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Adjuvant radiotherapy in breast cancer: A comparison of two accelerated hypofractionated protocols

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Abstract

Background: Accelerated hypofractionated approach is based on the radiobiologic model that a lower total dose delivered in fewer, larger fractions over a shorter period of time is at least as effective as the traditional longer schedule with increasing evidence of equivalent efficacy and toxicities from randomized trials comparing conventional radiotherapy schedules to different hypofractionated schedules.

Patients and methods: 100 female patients having breast cancer after finishing their chemotherapy if indicated, randomized into two arms of accelerated hypofractionation; 39Gy/13 fractions (group A) and 42.4Gy/16 fractions (group B) both regimens given as 5 fractions per week.

Results: The disease free survival was 93% and local recurrence was 1%. There were no statistically significant effects as regards recurrent rate in any studied factors. Radiation complications of patients, in terms of skin, subcutaneous, pulmonary, cardiac, ipsilateral arm lymphedema and brachial plexus toxicity, were assessed and graded in both group A and group B. There was significant increase of incidence of acute radiation dermatitis in patients receiving 39 Gy, as grade I and II reported in 82% and 46% for 39 Gy group and 42.4 Gy group respectively. In-addition, increased chronic subcutaneous fibrosis among patients with group A (28%) in comparison to group B (18%) that reach statistical significance. Type of surgery is the only factor that had significant effect on incidence of acute radiation dermatitis and chronic subcutaneous fibrosis.

Conclusion: Our study concluded Equivalent efficacy of 39 Gy in 13 fractions and 42.4 in 16 fractions regarded local control and survival. 39 Gy in 13 fractions is not recommended for patients underwent BCS.

Introduction

Conventional radiotherapy after breast surgery requires 5-7 weeks of daily treatment [1,2]. Such a long treatment schedule has major implications on both patient quality of life and radiotherapy departments, as a high number of breast cancer patients receive radiotherapy. A shorter breast radiotherapy schedule would be more convenient for patients (especially those coming from remote areas to radiotherapy facilities) and for health care providers, as it would increase the turnover in radiotherapy departments.

Accelerated hypofractionated approach is based on the radiobiologic model that a lower total dose delivered in fewer, larger fractions over a shorter period of time is at least as effective as the traditional longer schedule[3]. Increasing evidence from randomized trials comparing conventional radiotherapy schedules to different hypofractionated ones in whole breast irradiation after conserving surgery show that breast adenocarcinoma may be associated with lower α/β ratio than previously thought and closer to those of late-reacting healthy tissues [3-7]. The LQ model suggests that, when the α/β ratio for the tumor is similar to that of the surrounding late-responding normal tissue, the hypofractionated regimen may be equally or potentially more effective than the conventional one [8].

Accelerated hypofractionation using 4240 cGy in 16 fractions given in 3 weeks. This is accepted as a fairly standard dosage world over and at our institute. It is very well tolerated and its toxicity is comparable to the five weeks protocol [5]. In the published UK Start Trial A, women assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy or 41.6 Gy in 13 fractions of 3.2 Gy or 39 Gy in 13 fractions of 3.0 Gy and results revealed comparable efficacy and toxicities [4].

The aim of this study is to compare the efficacy and toxicities of two different protocols of accelerated hypofractionated radiotherapy in breast cancer patients treated as adjuvant setting.

Patients and Methods

This study included 100 female patients having breast cancer (50 patients in group A and 50 patients in group B). Those patients attended the Radiotherapy Department

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of South Egypt Cancer Institute, Assiut University, between December, 2009 and February, 2012. Patients' characteristics are listed in Table 1. Informed consent was given by every patient who participated in this study, and the study was approved by our ethical committee.

Eligible patients had histologically confirmed breast cancer; Age≥ 18 years; ECOG performance status 0-2; Negative histological margins (i.e., no invasive cells at surgical margin) or confirmed negative re-excision specimen; Adjuvant radiotherapy is indicated in breast conservative surgery (BCS), post-mastectomy RT, if T >5cm and/or positive axillary nodes.

