Toxicity and Cosmetic Outcome of Ultrahypofractionation Breast Radiotherapy: Predictive Clinical Factors

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Abstract

Background: The current gold standard for adjuvant radiotherapy for breast cancer in nowadays is hypofractionated radiotherapy.

Objectives: Here, we discuss early, late, and cosmetic results of 1 week adjuvant breast radiotherapy and to find the predicted indicators for toxicity .

Patients and methods: The study included 63 breast cancer patients. Invasive breast cancer patients who undergone mastectomy or breast conserving surgery (pT1-3, pN0-1, M0), were eligible if they were at least 18 years old. Patients got 26 Gy/5F/1-week. Individuals who underwent breast conservation and are younger than 50 years old may employ a sequential boost (dosage of 5.2 Gy/ 1 fraction). After radiation, physician-rated early and late toxicity as well as the cosmetic result were prospectively evaluated.

Results: 63 patient assessed early after 6 weeks from end of radiotherapy for acute skin toxicity with grade 2 was 27 % with univariate analysis show no significant association between occurrence of acute toxicity and different factors and after median follow up 25 months , the late toxicity assessment show that moderate & marked radiotherapy related fibrosis represent 6.3%, Telangiectasia(3.2%) and hyperpigmentation(6.3%) with univariate analysis show no significant association between occurrence of late toxicity and different factors. The rate of fair or poor cosmesis was 12.7%, univariate analysis of cosmetic outcome revealed only significant association between cosmosis and chemotherapy .

Conclusion: The findings support the viability and safety of 26 Gy in five fractions radiotherapy over 1 week in adjuvant setting in early breast cancer**.**

Keywords: Breast cancer; Ultrahypofractionation; Radiotherapy**.**

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Introduction

Radiation therapy is the recommended adjuvant treatment for early-stage breast cancer following breast-conserving surgery (BCS) to maximise local control and overall survival **(Clarke et al., 2005).** Adjuvant radiation has been demonstrated to improve local control as well as overall survival, with a 70% reduction in recurrence risk **(Darby et al., 2011**), and a 9-12% decrease in the probability of death **(Van de et al., 2000**). Patients who underwent mastectomy with axillary clearance greatly decreased loco regional recurrence saw a similar advantage. The total reduction in local recurrence was larger in lymph node positive patients than in lymph node negative patients (17% vs. 4%) **(Clarke et al., 2005).**

Hypofractionation is a way for reducing the total duration of radiation therapy. Compared to traditional radiation, which delivers the dose in a small number of fractions, this approach uses greater fraction doses (over 2 Gy). Consequently, the overall dose dropped. Radiobiologically and according to estimates, the α/β ratio value for breast cancer is 4 Gy, whereas the α/β ratio value for soft tissues is roughly 3.5 Gy. Therefore, Breast cancer is radiation sensitive in the same way as healthy tissues are responding. High fraction doses might be more effective at eliminating malignant cells, however, that increased fraction doses may potentially increase the occurrence and severity of late post-radiation responses. Compared to late reacting normal tissues, acute skin reactions are less sensitive to fraction size, so the trial's lower total doses are likely to minimize their severity and duration, despite the total treatment taking less time. After first surgery for early breast cancer, according to the 10 year findings of four randomised trials involving over 7,000 people, patients affirm that hypofractionated radiation is both safe and effective **(Yarnold et al.,2005; Owen et al., 2006; Whelan et al.,2010;Haviland et al.,2013)** 15- and 16-fraction regimens were defined as new standards of care administered over 21–22 days by the UK START-B and Ontario trials **(NICE clinical guideline; RCR clinical guideline 3rd edition; Smith et al., 2018).** Sensitivity to fraction size was tested in the START pilot and START-A trials by controlling for treatment time, generating an a/b estimate of 3.5 Gy for tumor control, similar to how late unfavorable effects are described (**Owen et al., 2006; Haviland et al., 2013;Bentzen et al., 2008).**

