Abd Elbaee et al. *SECI Oncology* 2016
DOI: 10.18056/seci2016.5

Evaluation of the efficacy and the safety of a hypofractionated radiotherapy course with weekly concomitant boost for breast cancer patients treated with conservative breast surgery

Abd Elbadee OM[1], Abd Elkareem S[2], El Sayed MI[1], Fathy S[1]

[1] Department of Radiation Oncology, South Egypt Cancer Institute, Assiut University
[2] Department of Clinical Oncology, South Egypt Cancer Institute, Assiut University

Correspondence should be addressed to Ossama Mostafa Abd Elbadee at Department of Radiation Oncology, South Egypt Cancer Institute, Assiut University Egypt, osamarth@yahoo.com

Abstract

Background: Radiation therapy after breast conserving surgery is a standard part of treatment for invasive breast cancer. Based on radiobiological models, it was found that shorter hypofractiontaed radiation schedules had equivalent local control to standard radiation therapy. Radiation boost to the tumor bed was evident to be associated with significant improvement in local control.

Methods: This study included 50 female patients with operable invasive stage I-II breast cancer. Patients underwent microscopic wide local excision of the primary tumor with axillary lymph node dissection. They received adjuvant radiotherapy with 42.5 Gy total dose in 16 fractions for whole breast and additional boost dose to tumor bed of 1Gy once weekly in three consecutive fractions for total boost dose of 3 Gy.

Results: Median age was 47 years: 60% of patients <50 years, most patients had stage T2-N0 disease, and Grade II was the most common one. Invasive ductal carcinoma was reported in 94% and hormone receptors were positive in 70% of patients. After median follow-up of 29 months, 2 year DFS was 94%, all patients were alive and ipsilateral local recurrence was reported in 2% only. Grade III-IV radiation toxicities were not observed. 36% and 12% had Grade I and II acute skin toxicity respectively. At 12 months, grades (I-II) were reported as (20%-8%) telangiectasia, (18%-2%) hyperpigmentation, (18%-4%) subcutaneous fibrosis, and (14%-8%) lymphedema respectively while at 24 months grade II only reported as 2% lymphedema. Acute radiation pneumonitis reported as 8%grade I and 4% grade II while chronic pulmonary fibrosis reported as 6% grade I and 2% grade II. Only 2 patients (7.6%) developed more than 10% drop in the left ventricular ejection fraction (LVEF).

Conclusion: The results of our study suggest there are no increased acute or late toxicities with comparable DFS and local control rates affiliated with the hypofractionated adjuvant breast radiotherapy schedule with once weekly concomitant boost as prescribed. Large randomized trials and long-term follow-up are needed to confirm these favorable findings**.**

Keywords: Breast cancer, Hypofractionated irradiation, Concurrent boost, Toxicity

Introduction:

Breast cancer is the most common cancer in women worldwide, about 12% of all new cancer cases and 25% of all cancers in women [1]. In Egypt it represents 32% of all women cancers [2]. Breast-conserving therapy (BCT) for early stages results in survival rates equivalent to that of mastectomy, therefore BCT became the standard treatment of stage I– II breast cancer [3-4]. Radiation therapy represents the standard adjuvant treatment after breast conserving surgery (BCS) as it associated with a 70% reduction in the risk of recurrence [5] and a 9-12% reduction in the risk of death [6-7]. Conventional radiotherapy given in 6-7 weeks has economic and logistic load on radiotherapy departments as well as negative impact on patient's quality of life [8]. Data from various studies suggests that the α/β ratio for breast cancer is closer to that of late-reacting tissues range between 3 and 4 Gy that may suggest a therapeutic benefit from accelerated schedules using a larger dose/fraction [9]. Over the last years, there has been renewed interest in hypofractionated whole breast irradiation (HF-WBI), defined as a larger daily dose delivered often over a shorter time period as large multicenter randomized trials of HF-WBI with 5 to 10-year follow-up data had shown equivalent efficacy and safety in terms of local control and patient survival [10]. Boost dose to the tumor bed after whole breast radiation is associated with improvement of the local control for all age groups with little or no affection of the late effects and cosmesis [11].This boost usually given sequentially in 10-16 Gy over 1-1.5 weeks that further prolongs the overall treatment period, so the incorporation of the boost dose within either a conventionally fractionated or hypofractionated whole

breast phase is definitely an interesting and promising field for clinical investigation as it allows for treatment acceleration and dose escalation in the area of higher risk of relapse [12]. In our prospective study we evaluated the efficacy and the feasibility of a hypofractionated radiotherapy schedule of 42.5 Gy/16 fractions to the whole breast with once weekly concomitant 3D photon boost of 1 Gy used as adjuvant radiotherapy for our eligible patients after breast conservative surgery.

