97%	0.498	1/34	97.1%	
T stage	**T1**	0/19	100%		0/18	100%	
	T2	3/43	93%	0.481	3/41	92.7%	
	T3	0/1	100%		0/6	100%	0.398
Nodal stage	**N0**	3/61	95.1%		2/52	96.2%	
	N1	0/2	100%	0.748	1/13	92.3%	0.554
Hormonal status	**ER+Her+**	1/5	80%		1/5	80%	
	ER+Her-	1/48	98%		2/51	96.1%	
	ER-Her+	0/2	100%	0.214	0/2	100%	0.365
	Triple -ve	1/8	87.5%		0/7	100%	
Grade	**G1**	0/14	100%	0.292	1/15	93.3%	
	G2	1/31	96.8%		0/33	100%	
	G3	2/18	88.9%		2/17	88.2%	0.156

Discussion:

Breast radiation therapy fractionation has been thoroughly researched and discussed. The accepted international standard is moderate hypofractionation, which uses 15 or 16 fractions over 3 weeks to produce total doses within 40 or 42.5 Gy. [18-20]. Recent researches on five-fraction breast radiation suggest straightforward, safe regimens that are likely to replace current standards of care. Results for disease control and normal tissue effects (NTE) for 26 and 27 Gy in five fractions over one week versus 40 Gy in 15 fractions over three weeks were reported in the phase III randomized FAST-Forward experiment [21]. had a 5-year incidence of ipsilateral local relapse of 2.1% after 40 Gy in 15 fractions; and absolute differences versus 40 Gy in 15 fractions were -0.3% for 27 Gy in five fractions and -0.7% for 26 Gy in five fractions, the incidence of any reported moderate or marked physician-assessed normal tissue effects in the breast or chest wall was reported for 9.9% of 40 Gy in 15 fractions patients, 15.4% of 27 Gy in 5 fractions patients, and 11.9% of 26 Gy in 5 fractions patients over a 5-year period. Across all physician assessments, late effect, patient, and photographic assessments revealed an increased risk of normal tissue effect for 27 Gy against 40 Gy, but not for 26 Gy versus 40 Gy. patient Previous studies, such as the United Kingdom FAST randomized control study of 915 patients testing 28.5 and 30 Gy in five fractions delivered once weekly against 50 Gy in 25 fractions over 5 weeks, provided guidance for the selection of total doses for ultrahypofractionation regimes, which has released 10-year findings demonstrating that for (71%) of eligible patients, five-year photos were available. For 30 Gy and 28.5 Gy against 50 Gy, the odds ratio for change in breast appearance in photographs was 1.64 and 1.10, respectively. Alpha/beta ratio calculated for photographic end point was 2.7 Gy, giving a 5 fractions schedule of 28 Gy estimated to be isoeffective with 50 Gy/25 fr. Breast shrinkage, induration, telangiectasia, and edema were all moderate/marked physician-assessed effects on normal tissue that had odds ratios of 2.12 for 30 Gy and 1.22 for 28.5 Gy against 50 Gy. With a median follow-up of 9.9 years, 96 deaths (50 Gy: 30 patients, 30 Gy: 33 patients, and 28.5 Gy: 33 patients) and eleven patients who acquired ipsilateral breast cancer occurrences (50 Gy: 3 patients, 30 Gy: 4 patients, and 28.5 Gy: 4 patients) have been recorded. [22]