The safety and non-inferiority of 15 or 16 portions of approximately 2.7 Gy to total doses of 40.0 Gy or 42.5 Gy are supported by mature evidence **(Owen et al., 2006; NICE clinical guideline),** Since 2009, the United Kingdom has used a 3-week schedule with 15 fractions as the standard of care for adjuvant locoregional radiation for early breast cancer, and it is now the norm worldwide (**NICE clinical guideline; Smith et al., 2018).** Given the radiobiological characteristics and fraction sensitivity of breast cancer, 3-weeks of radiation is not the absolute upper limit for the possibility of a decrease in total time. In the United Kingdom, the FAST study compared two hypofractionated radiation regimens of 5 fractions per week (28.5 Gy or 30 Gy) against the conventional arm of 50 Gy (**Agrawal et al., 2011**). Both the evaluation of breast appearance using photographs and the results of the acute toxicity tests revealed comparable

findings for various fractionation schedules. Both arms had equivalent locoregional control, with no differences in late toxicity profile or cosmesis. The same outcomes have been shown in several trials examining the efficacy and safety of a once-weekly regimen **(Sanz et al., 2018; Dragun et al., 2017).** The FAST Forward study was designed to contrast two schedules of five-fraction radiation delivered in a single week with the conventional arm of fifteen-fraction radiotherapy provided in three weeks. Based on the findings of the FAST trial and the possibility of improving tumor control with a shorter overall treatment period. Acute skin toxicity outcomes from this approach have been documented. The 26 Gy administered in 5 fractions regimen is linked with a grade 3 RTOG toxicity (Appendix 1) of 5.8%, compared to 13.6% for the control arm toxicity of 5.8%[Brunt et al. , 2016]. In neither of the groups, there were any patients who experienced CTCAE grade 3 toxicity **(Brunt et al., 2016)**. At 5 years, 121 of 1020 (11%) 26 Gy patients, 155 (15.4%) of 1005 (27 Gy patients, and 98 of 986 (9.9%) 40 Gy patients reported any significant or marked effects on the breast or chest wall's normal tissue, as judged by the physician. Higher normal tissue effect risk was seen in patient and photographic assessments for 27 Gy against 40 Gy but not for 26 Gy versus 40 Gy.Our study aims to Analyze predictive factors for toxicity in 1-week versus 3-weeks of hypofractionation radiotherapy for breast cancer patients.

Patients and Methods

Study design: This prospective trial evaluates the safety and efficiency of five-fraction adjuvant radiation treatments administered over a one-week period to the whole breast or chest wall and this trial considered rapid ultrahypofractionation deployment for postoperative breast radiotherapy at the time of a global health emergency caused by the COVID-19 pandemic.

Ethical consideration: This prospective study received institutional ethical committee approval at the South Egypt cancer institute, Assiut University, Egypt in December 2020 under approval No.518

Patients: Patients had to be at least 18 years old and had invasive breast cancer (pT1-3, pN0-1, M0) after a mastectomy or breast conserving procedure that completely removed the initial tumour on a microscopic level. Axillary surgery (sentinel node biopsy or axillary dissection) was performed on all patients; nodal irradiation was not permitted. Any patients with a history of breast cancer, epithelial carcinoma, multicentric illness, extra capsular nodal extension, bilateral breast cancer, cosmetic breast augmentation, collagen or vascular disease, pregnancy, or lactation were disqualified from the study. Patients were given 26 Gy in five 5.2 Gy fractions. A successive tumour bed radiation boost to the conserved breast for those less than 50 years old or those over 50 with high grade tumour or lymph vascular invasion was permitted (dose of 5.2 Gy/ 1 fraction). Every patient signed a written informed consent form.