Material and Methods:

This prospective study included eligible 50 female patients with early stage breast cancer who received adjuvant radiotherapy in the radiotherapy department of South Egypt cancer institute (SECI), Assuit University, Egypt, between November, 2013 and August, 2016. Patients with age of 18 years and above, with all histological types and grades, pathological T1-T2 tumors, N0 and N1 disease with negative surgical margins after breast conservative surgery were eligible. Patients with positive hormonal receptors received hormonal treatment sequentially after radiotherapy. All patients received adjuvant chemotherapy.

Radiation:

CT simulation was used for the localization and determination of the target volumes, organ at risk, and the field arrangement. The CT scans were done in the supine position from the level of the larynx to the upper abdomen with both lungs were included and the scan thickness was 5 mm. The Whole Breast Clinical Target Volume (WB-CTV) included the glandular breast tissue and did not extend to cover the pectorals major, the ribs or the skin. The Whole Breast Planning Target Volume (WB-PTV) was generated by the addition of a 5 mm margin around the WB-CTV. The Concomitant Boost Clinical Target Volume (CB-CTV) was generated by adding at least a 5 mm margin around the lumpectomy cavity and the corresponding PTV (CB-PTV) created by adding a further 5 mm margin. The definition of the lumpectomy cavity was guided by the presence of surgical clips, hematoma, seroma or other surgery-induced changes considered to be part of the cavity. The total whole breast radiation dose was 42.5 Gy in 16 fractions while the area of the lumpectomy cavity received additional 3Gy through once weekly 1 Gy concomitant photon boost. The energy used for the whole breast radiotherapy and the tumor bed boost was 6 MV photon beam.

Assessment and Follow up:

Patients were followed weekly during treatment and up to 6 weeks for assessment of acute toxicity and then every 3 months up to 2 years for evaluation of the late radiation toxicity, disease free survival and local control. The RTOG scoring system for radiation reactions was used to score radiation toxicity [13]. Late skin toxicities (telangiectasia and hyperpigmentation) and late subcutaneous toxicities (fibrosis) were graded using the modified late effects on normal tissues scoring system (LENT/Soma Tables) [33]. Cosmetic outcomes were subjectively assessed by the patient's thierselfes and scored as excellent, good, fair, and poor. All left sided patients were assessed by echocardiography before starting treatment and once at three months after finishing the radiation treatment [14]. Local DFS was calculated from date of diagnosis of ipsilateral tumor recurrence in the operated breast or overlying skin.

Statistical analysis: Data was analyzed using Graphpad Prism version 5. Univariate factors were analyzed using the chi-square test for categorical variables and differences were considered statistically significant at $P<0.05$.

Results:

Patient's characteristics: Table 1 summarized our patients and treatment characteristics. Median age was 47 years ranged from 27 to 68 years, 60% < 50 years old, 80% had T2, 78% N0, 70% G2 and 70% had positive hormonal receptors.

Table (1): patient's characteristics

Variable	No.	%
Age at time of diagnosis :		
<50 years	30	60%
≥50 years	20	40%
Range	27-68 yr	
Median	47 yr	
Laterality:		
RT side	24	48%
LT side	26	52%
Quadrant site		
UO (upper outer)	24	48%
UI (upper inner)	6	12%
LO (lower outer)	10	20%
LI (lower inner)	6	12%
CE (central)	4	8%
Tumor grade		
Grade 1	1	2%
Grade 2	35	70%
Grade 3	14	28%
Tumor histopathology		
IDC (infiltrating ductal carcinoma)	47	94%
ILC (infiltrating lobular carcinoma)	3	6%
T stage:		
T1	10	20%
T2	40	80%
Node stage:		
N0	39	78%
N1	11	22%
Hormonal receptors:		
Positive ER and/or PR	35	70%
Negative ER and/or PR	15	30%
Her 2 new Over-expression:		
No	41	82%
Yes	9	18%

