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ORIGINAL PAPER

Hypofractionation in post-mastectomy breast cancer patients: seven-year follow-up

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Abstract To compare three fractionation schedules in post-mastectomy patients treated with radiotherapy as regard acute and early late effects as well as local recurrence rates. One hundred and seven breast cancer patients treated with modified radical mastectomy and adjuvant radiotherapy ± adjuvant systemic treatments between November 2001 and July 2004 were enrolled in this study. Patients were categorized into three groups. Group A (41 patients) received conventional fractionation 50 Gy over 25 fractions. Group B (36 patients) received other fractionation regimen 45 Gy over 17 fractions. Group C (30 patients) received 40 Gy over 15 fractions. The median follow-up period was 23 months. There has been no statistical significant difference in local control ($P = 0.88$), pain ($P = 0.98$), telangectasis ($P = 0.23$), fibrosis ($P = 0.13$), arm oedema ($P = 0.96$) or pigmentation ($P = 0.80$) between the three groups. GII-III Erythema was significantly higher in the two hypofractionation arms compared to the control arm ($P = 0.001$). Although acute skin reactions were higher in the hypofractionated arms, there was no significant difference in the local recurrence rates or late radiation effects. A national randomized multicentre study is recommended to explore this further.

Keywords Breast cancer · Mastectomy · Radiotherapy · Fractionation

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Introduction

Conservative breast surgery followed by adjuvant radiotherapy in early-stage breast cancer is currently considered standard treatment [1, 2]. Many centres in Egypt have not yet adopted this approach and continue to perform modified radical mastectomy. Also, most of these patients received post-mastectomy radiotherapy though in some cases it might not be indicated. It is also worth to note that some recent reports still show an advantage for post-mastectomy radiotherapy even in T1-2 N0 disease [3]. Increasing the number of cancer centres treating with radiotherapy in Egypt over the past decade has not accommodated the increasing number of patients requiring radiotherapy treatment. This has resulted in increased waiting times to start radiotherapy for patients with breast cancer.

Hypofractionation regimens are particularly useful in solving such problems. However, a high dose per fraction is known to cause some unacceptable late effects. Although this may be of concern regarding the cosmoses after breast conservative surgery, it still carries a potential risk for soft tissue, ribs, lung, heart and brachial plexus as damage to these structures may not be clinically apparent for 10–20 years [4]. Using 50 Gy in 25 fractions of 2 Gy/fraction is considered to be the standard and the most commonly used regimen; however, many authors have described many different fractionations [5, 6].

Daily radiotherapy treatment over several weeks can be inconvenient for patients particularly in Egypt where patients often live quite a distance from the cancer treatment centres. Due to cultural habits, they are usually accompanied by members of the family thus creating more of a burden on the family during the long periods of radiotherapy.

The use of shorter fractionation schedules was reported in Britain and Canada [5, 7], for example 40 Gy in 16

fractions [8, 9], and others have used 42.5 Gy in 16 fractions over 22 days [10], 32.5 Gy in 5 fractions over 22 days [11] and 45 Gy in 17 fractions.

The UK START Trial published in 2008 comparing 50 Gy/25 fractions to 40 Gy/15 fractions has shown that 40 Gy in 15 fractions seems to offer rates of local–regional tumour relapse and late adverse effects at least as favourable as the standard schedule of 50 Gy in 25 fractions [12].

The aims of this pilot study were to assess two hypofractionation regimens compared with standard fractionation in the Egyptian patient population taking into consideration the differences in race and the subsequent effect in skin colour and tolerance to radiation, which might produce different outcomes from those results published in the Western population. The hypofractionation chosen were 45 Gy in 17 fractions and 40 Gy in 15 fractions to be compared with the standard 50 Gy in 25 fractions.

Patients and methods

Between November 2001 and July 2004, 107 breast cancer patients treated with modified radical mastectomy and adjuvant radiotherapy ± adjuvant systemic treatments were enrolled in this study. It was difficult to randomize patients in the pilot study as many patients were aware of the standard treatment arm, and receiving shorter fractionation was not acceptable to them. This, therefore, is a comparative study not a randomized trial.