Radiotherapy technique: From 5 mm below the skin's surface to the deep fascia, all of the soft tissues in the breast's clinical target volume were contoured. Clinical target volume for the post-mastectomy chest wall includes the deep fascia as well as the underlying soft tissues and post-operative skin flaps. During breast conserving surgery, surgeons were strongly advised to use

surgical clips to label the walls of the tumour cavity to help define the tumour bed. To produce a planning target volume, a typical margin of 10 mm was included around the breast or chest wall clinical goal volume, compensating for set-up error, breast swelling, and breathing (PTV). Organs at risk were identified prospectively, and a complete 3D CT set of outlines containing the entire breast and organs at risk was collected for all patients, with a slice separation of up to 5 mm. The whole PTV of the breast or chest wall was covered by a tangential opposing pair beam configuration, minimizing ipsilateral lung and heart exposure. With 3D dose compensation, the treatment plan was optimized to obtain the following PTV dose distribution: more than 95% of PTV received 95% of prescribed dosage, less than 5% of PTV received 105% or more, less than 2% of PTV received 107% or more, and a globally maximum of less than 110%. Dose constraints for the five-fraction schedules were as follows: volume of ipsilateral lung receiving 8 Gy less than 15%, and volume of heart receiving 1.5Gy less than 30% and that receiving 7 Gy less than 5%. The treatment used X-ray beam intensities of 6 MV or 10 MV, Electrons or photons were used to offer the tumour bed boost. KV x-rays were used for electronic portal imaging during the verification process. Once per week, treatment verification was needed with a tolerance of 5 mm and an adjustment for any systematic inaccuracy. Every fraction of the five-fraction programme required verification imaging, as well as suggestions for rectifying all measured displacements

Assessment and Follow up: Acute reactions of the skin of the treated breast were graded Using standard CTCAE criteria (v4.03) (**Appendix 1,2**). A healthcare practitioner performed toxicity assessments. The assessments were intended to be performed weekly during treatment and for 6 weeks after radiotherapy was completed.

At yearly follow-up visits, physicians evaluated patients for late effects on normal tissue. Beginning 12 months after the trial's start, late-onset effects on normal tissue (breast fibrosis, telangiectasia, and hyperpigmentation) in the ipsilateral breast or chest wall were graded using the modified late effects on normal tissues scoring systems (**Appendix 3**), and as far as the cosmetic outcome, photographs were taken at the beginning of the trial and 2 years after radiotherapy. On a Harvard scale for scoring cosmosis (**Appendix 4**). After surgery and before radiotherapy, the difference between the baseline and the photographed breast appearance was measured. The aesthetic outcomes were categorized into 4 grades: excellent, good, fair, and poor. Digital images were evaluated by two observers who were blind to the patient's name

Statistical analysis

The statistical package for social science (SPSS) version 20 was used to statistically analyze the data. As descriptive statistics, median, mean, number, and percentage were employed. Kaplan-Meier test **(Kaplan et al., 1958)** used for survival analysis and to assess the significance of differences between variables, the log-rank test was performed. The connection between the covariates and treatment response was assessed using the chi-square test. If the double-sided P value was less than 0.05, it was deemed significant.

Results

The characteristics of the patient were presented in Table 1. 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 ER receptor and negative Her2neu **, (Table.1).**

Table 1. Patients' characteristics

Variables	N(%)
1.Age at time of diagnosis :	
<50 years	30(47.6%)
≥50 years	33(52.4%)
Median	54
Range	32:72
2.Tumor grade	
Grade 1	14(22.2%)
Grade 2	31(49.2%)
Grade 3	18(28.6%)
3.Side	
Right	34(54%)
Left	29(46%)
4.T stage:	
T1	19(30.2%)
T2	43(68.3%)
T3	1(1.6%)
5.Node stage:	
N0	61(96.8%)
N1	2(3.2%)
6.Hormonal receptors:	
Positive ER& Positive Her2neu	5(7.9%)
Positive ER & Negative Her2neu	48(76.2%)
Negative ER & Positive Her2neu	2(3.2%)
Triple Negative	8(12.7%)

Features of the treatments indicated 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, **(Table.2)**.