Patient excluded if had lobular carcinoma in situ alone (i.e., no invasive component), inflammatory carcinoma of breast or non-epithelial breast malignancies (e.g., sarcoma or lymphoma); Prior radiotherapy for the current breast cancer; Pregnant woman and other malignancy within the past 5 years except for non-melanoma skin cancer (the disease-free interval from any prior malignancy must be continuous).

Pretreatment evaluation: Patients were evaluated as a baseline before treatment through history and clinical examination with assessment of performance status; Measurement of arm circumference 10cm above and below olecranon process; ECHO in case of left breast cancer; Complete laboratory investigations (complete blood picture, liver enzymes, albumin, bilirubin , serum urea and creatinine); Abdominal ultrasound; Chest radiographs and/ or C T chest.

Treatments: Patients, after finishing their chemotherapy if indicated, were randomized into two arms of accelerated hypofractionation; 39Gy/13 fractions (group A) and 42.4Gy/16 fractions (group B) both regimens given as 5 fractions per week. All patients who had undergone BCS and younger than 50years in both groups receive boost dose to tumor sit of 14 Gy using 2Gy per fractions

Re-evaluation during radiotherapy and one week after by clinical assessment every week for skin complications then patients were re-evaluated every 6 months, for local control, disease free survival and complications, for at least two years.

Skin, subcutaneous and pulmonary complications were scored using the RTOG/European Organization for Research and Treatment of Cancer (EORTC) Radiation Morbidity Scoring Scheme [9]. Echocardiography of left sided patients was done at two months after radiation. A fall of more than 10% in ejection fraction was taken as significant reduction in the LVEF whether symptomatic or not [10].

Lymphedema was monitored by the arm circumference, measured at 10 cm above and below the olecranon process of ulna. Measurements were taken at end of radiation 6 months, and one year and two years and graded [10]. Suspected injury to the brachial plexus causing weakness of the arm was documented by MRI.

Statistical methods: Data represented as numbers, percentages or means ± SD; t-test used to compare between means; Chi^2 test for comparison between groups; Local control and disease free survival calculated according to Kaplan-Meier method.

Table 1: Patients' characteristics.

Variable	Group A		Group B		Total		P value
	No.	%	No.	%	No.	%	
1. Age at diagnosis							
• <50 years	27	54	29	58	56	56	
• ≥50 years	23	46	21	42	44	44	> 0.05
• Range	30-66		30-65				
• Median	49		45				
2. laterality							
• Right	25	50	25	50	50	50	> 0.05
• Left	25	50	25	50	50	50	
3. Disease stage							
• stage I	3	6	3	6	6	6	> 0.05
• stage II	21	42	17	34	38	38	
• stage III	26	52	30	60	56	56	
4. Type of surgery							
• CBS	12	24	10	20	22	2	> 0.05
• MRM	38	76	40	80	78	78	
5. Nodal status							
• N0	17	34	11	22	28	28	
• N1	13	26	13	26	26	26	> 0.05
• N2	11	22	17	34	28	28	
• N3	9	18	9	18	18	18	
6. Hormonal receptor status							
• Positive	27	54	28	56	55	55	> 0.05
• Negative	17	34	13	26	30	30	
• Unknown	6	12	9	18	15	15	
7. Adjuvant systemic therapy							
• Hormonal therapy	33	66	37	74	70	70	> 0.05
• Chemotherapy	47	94	49	98	96	96	

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Table 2: Local recurrence and distant metastasis rates reported in both groups.

Variable	Group A		Group B		Total		P value
	No.	%	No.	%	No.	%	
• LR	1	2	0	0	1	1	
• DM	2	4	4	8	6	6	> 0.05
• Disease free	47	94	46	92	93	93	

Results

Pattern of failure: Rates of local recurrence and distant metastasis in group A versus group B were calculated and are shown in Table 2. Local recurrence occurred in 1 out of 50 patients (2%) at the site of scar and distant metastasis in 2 out of 50 (4%) patients (bone after 10 months and lung after 24 months disease free interval) at a median follow up period of 24 months in group A. Among group B no local recurrence occurred while four patients (8%) with distant metastases (one case was liver at 18 month and 3 cases were bone metastasis, at 6, 12 and 21 months) at a median follow up period of 24 months in group B.