All patients had to have a diagnosis of invasive breast cancer that had been treated with modified radical mastectomy with at least 5-mm resection margin from the tumour. The TNM Staging was reported according to the AJCC Staging in 1997 with no correction according to the recent modification of AJCC.

Patients who required supraclavicular lymph node or axillary irradiation were also included, making this study slightly different from the previous reports that excluded such patients [13].

Patients were categorized into three groups. Group A (41 patients) receiving conventional fractionation 50 Gy over 25 fractions; group B (36 patients) receiving the hypofractionation regimen 45 Gy over 17 fractions; group C (30 patients) receiving 40 Gy over 15 fractions.

Radiotherapy treatment

Patients received their treatment on a linear accelerator 6MV or $Cobalt^{60}$ machine. Patients were treated in the supine position with breast board and arm support. The target volume included the chest wall with or without axillary and supraclavicular lymph nodes. For the chest wall, margins were defined as the midline medially, midaxillary line laterally, the inferior aspect of the clavicle head superiorly and 2½ cm inferior to the opposite infra mammary fold inferiorly. The lung volume included in the field did not exceed 3 cm. A dose distribution was generated using a single midplan contour, which was obtained with a single CT slice in the middle of the field; wedges were used when necessary to optimize the dose homogeneity within the treatment volume. The field margin for the supraclavicular treatment extended from the midline medially to half way over the humeral head laterally with protection of the humeral head and from the inferior aspect of the clavicle head inferiorly to 5 cm above the superior aspect of the clavicular head superiorly. The field was angled at 10 degrees to avoid spinal cord irradiation. Radiotherapy was given as two tangential fields as well as an anterior axillary and supraclavicular field in 29/41, 27/36 and 20/30 patients in groups A, B and C, respectively, while two tangential fields only were used in 12/40, 9/36 and 10/30 patients in groups A, B and C, respectively.

Adjuvant systemic treatment

In group A 31/41 patients received adjuvant hormonal treatment compared to 25/36 and 24/30 patients in groups B and C, respectively, whereas adjuvant chemotherapy was given to 30/41 patients in group A and 24/36 and 20/30 patients in groups B and C.

Neoadjuvant chemotherapy to downstage the tumour was given in two patients in group A and one patient in each of groups B and C.

Follow-up

Follow-up of patients was carried out weekly during radiotherapy and up to 2 weeks after the end of the course. After that patients were seen every 3–6 months. The median follow-up period was 23 months. The primary endpoints were both early and late reactions. The secondary end-point was ipsilateral tumour recurrence.

An IBM compatible computer using SPSS program version 12.0 under Windows accomplished data entry, analysis and graphical design.

Differences between groups were tested using chi-square test (χ^2) for qualitative data and ANOVA (F) test for quantitative data.

Analysis of data was performed using the 0.05 as significance level and the 0.01 as highly significant.

Results

The data of 107 patients participating in this trial were analysed. The age range for group A was 25–67 years with

52 as an average age, whilst for groups B, it was 29–63 years with an average of 54 and 31–61 years with average of 51 for group C.

The patient, tumour and treatment characteristics are given in Table 1.

The three groups were well balanced as regards age, menopausal status, tumour grade, hormone receptor status and systemic treatment given. Thus, observed differences in the local control or in the treatment related reactions could be attributed to the fractionation regimen ($P > 0.5$ for all parameters between the three groups).

At 7-year follow-up, local recurrence has been reported in three patients in group A, one patient in groups B and two patients in group C; this was not statistically significant ($P = 0.86$). Four patients died in group A, two patients died in group B, and three patients were reported dead in group C. This difference between the groups was not statistically significant ($P = 0.83$).

