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Post-mastectomy Hypofractionation Radiotherapy in Breast Cancer Patients

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Abstract Background: Post-mastectomy radiotherapy reduces loco-regional recurrence in women with operable breast cancer and improves survival. Conventional fractionated radiotherapy has been limited by patient's compliance, travelling, unplanned interruption and others. Hypofractionated schedule would be more appealing and convenient. The present study was carried out to compare overall survival, disease free survival, loco regional control, and treatment toxicities, in patients treated with conventional fractionated radiotherapy and hypofractionated schedules. Methods: Forty-seven patients with breast cancer (stage T2-4, any N), underwent surgery and received adjuvant systemic treatment and radiotherapy. These patients randomly divided into two groups; conventional fractionated radiotherapy group (N: 22), and hypofractionated radiotherapy group (N: 25). Data of radiation toxicities, and disease relapse in both groups were compared using Chi-square test. Results: The median follow-up was 34 months (range: 13 – 53 months). Four-year overall survival rates were 100% for conventional radiotherapy group and 96% for hypofractionated radiotherapy group, with no significant difference (P value= 0.37). The 4 year disease free survival rate were 81% and 92% for conventional radiotherapy group and hypofractionation radiotherapy group, respectively (p-value= 0.47) and hazard ratio= 0.52 (0.09-2.13). Toxicities were comparable between the both groups. Conclusions: these data showed that hypofractionation 42 Gy radiotherapy in 16 fractions was safe and comparable to conventional fractionation in terms of overall survival, loco-regional tumor control and toxicities. These results need to be tested in large-scale multicenter randomized control trials.

Keywords Breast Cancer; Hypofractionation; Radiotherapy

1. Introduction

Breast carcinoma is the leading cancer in women [1]. Radiation therapy is a part of management in all breast conservation surgeries (BCSs) and for a large percentage of post-mastectomy patients. Conventional fractionated radiotherapy (CF) lasts 6 weeks for post- breast conservative surgery (BCS) patients and nearly 5 weeks for post-mastectomy patients. A number of studies using 1.8 to 2.0 Gy per fraction reported that, 60% to 90% of patients had good cosmetic outcome. [2]

Therefore, a technique that reduces the treatment time by half (3 weeks instead of the present 6 weeks) while maintaining cosmetic and control rates needs to be investigated with great interest. In this context, recent studies examining 13 to 16 fractions of hypofractionated radiotherapy (HF) compared with the present 25 fractions are providing crucial supportive evidence. [3, 4, 5].

Advantages of HF include patient convenience and lower out-of- pocket costs because of fewer travels compared with an extended course of radiotherapy [6]. On the other hand, hypofractionation, with larger radiation dose per fraction increases the possibility of late normal tissue damage [7, 8]. However, the linear-quadratic model predicts that the normal tissue toxicity is not increased when the fraction dose is modestly increased and the total dose is reduced [9]. Results of many trials confirmed that, hypofractionated radiotherapy protocols are as effective as the conventional radiation of 50 Gy in 25 fractions [10, 11] regardless of disease stage or type of breast surgery [12].

Due encouraging data, HF has been used in curative setting in BCSs and yet no enough data about its use in post-mastectomy setting in Egyptian patients. To examine the differences between HF and CF in breast cancer patients, we prospectively evaluated overall survival (OAS), disease free survival (DFS), loco-regional control, and treatment toxicities, of these two schedules in breast cancer patients treated at our center.

2. Patients and Methods

After informed consent and approval of the Ethical Review Board, 47 patients from the clinical oncology department at Sohag University hospital with breast cancer

(proved pathologically and underwent modified radical mastectomy) were included in this study during the period from June 2009 to October 2012. Patients with age >18 years, T1-4/N0-3/M0, and the distance from midline to mid-axillary line <25cm were considered eligible for the study. Patients with history of serious nonmalignant disease (e.g., cardiovascular or pulmonary), severe mental or physical disorder were excluded from the study.

The initial evaluation included chest radiography, abdominal ultrasound, bone scan when indicated, full blood picture, kidney and liver function tests. Patients were randomly assigned to treatment groups: group A of CF (50 Gy/25fractions, 2Gy per fraction and 5 fractions per week) and group B: HF (42.72 Gy/16 fractions, 2.67Gy per fraction and 5 fractions per week).

Radiation technique:

All patients were planned using 2D system; two tangential portals for the chest wall were planned using simulator-based planning. Direct anterior field to the supraclavicular and axillary areas was planned with < 0.5 cm gap junction from tangential fields, superior divergence of tangential portals was eliminated by 5° couch rotation and head of humerus was shielded.

Patients were treated in the supine position and properly positioned using breast wedge. The medial border of the target volume was located at the mid-sternal line, and the lateral border at the mid-axillary line (to include the chest wall and to limit the lung volume at the central plane to less than 2.5-3cm). The superior border was located at a horizontal line drawn through the suprasternal notch- if no supraclavicular lymph node treated, and the inferior border 2cm below the contralateral infra-mammary fold. For determination of the target volume and separation, CT cuts were done and transferred to the planning system. Patients were treated using a 6-MV linear accelerator.