Factors affecting recurrent (locally and distant metastasis) rate in patients in group A and group B are shown in (Table 3). There were no statistically significant effects regarding recurrent rate in any studied factors. The 2-year actuarial disease free survival rate in women in all patients (both groups A& B) was 93% as shown in Figure 1. Figure 2 demonstrated the different DFS between both groups using Kaplan Myer survival curves with no differences among both groups (p=0.7).

Table 3: Prognostic factors affect recurrent (locally and distant metastasis) rate in both groups.

Variable	Group A			Group B		
	Total	DF No (%)	Recurrent No (%)	Total	DF No (%)	Recurrent No (%)
Age at diagnosis						
• <50 years	27	26 (96.2)	1 (3.8)	29	27 (93.1)	2 (6.9)
• ≥50 years	23	21 (91.3)	2 (8.7)	21	19 (90.4)	2 (9.6)
P value		> 0.05			> 0.05	
Type of surgery						
• CBS	12	12 (100)	0 (0)	10	9 (90)	1 (10)
• MRM	38	35 (92.1)	3 (7.9)	40	37 (92.5)	3 (7.5)
P value		> 0.05			> 0.05	
Ax. LN Metast.						
• Negative	17	15 (88.2)	2 (11.8)	11	9 (81.8)	2 (18.2)
• Positive	33	32 (96.9)	1 (3.1)	39	37 (94.8)	2 (5.2)
P value		> 0.05			> 0.05	
Hormonal receptor						
• Positive	27	25 (92.5)	2 (7.5)	28	26 (92.8)	2 (7.2)
• Negative	17	16 (94.1)	1 (5.9)	13	12 (92.3)	1 (7.7)
• Unknown	6	6 (100)	0 (0)	9	8 (88.8)	1 (11.2)
P value		> 0.05			> 0.05	

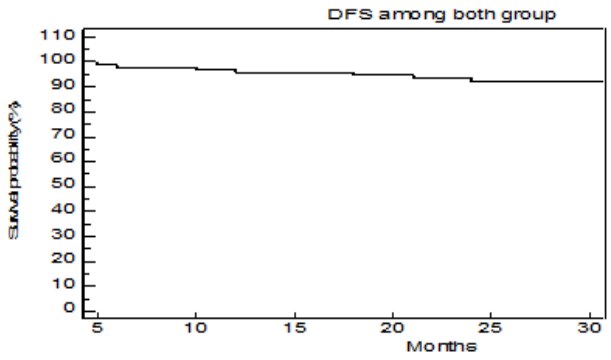

Figure 1: The 2-year disease free survival rate in women in all patients (both groups A& B).

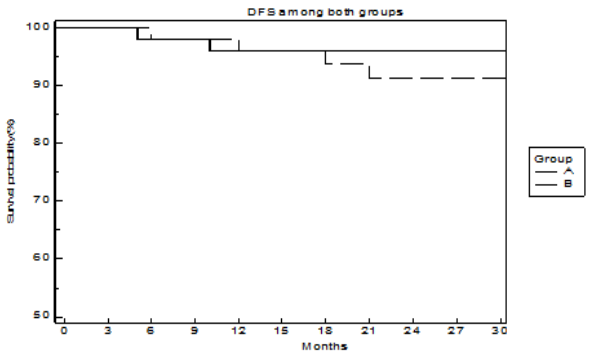

Figure 2: The 2-year disease free survival rate in women for group A& B.

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Radiation Complications: Radiation complications of patients, in terms of skin, subcutaneous, pulmonary, cardiac, ipsilateral arm lymphedema and brachial plexus toxicity, were assessed and graded in both group A and group B.