Disease relapse and DFS: In our study, the local relapse was reported in one patient (2%) at the site of operated scar, bone metastasis reported in one patient (2%) as well as liver metastasis reported in another patient (2%) at 15, 18, and 20 months of disease free interval (DFI) respectively. The median follow up period was 29 months ranged from 25 to 32 months and the median DFS is 28.5 months ranged from 15 to 32 months and the 2 year DFS was 94% as shown in figure (2). Univariate analysis for the factors that may affect the 2 year DFS including the age, T stage, N stage, and hormonal receptor status (P value >0.005) showed no factor of them had significant effect on the patient DFS (P > .05) as shown in table (2).

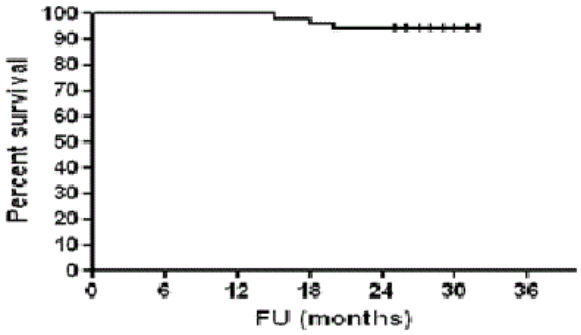

Figure (1): 2 year DFS for all patients

Toxicity: at the end of radiotherapy, grade 0, 1, and 2 acute skin toxicities were 52%, 36%, and 12% respectively while at 6 weeks after radiotherapy grade 0 and grade 1 were 41% and 9% but grade 2 disappeared. At 12 months of follow up telangiectasia occurred as grade 0, 1, and 2 in 41%, 5%, and 4% of patients respectively while at 24 months 4% had grade 1 and only 1% had grade 2. Grade 1 hyperpigmentation was reported in 8% and grade 2 in 2% of patients at 12 months whereas only 6% of patients showed grade 1 at 24 months of follow up. Subcutaneous fibrosis was reported as grade 1 in 18% and grade 2 in 4% of patients at 12 months whereas only 18% of patients showed grade 1 and no grade 2 at 24 months of follow up. Regarding acute lung toxicity, only 6 patients (12%) developed acute pneumonitis, 2 of them only(4%) received antitussive and steroid therapy (grade 2) within 3 months after treatment, while regard the chronic lung toxicity, only one patient(2%) who received treatment (grade 2) from 4 patient (8%) that developed the toxicity. Those patients underwent a chest X ray that showed ground glass opacities. In our study we had only 2 asymptomatic patients (7.6%) who showed drop more than 10% below the base line left ventricular ejection fraction (LVEF) in the left sided patients. Cosmetic outcome was scored as excellent and good in 78% off patients. Lymphedema occurred as grade 1 in 14% and as grade 2 in 8% at 12 months while at 24 months of follow up grade 1 reported in 18% and grade 2 in 2% only. Table 3 summarized the acute and late radiation toxicities while table 4 and 5 show the univariate analysis of factors (age, T stage, N stage, and hormonal receptor status) that may affect acute skin toxicity reported at the end of radiotherapy, cosmetic outcome, subcutanoues fibrosis at 12 months, and lymphedema at 12 months that showed no significant effects of any of these factors on the previous toxicities (P > .05).