Acute reactions

Erythema was the only acute reaction observed. Grade II erythema was seen in two patients (5%), ten patients (28%) and nine patients (30%) in groups A, B and C, respectively. However, grade III erythema was only noticed in two patients in each of groups B and C. The difference in

Table 1 The patient, tumour and treatment characteristics

	Group A (41 patients)	Group B (36 patients)	Group C (30 patients)	*P* value
Age				
Average ± SD	52 ± 9.6	54 ± 8.8	51 ± 8.8	0.49
Range	25–67	29–68	31–66	0.69
Menopausal				
Premenopausal	17	13	14	
Postmenopausal	24	23	16	0.71
T stage				
T_1	1 (2%)	–	–	
T_2	37 (90%)	32 (89%)	28 (93%)	
T_3	3 (7%)	4 (11%)	2 (7%)	0.91
N stage				
N0	7 (17%)	5 (14%)	4 (13%)	
N1	30 (73%)	29 (18%)	25 (83%)	
N2	4 (10%)	3 (8%)	1 (3%)	0.75
Histology				
Ductal	37 (90%)	34 (6%)	27 (10%)	
Lobular	4 (10%)	2 (6%)	3 (10%)	0.56
Grade				
I	5 (12%)	2 (6%)	1 (3%)	
II	31 (76%)	28 (77%)	26 (87%)	
III	5 (12%)	6 (17%)	3 (10%)	0.85
Hormonal receptor status				
ER or PR +ve	26 (63%)	24 (67)	18 (60%)	
ER and PR −ve	10 (24%)	9 (25%)	10 (33%)	
Unknown	5 (12%)	3 (8%)	2 (7%)	0.66
Adjuvant hormonal				
Yes	31 (76%)	27 (75%)	20 (67%)	
No	10 (24%)	9 (25%)	10 (33%)	0.61
Adjuvant chemotherapy				
Yes	30 (37%)	24 (67%)	24 (80%)	
No	11 (27%)	11 (31%)	6 (20%)	
Chemotherapy and hormonal therapy	20 (49%)	17 (47%)	14 (47%)	0.98
Neoadjuvant chemotherapy				
Yes	2 (5%)	3 (8%)	1 (3%)	
No	39 (95%)	33 (92%)	29 (97%)	0.66

Table 2 Reaction to radiation by group

	Group A (41 patients)	Group B (36 patients)	Group C (30 patients)	*P* value
Acute reactions				
Erythema G I	28(68%)	21(58%)	17(66%)	0.001
G II	2(5%)	10(28%)	9(30%)	
G III	–	2(6%)	2(7%)	
Late reactions				
Pain (GII–GIII)	5(12%)	9(25%)	10(33%)	0.1
Telangiectasis (II–III)	4(10%)	8(22%)	7(23%)	0.23
Fibrosis (GII–GIII)	7(17%)	12(33%)	11 (37%)	0.13
Arm oedema (II–III)	6(15%)	6(17%)	5(17%)	0.96
Pigmentation (II)	7(17%)	5(14%)	6(20%)	0.8

erythema was statistically significant between groups A and B ($P = 0.006$) and groups A and C ($P = 0.003$) but not between groups B and C ($P = 0.988$).

There was no significant correlation between erythema and other patient, tumour or treatment characteristics.

Late reactions

1. Fibrosis: Grades II–III was noticed in seven patients (17%) in group A and twelve patients (33%) and eleven patients (37%) in groups B and C, respectively.
2. Pain: Grades II–III was reported in five patients (12%), nine patients (25%) and ten patients (30%) in groups A, B and C, respectively.
3. Telangectesia: Grades II–III was only seen in four patients (10%) in group A, eight patients in group B (8%) and seven patients (7%) in group C.
4. Arm oedema: Grades II–III occurred in six patients (15%), six patients (17%) and five patients (17%) in groups A, B and C, respectively.
5. Pigmentation: Hypo- or hyperpigmentation was seen in seven patients (17%) in group A, five patients (14%) in group B and six patients (20%) in group C.

Table 2 illustrates the different acute and late reactions.

Treatment interruption

Radiotherapy treatment interruption did not occur in group A, while it was necessary in three patients in each of groups B and C (3%) (Fig. 1).