Skin complications: Acute radiation dermatitis in group A versus Group B is shown in Table 4, it was found that there was with significant increases of incidences of acute radiation dermatitis inpatients receiving 39 Gy as grade I and II reported in 82% and 46% for group A and B respectively (P=0.0008). Type of surgery is the only factor that had significant effect on incidence and grade of acute radiation dermatitis among group A and B, however age, stage, laterality and hormonal therapy had no significant effects. According to type of surgery in group A, patients underwent BCS had more acute radiation dermatitis 100%, while 76.3% (29 out of 38 patients) for patients underwent MRM (P=0.0001). Similar, in group B, underwent BCS had more acute radiation dermatitis 60%, while 42.5% (17 out of 40 patients) for patients underwent MRM (P = 0.017). Chronic radiation dermatitis in group A versus Group B is shown in Table 5, and without any significant differences between both groups.

Table 4: Acute radiation dermatitis in patients reported in both groups.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0 dermatitis	9	18	27	54	
GI dermatitis	34	68	20	40	0.0008
GII dermatitis	7	14	3	6	

Table 5: Chronic radiation dermatitis reported in group A versus Group B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0	46	92	48	96	
GI	4	8	1	2	>0.05
GII	0	0	1	2	

Pulmonary toxicity: Acute pulmonary symptoms reported in 12% of all patients (Table 6), however only 5 patients (one patient group A and four patients group B) required medical antitussive therapy (GII) and the remaining 7 patients had mild cough and did not required medical treatment (GI). Eight percent of patients had pulmonary symptoms developed after 6 months (chronic radiation pneumonitis), 7% of them were grade I (mild cough) and only one patient in group B need medical treatment, Table 7. We studied age, laterality; type of surgery, and hormonal therapy; however none of these factors had significant effect on neither acute nor chronic pneumonitis. Chest x-ray radiological opacities reported in 8% (n=8), all detected in supraclavicular region as represented in Table 8.

Table 6: Acute pneumonitis in patients in group A versus group B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0	43	86	45	90	
GI	6	12	1	2	>0.05
GII	1	2	4	8	

Table 7: Chronic pneumonitis in patients reported in group A versus group B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0	46	92	46	92	
GI	4	8	3	6	>0.05
GII	0	0	1	2	

Table 8: Chest X ray in patients reported in group A versus group B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
No opacities	46	92	46	92	>0.05
Opacities	4	8	4	8	

Subcutaneous fibrosis: Assessment for chronic subcutaneous fibrosis according to RTOG revealed increased subcutaneous fibrosis among patients with group A (28%) in comparison to group B (18%) that reach statistical significance (Table 9). The different prognostic factors that could influence the chronic subcutaneous fibrosis were age, laterality; type of surgery and hormonal therapy however, only type of surgery had significant effect.

Table 9: subcutaneous fibrosis reported in group A and B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0	36	72	42	82	
GI	4	8	7	14	0.002
GII	10	20	2	4	

Cardiac toxicities: Cardiac function was assessed by the ejection fraction determined by echocardiography, for left-sided patients. As shown in Table 10, four patients (16%) in group A and 3 patients in group B (12%) had less than 10% decrease in the ejection fraction value.

Table 10: Cardiac toxicities reported in left sided patients of group A and B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
No	21	84	22	88	>0.05
Yes	4	16	3	12	

Lymphedema: Lymphedema was graded according the changes of arm circumference during follow up

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compared to pre-radiotherapy measurement. G1 or GII toxicities were reported in 38% and 22% of patients for group A and B respectively (> 0.05), (Table 11). Studied prognostic factors that may affect the development of lymphedema complications were age, type surgery, stage. However, none of them had significant effects.

Table 11: Lymphedema reported in group A and B.

Variable	Group A		Group B		P value
	No.	%	No.	%	
G0	31	62	39	78	
GI	6	12	6	12	>0.05
GII	13	26	5	10	

Brachial pleuxopathy: No patient had any symptoms or signs suggesting brachial plexus radiation injury.

Discussion

Adjuvant radiation therapy in the management of early breast cancer after conservative surgery carries the purpose of reducing local–regional recurrence probability.