Early toxicity assessment 6 weeks after finish radiotherapy show 61.9% with grade 1 dermatitis according to CTCAE, 27% with grade 2 and only 11.1% not reported any skin toxicity and no any patient report grade 3 toxicity **(Table 3)** and univariate analysis for predictive factors for occurance of acute toxicity not significant for any predictive factor **(Table 4)**.

Table 2. Treatment characteristics

Variables	N(%)
1.Surgery :	
Breast conservative surgery	55(87.3%)
Modified radical mastectomy	8(12.7%)
2.Chemotherapy:	
No chemotherapy	29(46%)
Adriamicin/cyclophosphamide with taxanes	26(41.3%)
Fourouracil/Epirubcin/Cyclophosphamide	8(12.7%)
3.Trastuzumab	
No	56(88.9%)
Yes	7(11.1%)
4.Hormonal therapy	
Not received hormonal therapy	10(15.9%)
Tamoxifen (TAM)	11(17.5%)
Aromatase inhibitors (AI)	42(66.7%)
Switched from TAM to AI	0
5.Boost	
No	24(38.1%)
Yes	39(61.9%)

Table 3. Early skin toxicity according to CTCAE Score

Grades	26Gy/5fractions N=63
Grade 0	7(11.1%)
Grade 1	39(61.9%)
Grade 2	17(27%)
Grade 3	0

Table 4.Univariate analysis for occurrence of early skin toxicity

Variable		Skin toxicity CTCAE grade			P value
		G1	G2	G3	
Age at diagnosis	<50 yrs	4	17	9	0.704
	≥50 yrs	3	22	8	
T stage	T1	3	10	6	0.803
	T2	4	28	11	
	T3	0	1	0	

Nodal stage	**N0**	7	38	16	0.711
	N1	0	1	1	
Hormonal status	**ER+Her+**	1	2	2	0.158
	ER+Her-	3	32	13	
	ER-Her+	0	2	0	
	Triple -ve	3	3	2	
Grade	**G1**	2	8	4	0.891
	G2	2	20	9	
	G3	3	11	4	
surgery	**BCS**	5	36	14	0.241
	MRM	2	3	3	
Chemotherapy	**No**	1	21	7	0.275
	AC taxol	4	15	7	
	FEC	2	3	3	
Hormonal Treatment	**No**	3	5	2	0.362
	TAM	1	7	3	
	AI	3	27	12	
Trastuzumab	**Yes**	1	4	2	0.948
	No	6	35	15	
Boost	**Yes**	5	24	10	0.844
	No	2	15	7	

After median follow up 25 months ranged from 21 to 30 months, the late toxicity assessment listed in table 5 & 6 show 15.9 % with mild fibrosis, 6.3% with moderate and marked fibrosis .As regard telangiectasia 9.5% with mild degree, 3.2% with moderate and marked telangiectasia. As regard hyperpigmentation 6.3% with mild hyperpigmentation, 6.3% with moderate and marked hyperpigmentation **(Table. 5& 6)** . Univariate analysis for predictive factors for occurrence of moderate and marked late toxicity show no significant for any predictive factor as shown in **(Table.7).**

Table 5. Incidence of late toxicity

Late toxicity	Grade	N(%)
fibrosis	**None**	49(77.8%)
	Mild	10(15.9%)
	Moderate	3(4.8%)
	Marked	1(1.6%)
Telangiectasia	**None**	55(87.3%)
	Mild	6(9.5%)
	Moderate	2(3.2%)
	Marked	0
Hyperpigmentation	**None**	55(87.3%)
	Mild	4(6.3%)
	Moderate	3(4.8%)
	Marked	1(1.6%)

Table 6.Incidence of moderate / marked Late toxicity

Moderate/Marked Event	N(%)
Fibrosis	4(6.3%)
Telangiectasia	2(3.2%)
Hyperpigmentation	4(6.3%)