Table (2): Univariate analysis of factors that may affect the 2 years DFS

Variable		2 year DFS %	P value	Hazard Ratio (HR)	95% CI of Ratio
Age at diagnosis	<50 yrs (30)	96%			
	≥50 yrs (20)	90%	0.361	0.331	0.0239-3.334
T stage	T1 (10)	100%			
	T2 (40)	92%	0.380	0.284	0.0171-4.716
Nodal stage	N0 (39)	95%			
	N1 (11)	90%	0.583	0.478	0.0298-7.676
Hormonal status	+ve (35)	94.4%			
	-ve (15)	92.8%	0.791	0.733	0.0575-9.333

Table 3: Incidence and Grades of Acute and Late Radiation Toxicities

Toxicity		Grade 0	Grade 1	Grade 2
Acute dermatitis	At the end of radiotherapy	26 (52%)	18 (36%)	6 (12%)
	At 6 weeks	41 (82%)	9 (18%)	0 (0%)
telangiectasia	At 12 months	36 (72%)	10 (20%)	4 (8%)
	At 24 months	41 (82%)	9 (18%)	0 (0%)
hyperpigmentation	At 12 months	45 (90%)	4 (8%)	1 (2%)
	At 24 months	47 (94%)	3 (6%)	0 (0%)
subcutaneous fibrosis	At 12 months	39 (78%)	9 (18%)	2 (4%)
	At 24 months	41 (82%)	9 (18%)	0 (0%)
Lymphedema	At 12 months	39 (78%)	7 (14%)	4 (8%)
	At 24 months	40 (80%)	9 (18%)	1 (2%)
Lung toxicity	Acute	44 (88%)	4 (8%)	2 (4%)
	Chronic	46 (82%)	3 (6%)	1 (2%)

Table 4: Univariate Analysis of factors that may affect acute skin toxicity reported at the end of radiotherapy and cosmetic outcome.

	Acute radiation skin toxicity			Cosmetic outcome		
	Grade 0 NO (%)	Grade 1-2 NO (%)	P value	Excellent & Good NO (%)	Fair & Poor NO (%)	P value
Patient age						
<50 yrs (30)	14(46.66%)	16 (53.33%)	**0.355**	24(79.99%)	6 (20.01%)	**0.157**
≥**50 yrs** (20)	12 (60%)	8 (40%)		15 (75%)	5 (25%)	
Laterality						
Rt. side (24)	14(58.33%)	10 (41.66%)	**0.389**	20(83.33%)	4 (16.66%)	**0.381**
Lt. side (26)	12(46.15%)	14 (53.84%)		19(73.03%)	7 (26.92%)	
T stage						
T1 (10)	7 (70%)	3(30%)	**0.202**	8 (80%)	2(20%)	**0.864**
T2 (40)	19 (47.5%)	21 (52.5%)		31 (77.5%)	9 (22.5%)	
Nodal stage						
N0 (39)	20(51.28%)	19 (48.71%)	**0.848**	30(76.92%)	9 (23.07%)	**0.73**
N1 (11)	6 (54.54%)	5 (45.45%)		9 (81.81)	2 (18.18%)	
Hormonal therapy						
Yes (35)	20(57.14%)	15(42.85%)	**0.266**	28(79.99%)	7 (20.01%)	**0.602**
No (15)	6 (39.99 %)	9 (59.99%)		11 (73.33)	4 (26.66%)	

Table 5: Univariate Analysis of factors that may affect subcutaneous fibrosis and lymphedema at 12 months follow up.

	Subcutaneous fibrosis			Lymphedema		
	Grade 0 (%)	Grade 1- 2 (%)	**P value**	Grade 0 (%)	Grade 1- 2 (%)	**P value**
Patient age						
<50 yrs (30)	22(73.33%)	8 (26.6%)		21(69.99%)	9 (30.01%)	
≥**50 yrs** (20)	17 (85%)	3 (15%)	**.329**	18 (85%)	2 (15%)	**0.0944**
Laterality						
Rt. side (24)	16 (66.6%)	8 (33.33%)		16 (66.6%)	8 (33.33%)	
Lt. side (26)	23 (88.4%)	3 (11.53%)	**.06**	23 (88.4%)	3 (11.53%)	**0.06**
T stage						
T1 (10)	8 (80%)	2(20%)		6 (60%)	4(40%)	
T2 (40)	31 (77.5%)	9 (22.5%)	**.864**	33 (82.5%)	7 (17.5%)	**0.124**
Nodal stage						
N0 (39)	32(82.05%)	7 (17.94%)		32(82.05%)	7 (17.94%)	
N1 (11)	7 (63.6%)	4 (36.4%)	**.192**	7 (63.6%)	4 (36.4%)	**0.192**
Hormonal therapy						
Yes (35)	27(77.14%)	8 (22.85%)	**.823**	28(79.99%)	7 (20.01%)	**0.602**
No (15)	12 (79.99)	3 (11.99%)		11(73.33%)	4 (26.66%)	