Conventional fractionation, with daily fractions of 1.8–2 Gy, became the standard option mainly based on empirical considerations or resource evaluations. the University of Florence treated 539 patients (pTis-pT1-pT2) with AWB-RT up to a total dose of 44 Gy given in 16 fractions (2.75 Gy each day) with a subsequent boost dose of 10 Gy in five fractions to the tumor bed: with a median follow up of 4.3 years, only 1.8% of the patients experienced local relapse and only 2.5% showed major late effects (grade 3 or more) [11].

Randomized phase III trials seem to reach satisfactory evidence of promising cosmetic outcome with hypofractionated adjuvant radiation for EBC. The Ontario Clinical Oncology Group (OCOG) trial randomized 1,234 women, after breast-conserving surgery and axillary dissection, to receive accelerated hypofractionated AWB-RT of 42.5 Gy in 16 fractions over 22 days or a standard radiation course of 50 Gy in 25 fractions over 35 days [5].

The disease free survival was 93% the same that reported by the START trialists group [5]. local recurrence was only 1% that is similar to Whelan et al[12].

The following prognostic factor were studies; age, type of surgery, axillary lymph nodes involvement, and hormonal receptor status, however none of these factors affecting disease free survival this could be because of short follow up period only 30 months in addition, small number of patients, only 50 patients on both groups. In addition our results is similar to Whelan 2012 how reported that age, hormonal receptor and systemic therapy has no statistically significant effects [12].

Acute radiation dermatitis assessed weekly during radiotherapy and one week after by clinical assessment with significant increases of incidences of acute radiation dermatitis inpatients receiving 39 Gy as grade I and II reported in 82% and 46% for 39 Gy group and 42.4 Gy group respectively. Grade II reported in 10% that is matched with Pinnaro as he reported 4 out of 39 (10.2%) patients had GII dermatitis. However our date Is much less than that reported by Taher et al., [13] as he reported 86.7% in 42.4Gy arm with 40% GII or more this because all patients of this study underwent BCS.

The present study did not reveal a significant impact of any of the studied factors on the rate of acute radiation dermatitis except type of surgery performed and this in agreement with Elsayed et al.,[14] .

Chronic radiation dermatitis was 6% with only 2% had grade II which is matched with Whelan and his colleagues as they reported 2.6% grade II skin complication [12], however this disagreement with Hijaland his colleagues who reported 83% this because they study on BCS patients only.

Acute radiation pneumonitis reported on 12% however only 5 patients (one patient in 39 Gy group and four patients in 42.4 Gy group) required medical antitussive therapy (GII) and the remaining 7 patients had mild cough and did not required medical treatment (GI), that is the same reported by Shaaban et al.,[15]. There is no significant difference between 39 Gy group and 42.5 Gy group that could explained because radiation-induced lung injury (RILI) risk is considered more likely to be related to volume than to dose per fraction; hence, an increased RILI rate is unlikely to be seen with large dose per fraction without an association with a substantial irradiated volume of the lung.

After 6 months, only 8% of patients in 39 Gy group and 6% of 42.4 Gy group had grade I pulmonary symptoms. one patient (2%) of 42.4 Gy group need steroid treatment, this is similar to what reported by Shaaban [15] they reported at 6 months smaller numbers of patients were complaining of mild or moderate reaction (6.7% and 4.7% respectively). However; most of them were mild and self-limiting with most of cases showed resolution within 12 months. The above results also matched with Lingos et al., [16] and Ibrahim et al., [14] as they reported incidences of radiation pneumonitis that required steroid to be 2.9% and 2.7% respectively. Also Abbas et al., reported the same conclusion [17]. In contrast, Lind et al.,[18] and Hanna et al., [19] reported that 9% - 15% of patients had radiation pneumonitis that required steroid. The difference could be explained on the ground that Lind and his colleagues irradiated internal mammary nodes in 95% of patients and 21% of patients received CMF regimen which contains methotrexate with high tendency to cause pulmonary complications. Also the percentage of irradiated lung volume that received ≥ 25 Gy was 32%. In addition, Hanna et al., and had higher incidences of pulmonary complications, as they reported 15% of patients, required steroid for treatment of radiation pneumonitis [19], and this may be explained by the use of adjuvant paclitaxel-containing chemotherapy., which is known to reduce the lung tolerance. Taghian et al., [20] found that the rate of radiation pneumonitis in the paclitaxel-treated group was 15.4% compared with smaller percentage 0.9% among breast cancer patients treated with RT and non-paclitaxel-containing chemotherapy as in this study