In our ongoing randomized phase III study, conducted at the South Egypt Cancer Institute and Assiut University in Egypt, we are comparing the safety and effectiveness of five-fraction adjuvant breast radiotherapy schedules delivered to the chest wall or whole breast delivered in 1 week to the United Kingdom standard 15-fraction over 3-week schedule. Our phase III trial was developed for two reasons: first, to provide a suitable alternative to daily standard Hypofractionated-RT in order to reduce treatment costs and time, as well as travel for adjuvant oncology services (23); and second, to confirm the promising early outcomes with Ultrahypofractionation and to expand the criteria to include more high-risk patients than were previously taken into account for this approach. The research presented here is a planned early examination of acute toxicity, late effect on normal tissues, and efficacy following the trial's projected 2-year completion. The median age of our patients in both arms 54 years ranged from 32:72 years in ultrahypofractionation arm and 50 years ranged from 30:72 years in control arm and about half of the patients above 50 years old and other half below 50 years old in both arms , about half of patients in both groups with grade 2 Invasive ductal carcinoma and about two third in both groups with T2 tumor and about three fourth in both arms with ER positive, Her2 negative and only within 10% of both arms triple negative , Majority of patients in both arms underwent conservation surgery

The acute skin toxicity was assessed during the period between the completion of treatment and 6 weeks after therapy. Low rates of clinically relevant early toxicity were observed when radiation therapy was completed. The prevalence rates show that erythema after the 1-week plan is less extreme than after the 3-week schedule, which is consistent with the FAST Forward trial's acute skin toxicity substudy [15]. The absence of grade-3 toxicity is a significant discovery. The initial cutaneous toxicity associated with the 5-fraction regimens was expected to be modest. Turesson and colleagues conducted a series of classic studies in the 1980s and 1990s to test the dependence of acute skin toxicity on total dose, fraction size, inter-fraction interval, and overall treatment time, using reflectance spectrophotometry to quantify erythema and clinical grading to score moist desquamation. [24–28].

Early NTE is far less responsive to fraction size than late NTE, with the overall dose contributing significantly more [29]. A notable example is provided by the FAST-Forward Acute toxicity substudy, which found that breast erythema settled a fortnight earlier and less intensely after five-fraction schedules than after 15-fraction schedules [15]. In this case, the milder erythema was a response to overall dose levels of 26 Gy significantly higher than fraction sizes of 5.2. Acute reactions were also milder in five-fraction arms (total doses 28.5 and 30 Gy) of the First results of the randomized United Kingdom FAST Trial than the 50 Gy schedule that show grade 3 RTOG toxicity (appendix 4) 10.9%,2.7% & 1.9 % for 50 Gy,30 Gy & 28.5 Gy respectively [12].

After median follow up 25 months ranged from 21 to 30 months

As regard Late normal tissue effect in our study assessment show that radiotherapy related fibrosis, Telangiectasia and hyperpigmentation was comparable between both groups($p>0.05$).

After a two-year follow-up, the most prevalent moderate or noticeable consequence was fibrosis within the tumor bed, reported in 2 patients (3.1%) of 65 patients received 40 Gy, 4 patients (6.3%) of 63 patients received 26 Gy Which mirrored to the result Fast-forward Trial [21] as there was not significant difference between 40 Gy and 26 Gy ($p=0.17$).

Breast shrinkage was the most frequently observed moderate or significant impact at 5 years follow up, with 50 patients (5.5%) of 916 patients receiving 40 Gy patients and 65 patients (6.8%) of 954 patients receiving 26 Gy patients. Following whole-breast radiation therapy, the cosmetic outcome has long been used to predict late radiation damage (fibrosis). Over the past ten years, a lot of study has been conducted to determine how several factors, such as surgical technique, radiation volume, dosimetry and fractionation, and patient comorbidities, may affect cosmesis. (30-32).