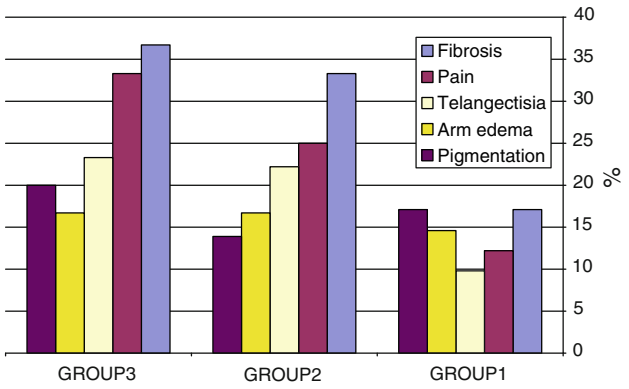

Fig. 1 The incidence of late complications among the studied groups

Discussion

In the adjuvant treatment for breast cancer, the total dose of radiation required to eradicate microscopic disease is 40–50 Gy in 15–25 fractions. This dose may be increased for macroscopic disease or for areas at higher risk of recurrence such as excision areas after breast conservative surgery. It is generally accepted that fraction size significantly over 2 Gy may lead to an increase in delayed side effects observed depending on tissue type, volume and total dose [14].

Among the various fractionation options that have been evaluated in patients with breast cancer, we have chosen 40 Gy given over 15 fractions and 45 Gy given over 17 fractions as an alternative to the standard 50 Gy given over 25 fractions, making a 3-arm study.

There are number of factors which are known to be associated with an increased risk of local recurrence in patients with breast cancer other than the total dose and fractionation of radiation administered. Patient characteristics such as age and menopausal status have been related to breast relapse in some published series. Tumour characteristics such as histology, grade, multifocality, lymphatic space invasion, hormone receptor status and the presence of extensive intraductal disease within and around the invasive tumour, particularly if the resection margins are positive, have all been associated with risk of breast relapse [15–18].

The number of studies evaluating different fractionations after mastectomy is limited.

In a study reported by Wu et al. [18], 149 patients were given conventional radiotherapy 50 Gy in 25 fractions over 5 weeks, compared with 177 patients who received 45 Gy in 15 fractions over 5 weeks. Another 40 patients were treated with 23 Gy in 4 fractions over 17 days. Although this study did not report the radiotherapy reactions, it found no significant difference as regards local control, 5-year survival or 5-year disease-free survival between the 3 fractionations. The locoregional failure rates were 2.7%, 2.8% and 2.4% for the three groups [18].

In another study reported by Goel et al. [19], two fractionation regimens were examined in 108 breast cancer patients who underwent modified radical mastectomy. Patients received either 40 Gy in 17 fractions over 3.2 weeks or 45 Gy in 20 fractions over 4 weeks. There was no significant difference in local control between the two arms with local failure rate of 13% in the 40 Gy in 17 fractions arm and 12.6% in the 45 Gy in 20 fractions arm [18].

Our study demonstrated no significant difference in disease-free survival or overall survival between the groups; however, it is very early to make a conclusion about these parameters at this stage. Further longer follow-up is needed to make a conclusion in this patient population.

In post-conservative breast surgery radiotherapy, the Canadian study by Whelan et al. compared 50 Gy in 25 fractions to 42.5 Gy in 16 fractions over 22 days. The study did not demonstrate any significant difference in cosmesis or local recurrence between both groups. According to this trial, in June 2003, the National Surgical Adjuvant Breast and Bowel Project in Canada has permitted the Canadian formulation as an acceptable alternative to the more traditional 50 Gy in 25 fractions [10, 20].

Another retrospective Canadian study published by Shelley et al. [13] using 41 Gy in 16 fractions daily with no boost has also reported a 5-year breast relapse rate of 3.5% with an overall 5-year survival and breast cancer–specific survival of 87.8 and 92.1 months, respectively. This correlates well with known figures for conventional fractionation [13].

A German randomized trial from Vancouver studying 186 lymph node-negative patients treated with 44 Gy in 16 fractions (2.75 Gy per fraction) also reported a 6% recurrence rate with a follow-up of 6.7 years [21].

A French trial reported by Ortholan et al. [11] used hypofractionation radiotherapy with once weekly fractions up to 5 fractions of 6.5 Gy per fraction to a total dose of 32.5 Gy following surgery. With a median follow-up of 65 months, the long-term local recurrence rate was 2.3% and 5-year disease-free survival was 80% and 5-year overall survival was 71.6% [11].