The different prognostic factors that can influence the pulmonary complications age, laterality, type of surgery, and hormonal therapy, and however none of these factors has significant effect for both acute and chronic

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complications this is the same conclusion of Elsayed et al.,[14] and Mahmoud et al., [21].

Assessment for chronic subcutaneous fibrosis according to RTOG revealed increased subcutaneous fibrosis among patients received 39 Gy (28%) in comparison to 42.4 Gy group (18%) that reach statistical significance and only type of surgery had statically significant effects. For 42.4 Gy group, GII subcutaneous fibrosis detected in 4% that is similar to 4.7% that reported by Whelan [12], however in 39 Gy group, GII subcutaneous reported in 20% and this explained by higher dose per fraction for 39 Gy group (300 cGy) compared to 42.4 Gy group (265cGy) and late effects such as subcutaneous fibrosis are more sensitive than acute reactions to altered fraction size [4].

Concerns about the sensitivity of the heart to hypofractionation have been expressed but the heart is vulnerable to radiotherapy whatever fractionation schedule is used, and there appears to be no lower dose threshold for injury [22] Cardiac function, assessed by the ejection fraction determined by echocardiography, for left-sided patients. four patients (16%) in 39 Gy and 3 patients in 42.4 Gy group (12%) had less than 10% decrease in the ejection fraction value without statistically significant difference between both group this because our results is comparable to what 16% reported by Mahmoud et al [21].

Among our patients, there is no cases with brachial pleuxopathy that could be explained because where the brachial plexus is concerned, 39 Gy in 13 fractions is expected to be a safe schedule if delivered using a technique and reference point of proven safety with 50.0 Gy in 25 fractions.

Assuming an α/β value of 2.0 Gy for brachial plexus injury, 39 Gy in 13 fractions is equivalent to 48.75 Gy in 2.0 Gy. In other words, 39 Gy in 13-fraction regimen is likely to be less damaging to the brachial plexus than 50.0 Gy in 25 fractions. In the START Trials where 11% of patients received regional radiotherapy, with only one confirmed case of brachial pleuxopathy in a patient treated with 41.6 Gy in 13 fractions. A review done by Galecki, reported that doses ranging from 34 - 40 Gy in fraction sizes ranging from 2.2 - 2.5 Gy appear to be associated with a low risk of radiation-induced brachial pleuxopathy comparable to the risk associated with 50 Gy in 25 fractions [23]. Long term follow up for our patients is necessary as pleuxopathy is a long term toxicity, a retrospective study using Supraclavicular radiation to a dose of 52 Gy in 20 fractions to a depth of 3 cm using Co-60 resulted in a 56% risk of brachial pleuxopathy at 20 years, with the annualized risk relatively constant throughout the follow up period. Median follow up was 8.2 years in surviving patients [24].

Our study concluded Equivalent efficacy of 39 Gy in 13 fractions and 42.4 in 16 fractions regarded local control and survival. 39 Gy in 13 fractions is not recommended for patients underwent BCS.

Abbreviations

AWB-RT	Adjuvant whole breast radiotherapy
CBS	Conservative breast surgery
EBC	Early breast cancer
EBCTCG	Early breast cancer trialists' collaborative group
ECOG	European cooperative oncology group
EORTC	European Organization for Research and treatment of cancer
Gy	Gray
LQ	Linear quadratic
MRM	Modified radical mastectomy
OCOG	Ontario Clinical Oncology Group
RILI	Radiation-induced lung injury
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

All the work was done by the first author under supervision and guidance by the remaining authors.

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