For ultrahypofractionation, the ratio of excellent or good cosmesis to fair or poor cosmesis was 87.3% versus 12.7%, which is statistically insignificant (p=0.9). Thus, the findings of our investigation were consistent with those of the FAST forward trial [21] that shown the frequency of Change in Breast Appearance in Photographs at 2 years (breast conservation surgery patients) by fractionation schedule as follow no change represent 91.5% in 40Gy/15 fractions arm and 89.2 % in 26 Gy/5 fractions arm, and mild/ marked change represent 8.5% in 40 Gy arm and 10.7 % in 26 Gy arm

In our study Boost dose in both groups not statistically significant for change in photographic appearance

In terms of Treatment outcome, 2 years Locoregional recurrence (LRR) free survival was 96.9% in control group and 98.4 % in ultrahypofractionation group which statistically insignificant and there were 2 patients

who had LRR (3.1%) in control group and 1 (1.6%) patient in ultrahypofractionation group mostly LRR occur in patient with high grade tumor G3 and triple -ve and also distant metastasis DM occur in 1 case in control arm after 11 months follow up and occur in 2 cases in ultrahypofractionation arm after 16 and 17 months follow up

Age, T stage, N stage, tumor grade, and hormone receptor status were found to have no significant impact on survival rates (P-value > 0.05) when compared to prognostic markers that could alter the LRR free survival. Disease free survival was 95.3% in control arm and 95.2 % in ultrahypofractionation arm which statistically insignificant , Age, T stage, N stage, tumor grade, and hormonal receptor status were determined to be prognostic factors that might affect disease-free survival, but these factors did not significantly affect survival rates (P-value > 0.05), which is comparable to the results of the fast forward trial [22], which showed that the disease outcomes including locoregional relapse, distant relapse, disease-free survival, and overall survival were equal between groups with statistically insignificant differences. & incidence of ipsilateral breast tumor local relapse, regional relapse, and distant relapse in fast forward trial were listed according to age, grade, and ER and HER2 status for descriptive rational; whish revealed that The patients with higher-grade original tumors were more likely to experience ipsilateral breast tumor relapse. Longer term follow-up will be mandatory to evaluate the stability of these most crucial endpoints in our study.

Conclusion:

Regarding effects on normal tissue up to 2 years, 26 Gy in 5.2 Gy per fraction daily over 1 week is equivalent to the standard of 40.05 Gy in 2.67 Gy per fraction daily over 3 weeks for patients who received adjuvant radiotherapy after surgical resection for early-stage breast cancer, and longer follow-up is required for local tumor control and to confirm study results.

References:

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87-108.

[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] Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011 Nov 12;378(9804):1707-16.

[4] EBCTCG (Early Breast Cancer Trialists' Collaborative Group); McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

[5] Cohen L. Radiotherapy in breast cancer. I. The dose-time relationship theoretical considerations. Br J Radiol. 1952 Dec;25(300):636-42.

[6] Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006 Jun;7(6):467-71.

[7] Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol. 2005 Apr;75(1):9-17.

[8] Whelan TJ, Pignol J-P, Levine MN, et al. Are three weeks of whole-breast radiotherapy as good as five weeks in early breast cancer?–10 year follow-up in the Canadian Trial of Hypofractionated Radiation Therapy. Breast Care (Basel). 2010 Aug;5(4):272-274.

[9] Haviland JS, Mannino M, Griffin C, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018 Jan;126(1):155-162.

[10] START Trialists' Group; Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008 Mar

29;371(9618):1098-107.

[11] START Trialists' Group; Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008 Apr;9(4):331-41.

[12] FAST Trialists group; Agrawal RK, Alhasso A, et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015): The FAST Trialists group. Radiother Oncol. 2011 Jul;100(1):93-100.

[13] Sanz J, Zhao M, Rodríguez N, et al. Once-weekly hypofractionated radiotherapy for breast cancer in elderly patients: efficacy and tolerance in 486 patients. Biomed Res Int. 2018 Mar 15;2018:8321871.

[14] Dragun AE, Ajkay NJ, Riley EC, et al. First results of a phase 2 trial of once-weekly hypofractionated breast irradiation (WHBI) for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2017 Jul 1;98(3):595-602.

[15] Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol. 2016 Jul;120(1):114-8.

[16] US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.03. 2010. USA: National Institutes of Health, National Cancer Institute. 2016.

[17] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. JASA 1958; 53(282):457-481.