Table 7.Univariate analysis for occurrence of moderate/marked late toxicity

Variables		Moderate/Marked Fibrosis	P value	Moderate/Marked Telangectasia	P value	Moderate/Marked Hyperpigmentation	P value
Age at diagnosis	**<50 yrs**	1	0.349	2	0.132	1	0.349
	≥50 yrs	3		0		3	
T stage	**T1**	2	0.659	1	0.817	1	0.935
	T2	2		1		3	
	T3	0		0		0	
Nodal stage	**N0**	4	0.708	2	0.795	4	0.708
	N1	0		0		0	
Hormonal status	**ER+Her+**	0	0.721	0	0.886	0	0.721
	ER+Her-	4		2		4	
	ER-Her+	0		0		0	
	Triple -ve	0		0		0	
Grade	**G1**	1	0.404	1	0.520	2	0.366
	G2	3		1		1	
	G3	0		0		1	
surgery	**BCS**	4	0.431	2	0.584	3	0.445
	MRM	0		0		1	
Chemotherapy	**No**	3	0.218	1	0.857	2	0.728
	AC taxol	0		1		2	
	FEC	1		0		0	
Hormonal Treatment	**No**	0	0.344	0	0.435	0	0.650
	TAM	0		1		1	
	AI	4		1		3	
Trastuzumab	**Yes**	0	0.465	0	0.611	0	0.465
	No	4		2		4	
Boost	**Yes**	3	0.577	2	0.260	1	0.116
	No	1		0		3	

(**Table .8**) showed the incidence of change in photographic breast appearance after 2years from end of radiotherapy in BCS patients only (55 patient) that show Excellent outcome in 36.4%,50.9% show good outcome,9.1% show fair outcome and only 3.6% show poor outcome in other speech the rate of excellent or good cosmesis versus fair or poor cosmesis was 87.3% versus 12.7%. Univariate analysis for predictive factors for cosmetic outcome (fair and poor outcome) show only significant association between cosmetic outcome and administration of chemotherapy (p value <0.05) as shown in **(Table.9).**

Table 8. Incidence of Change in photographic breast appearance at 2year (BCS Patients)

Variables	N total = 55 N(%)
Excellent	20(36.4%)
Good	28(50.9%)
Fair	5(9.1%)
Poor	2(3.6%)

Table 9. Univariate analysis for fair and poor cosmetic outcome

Variables		Fair/poor cosmetic outcome	P value
Age at diagnosis	**<50 yrs**	3	0.883
	≥50 yrs	4	
T stage	**T1**	3	0.786
	T2	4	
	T3	0	
Nodal stage	**N0**	7	0.582
	N1	0	
Hormonal status	**ER+Her+**	0	0.619
	ER+Her-	7	
	ER-Her+	0	
	Triple -ve	0	
Grade	**G1**	1	0.647
	G2	4	
	G3	2	
Chemotherapy	**No**	4	0.001
	AC taxol	0	
	FEC	3	
Hormonal Treatment	**No**	0	0.515
	TAM	1	
	AI	6	
Trastuzumab	**Yes**	0	0.322
	No	7	
Boost	**Yes**	5	0.974
	No	2	

Discussion

After breast-conserving surgery for early breast cancer, the delivery of daily doses more than 1.8-2 Gy with a hypofractionated schedule is a popular method of performing whole breast irradiation (**Coles et al., 2013).** Hypofractionation whole breast irradiation has been utilised for decades in numerous institutions and has been tested in randomised studies **(Holloway et al., 2010;Lievens, 2010)**. Recent research on five-fraction breast radiation suggests straightforward, safe regimens that are likely to replace current standards of care. More than 4000 patients included in the phase III randomized Fast-Forward trial compared 40 Gy administered in 15 fractions over 3 weeks to 26 and 27 Gy administered in 5 fractions over 1 week for tumor control and normal tissue effects (NTE). Prior studies, such as the FAST study with 915 patients testing 28.5 and 30 Gy in five fractions delivered once weekly against 50 Gy in 25 fractions over 5 weeks, which has since published 10-year data **(Brunt et al., 2020)**, were used to help choose the total doses for the five-fraction regimens.