Discussion:

Based on radiobiological models, it was evident that hypofractionated radiation schedules used as adjuvant treatment for breast cancer offer the promise of equivalent local control to standard conventional radiation therapy by giving larger doses per fraction in shorter period of time [15]. Results of retrospective studies of hypofractionated RT in early breast cancer suggest satisfactory outcomes as regard tumor control and late adverse events [16]. In our current study we tested a hypofractionated dose of 42.5 Gy in 16 fractions used as adjuvant treatment for the whole breast after conservative surgery in early stage 1-2 with a 3D photon concomitant boost of 1 Gy once weekly for a total boost dose 3 Gy to the tumor bed. The median age of our patients was 47 years which is similar to that reported by Motawy et al. [17]. after a median follow up period of 29 months the 2 year DFS was 94% for the whole patients which is comparable to the median DFS rate at Corvo et al[18] which was 97% and the DFS at Cante et al. [19]that was 93.1%. Also similar results (> 90% 2 year DFS) were reported by the START trialists group [20]. Our study revealed reasonably good feasibility in terms of acute toxicity as no grade III or IV reaction was found. Acute skin complication reported in our study as grade 2 in 12% of patients which is comparable to results at Guenze et al. [21] Corvo et al. [18], Freedman, et al. [22], and Sayed MM et al. [23] where grade 2 was reported in 9%, 7%, 15%, and 10.5% respectively. Our initial results of late effects appear promising as no grade III-IV toxicity were reported which is similar to that reported by Guenzi et al. [21], Ciammella et al. [24], and Scorsetti et al. [25]. Grade 2 hyperpigmentation was reported in 2% of patients at 12 months of follow up while 11.8% and 8.3% were reported by Sayed MM et al. [23] and El-Hadaad et al. [26] respectively. Telangiectasia in our patients was reported as grade 2 in 8% at 12 months follow up which in comparable to reported by Romestaing P et al.[27] and El-Hadaad et al.[26] Regarding subcutaneous fibrosis, in our study grade 2 was reported in 4% of patients at 12 months of follow up and disappeared at 24 months of follow up that is similar to 3% reported by Guenze et al.[21] and Formenti, et al. [28]. The cosmetic outcome in our current study showed that (78%) of patients had excellent and good cosmesis. In the reported studies the excellent and good cosmesis were reported in more than 90% of patients (McDonald et al., Corvo et al., Cante et al., and Ciammella et al. [29-18- 19-24]). While at START A trial, excellent and good scores were reported in 66% of patients [20] and at the Canidian trial studied by Whelan et al. [8] 69.8% of the women in the hypofractionated radiation group had a good or excellent cosmetic outcome. Also Polgár C et al. [30] reported that the cosmesis was scored as excellent/good in 82.7% of patients treated with electron beam for boost delivery. The acute radiation induced pulmonary toxicity was reported as grade 2 in 4% (required steroid therapy) while the chronic toxicity reported as grade 2 in 2% (received steroid treatment). These results also are comparable to those reported by Shahid et al. [14]. We reported that 2 patients (7.6%) of the left sided patients developed asymptomatic drop in the LVEF of more than 10% below the baseline which is comparable to the results reported by Cao L et al. [31] and Shahid, et al. [14]. Regarding the ipsilateral lymphedema, in our study grade 2 lymphedema reported in 6% of patients at 12 months and in 2% of patients at 24 months follow up which is similar to the recently published systematic

review and meta-analysis on the incidence of unilateral lymphedema after breast cancer where a pooled estimate of lymphedema in the 72 studies showed an incidence of edema of 16.6%(as reported by Disipio et al. [32]

Conclusion:

The results of our study suggest there are no increased acute or late toxicities with comparable DFS and local control rates affiliated with the hypofractionated adjuvant breast radiotherapy schedule with weekly concomitant boost as prescribed. Large randomized trials and long-term follow-up are needed to confirm these favorable findings.

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