[18] Smith BD, Bellon JR, Blitzblau R et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol. 2018 May-Jun;8(3):145-152.

[19] Lewis P, Brunt AM, Coles C, et al. Moving forward fast with FAST-Forward. Clin Oncol (R Coll Radiol). 2021 Jul;33(7):427-429.

[20] Marta GN, Coles C, Kaidar-Person O, et al. The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical practice: A critical review. Crit Rev Oncol Hematol. 2020 Dec;156:103090.

[21] Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020 May 23;395(10237):1613-1626.

[22] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol. 2020 Oct 1;38(28):3261-3272.

[23] Barry PN, Dragun AE. Once-weekly hypofractionated breast irradiation: fool's gold or diamond in the rough? J Comp Eff Res. 2015 Mar;4(2):147-56.

[24] Turesson I, Notter G, Wickström I, et al. The influence of irradiation time per treatment session on acute and late skin reactions: a study on human skin. Radiother Oncol. 1984 Oct;2(3):235-45.

[25] Turesson I, Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation, and telangiectasia after 3 and 5 year's follow-up. Radiother Oncol. 1989 Jun;15(2):169-88.

[26] Nyman J, Turesson I. Does the interval between fractions matter in the range of 4–8 h in radiotherapy? A study of acute and late human skin reactions. Radiother Oncol. 1995 Mar;34(3):171-8.

[27] Böhner AMC, Koch D, Schmeel FC, et al. Objective evaluation of risk factors for radiation dermatitis in whole-breast irradiation using the spectrophotometric L*a*b color-space. Cancers (Basel). 2020 Aug 28;12(9):2444.

[28] Hinkelbein W, Bruggmoser G, Frommhold H, et al. (Eds.). Acute and long-term side-effects of radiotherapy: biological basis and clinical relevance (Vol. 130). Springer Science & Business Media, 2012.

[29] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989 Aug;62(740):679-94.

[30] Peterson D, Truong PT, Parpia S, et al. Predictors of adverse cosmetic outcome in the RAPID trial: an exploratory analysis. Int J Radiat Oncol Biol Phys. 2015 Apr 1;91(5):968-76.

[31] Taylor ME, Perez CA, Halverson KJ, et al. Factors influencing cosmetic results after conservation therapy for breast cancer. Int J Radiat Oncol Biol Phys. 1995 Feb 15;31(4):753-64.

[32] Brands-Appeldoorn A, Maaskant-Braat S, Janssen L, et al. Factors influencing cosmetic outcome of breast-conserving treatment in breast cancer: a narrative review. Eur. J. Gynaecol. Oncol. 2021, 42(3), 425–433.

APPENDIX 1: Acute skin reactions scoring scale (CTCAE version 4.03)

Grade	Description
Grade 0	No changes
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin fold and creases; moderate oedema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Grade 5	Death

Appendix (2): Modified late effects on normal tissues (LENT SOMA tables)

The late effect	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (marked)	Grade 4
fibrosis	Barely palpable increased	Definite increased density and firmness	Very marked density, retraction, and fixation	
Telangiectasia	< 1 cm^2	1-4 cm^2	> 4cm^2	
Hyperpigmentation	mild	moderate	sever	
Retraction/Atrophy	10 - 25%	> 25 - 40%	> 40 - 75%	Whole breast

Appendix (3): Harvard Scale for the cosmetic outcome

Excellent	The irradiated breast looks like the contralateral one.
Good	Minimal but identifiable radiation effects on treated breast.
Fair	Significant effects on treated breast which clearly visible.
Poor	Sever morbid radiation sequels.

APPENDIX (4): Acute skin reactions scoring scale (Modified RTOG scale)

Grade	Description
Grade 0	No visible change
Grade 1	Faint/dull erythema
Grade 2	Tender/bright erythema +/- dry desquamation
Grade 3	Patchy moist desquamation, moderate oedema
Grade 4	Confluent moist desquamation, pitting oedema