In our current study, done at south Egypt cancer institute ,Asyut university , Egypt, investigating the safety of one-week, five-fraction adjuvant radiation regimens for the whole breast or chest wall. In the six weeks following the conclusion of treatment, the acute cutaneous toxicity was evaluated. After completing radiation therapy, there were few cases of clinically significant early toxicity. The absence of grade-3 toxicity is a significant discovery. The mildness of the acute skin toxicity associated with the 5-fraction regimens was expected, similar to the acute toxicity sub study of FAST Forward trial **(Brunt et al., 2016)** and univariate analysis for predictive factors for occurrence of acute toxicity not significant for any predictive factor after median follow up 25 months ranged from 21 to 30 months, the late toxicity assessment show that moderate & marked radiotherapy related fibrosis represent 6.3%, Telangiectasia(3.2%) and hyperpigmentation(6.3%) Which similar to the Fast-forward Trial **(Brunt et al., 2020)** as breast shrinkage, which was recorded in 65 (6.8%) of 954 patients received 26 Gy, was the most common mild or noticeable consequence at 5 years .

Univariate analysis for predictive clinical factors associated with acute and late toxicity show no significant association with any factor and this mirrored to, retrospective subgroup analyses in Fast-Forward as clinician-assessed moderate or marked adverse effect in the breast or chest wall for 26 Gy versus 40 Gy provided no evidence of a differential effect of the five-fraction schedule according to age, breast size, surgical deficit, tumor bed boost or adjuvant chemotherapy. After whole-breast radiation therapy, cosmetic result has long been a typical predictor of late radiation damage (fibrosis). Over the past ten years, a tonne of literature has been written about how a variety of variables, including surgical technique, radiation volume, dosimetry and fractionation, and patient comorbidities, may influence cosmesis **(Peterson et al., 2015;Taylor et al., 1995).**

The rate of excellent or good cosmesis versus fair or poor cosmesis was 87.3% versus 12.7% for ultrahypofractionation so Our study mirrored the results seen in the United kingdom FAST forward trial **(Taylor et al., 1995),** that showed Change in

photographic breast appearance at 2 years (breast conservation surgery patients) with no change represent 89.2 % in 26 Gy/5 fractions arm , and mild/ marked change represent 10.7 % in 26 Gy arm . Univariate analysis for fair and poor cosmetic outcome with various clinical factors revealed only association with chemotherapy administration and this result have a great controversy between various studies that investigate effect of chemotherapy on cosmetic outcome in breast cancer patient with some studies favor this relationship and others show insignificant relationship and in other word this result may explained by chemotherapy's deteriorating effects on chronic fibrosis and breast edema and our result similar to Ciammella et al that evaluate predictive clinical factors for Hypofractionated whole breast irradiation patients who received adjuvant chemotherapy (mostly based on anthracyclines) saw significant increases in late subcutaneous toxicity and had poorer overall cosmetic outcomes **(Ciammella et al., 2014),** and in another trial by Jhoansen and his colleagues who show that CMF had a detrimental impact on overall cosmetic outcome scores following breast conservation in premenopausal individuals, according to the effect of adjuvant systemic treatment on cosmetic outcome after breast conservation **(Johansen et al., 2007)** . Obviously this finding need more investigate with larger sample size to clarify this relationship and longer-term monitoring will be required to assess the stability of these parameters determining toxicity and cosmetic result in breast cancer patients

Conclusion

26 Gy in five fractions over the course of one week is safe and feasible for individuals who are administered adjuvant local radiation after primary surgery for early-stage breast cancer with effects on normal tissues lasting up to two years and to confirm study result need longer follow up and more sample size .

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