Yoshiya et al. [22] reported in matched pair analysis of early-stage invasive breast cancer treated adjuvantly with two different fractionation schedules, 40 Gy over 16 fractions were compared to 50 Gy over 25 fractions in 118 patients. The local recurrence rate at 5 years for those treated with 40 Gy was 20.7% and those treated with 50 Gy was 6.8%, respectively, and the difference was not statistically significant. Overall survival was 84% at 5 years for both groups [22].

As regards acute radiation reaction, it is extremely difficult to compare results between trials that have addressed this issue. The different fractionation regimens and scores used in assessing reactions as well as different end-points considered in each trial give an unclear picture of the acute reactions.

In our study there has been significant difference between the three groups regarding erythema with GII-III more encountered in groups B and C ($P = 0.002$).

In a study published by Lopez et al. [23], the acute radiation toxicity using a standard fractionation of 50 Gy over 25 fractions reported erythema in 91.7%, dry desquamation in 29.6% and moist desquamation in 35.2% of 108 patients studied [22]. The frequency of acute reactions becomes more intense when using electron beam. Spierer et al. [24] reported that 52% of their 118 patients developed acute grade 3–4 skin toxicity, with a treatment break required in 33 patients [24].

In the study by Ortholan et al. [11] using 32 Gy in a once weekly 6.5 fractions in an elderly patient population, the erythema noted was mild and observed in less than 30% of patients. These values were lower than those expected after standard breast radiotherapy fractionation and even lower than that observed in other small series that used a similar once weekly regimen [25].

In an Egyptian study published by Taher et al. [26] comparing two fractionations regimen 50 Gy over 25 fractions versus 42.5 Gy over 16 fractions in patients with breast cancer who had undergone breast conservative surgery, there was no significant difference between both groups regarding the acute skin reactions observed ($P = 0.47$).

Shaid etal in a Pakistanin trial has randomized three hundred patients into three arms after mastectomy as follows: Arm A received 27 Gy in 5 fractions (1 week); 35 Gy in 10 fractions (2 weeks), arm B; and 40 Gy in 15 fractions (3 weeks), arm C. Acute skin reactions in arm A were significantly worse in arm A compared to the other two arms (37 versus 28 and 14%, respectively) [27].

Regarding late reactions; in our study, there was no statistically significant difference between the three groups regarding pain, telangectasia, fibrosis, arm oedema or pigmentation. Although there was a trend for pain to be more prevalent in groups B and C, where 9 (25%) and 10 (33%) of patients in both groups, respectively, developed

grade II–III pain compared to 5 patients representing 12% only in group A.

This finding is in agreement with other similar studies reported by Goel et al. [19] and Marcenaro et al. [28] that used different fractionation schedules. It is also worth noting that adding 10 Gy boost to the whole breast radiotherapy with 50 Gy in 25 fractions is associated with increased intensity of telangectasia (reported by Romestaing et al. [29]). Also observed by Hoellar et al. [30]. who used 55 Gy to the whole breast.

In the UK START trial, there has not been any significant difference among the trial arms regarding patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer at 5-year follow-up [31].

It is also of importance to note that in many studies, quantitative measures of late cutaneous effects have been used such as skin thickness by ultrasound [32, 33] skin erythema by optical means [34] and skin water content by dielectric constant [35]. Recently, Gorodetski et al. [36] studied the variations of skin viscoelasticity with a dedicated device [36].

It has also been reported that changing the scoring system from the RTOG/EORTC to the LENT/SOMA scores to assess late skin toxicity has led to an increased rate of observed toxicity [30].

Conclusion

Our study demonstrates the feasibility of delivering a hypofractionation radiotherapy protocol to Egyptian patients with breast cancer following mastectomy. Local breast cancer recurrence rates and late radiation effects are similar to those of the Western populations, but there is a significant increase in acute skin reactions. A national randomized multicentre study is needed to examine this in detail before drawing conclusions about shifting to hypofractionation regimen in the adjuvant treatment for breast cancer. The discrepancy between our results and international results regarding the acute reactions with hypofractionation needs to be further studied.

Conflict of interest The authors have no financial or personal relationship that could inappropriately influence/bias this work.

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