Assessment of treatment outcomes and toxicities

The primary endpoint was radiation toxicities in both groups. Secondary endpoints were OAS and DFS. DFS was defined as the interval from enrollment of patients to the date of first event (relapse, progression, or death from any cause) or to the date of last follow-up. OAS was defined as the interval from enrollment to the date of death from any cause or to last follow-up. Early and late toxicities were scored according to the Radiation Therapy Oncology Group criteria in both groups of patients.

Statistical analysis

The study cutoff point was December 2013. Disease free survival and OAS rates were estimated using Graphed prism program, and compared between the CF and HF groups by the log-rank test. Data of radiation toxicities and disease relapse in the two studied groups were compared using Chi-square test. The p-value reports are two-tailed and an alpha level of 0.05 was used to assess statistical significance.

Table 1. Patients' characteristics in hypofractionated and conventional radiotherapy groups

	Conventional N=22	Hypofractionation N=25	P value
Age			
Mean (SD)	49.41 (11.26)	53.44 (8.05)	0.16
Median (range)	46.50 (35-70)	55 (33-69)	
Performance status			
0	1 (4 %)	4 (16. %)	0.20
1	21 (95 %)	21 (84. 0%)	
Residence			
Sohag	17 (77 %)	18 (72%)	
Qena	5 (22 %)	5 (20 %)	0.61
Luxury	0 (0 %)	1 (4 %)	
Assuit	0 (0 %)	1 (4 %)	
Performance status			
0	1 (4 %)	4 (16 %)	0.20
1	21 (95 %)	21 (84 %)	
Menopausal status			
Pre	10 (45 %)	5 (20 %)	
Peri	2 (9 %)	1 (4 %)	0.10
Post	10 (45 %)	19 (76 %)	
Contraception use			
No	19 (86 %)	20 (80 %)	0.56
Yes	3 (13 %)	5 (20 %)	
Heart disease			
No	21 (95 %)	25 (100 %)	0.28
IHD	1 (4 %)	0 (0 %)	
Liver disease			
No	17 (77 %)	17 (68 %)	0.48
Yes	5 (22 %)	8 (32 %)	

t test was used for quantitative data and chi square was used for categorical data.

3. Results

Forty- seven female patients were eligible with above criteria for randomization, patients were treated initially by MRM followed by systemic treatment then allocated for randomization. Average age for HF patients was 55 years (range 33-69 years) and 46.5 years for CF patients (range 35-70 years); with no statistically significant difference (p=0.16). Both groups were evenly distributed and most of patients were with performance status 1 in either group (95% and 84% for CF and HF respectively). They also had an average travel distance from their home to the treating facility by more than 100 kilometers (28% in HF compared to 22% in CF). No significant differences were found among patients receiving CF compared to HF with regard to laterality (left or right-sided breast), comorbid conditions (lupus, diabetes, cardiac comorbidities) with 5% of CF group having ischemic cardiac disease [Table 1].

Analysis of Disease Characteristics

Regarding disease characteristics, patients receiving HF had smaller tumor size, were less likely to have positive lymph nodes but more likely to have a right breast cancer, all these differences were not statistically significant. Invasive ductal carcinoma was the commonest pathological type in both arms (95% and 88% for CF and HF respectively) while invasive lobular carcinoma was found in two patients of HF group (8%). Stage II disease was the highest in both arms followed by stage III (53%, 56% and 30%, 36% for CF and HF respectively). Patients receiving HF were more likely to have positive hormonal receptors, 68% compared to 54.5% in CF but not statistically significant [Table 2].

Table 2. Comparison between Conventional and Hypofractionation group as regard tumor characteristics

	Conventional N=22	Hypofractionation N=25	P value
Pathology			
IDC	21 (95.45%)	22 (88 %)	
ILC	0 (0 %)	2 (8 %)	0.40
Mixed	1 (4.55%)	1 (4 %)	
Tumor grade			
2	18 (81.82%)	18 (72 %)	0.43
3	4 (18.18%)	7 (28 %)	
Anatomical side			
Left	13 (59.09%)	11 (44 %)	0.30
Right	9 (40.91%)	14 (56 %)	
Stage			
IIA	3 (13.64%)	7 (28 %)	
IIB	9 (40.91%)	7 (28 %)	
IIIA	5 (22.64%)	8 (32 %)	
IIIB	1 (4.55%)	0 (0 %)	0.41
IIIC	1 (4.55%)	1 (4 %)	
TxN0M0	0 (0 %)	1 (4 %)	
TxN1M0	0 (0 %)	1 (4 %)	
TxN2M0	2 (9.09%)	0 (0 %)	
T3NxM0	1 (4.55%)	0 (0%)	
Tumor size			
Mean (SD)	5.20 (1.21)	4.65 (1.36)	0.18
Median (range)	5 (3-7)	4.5 (3-8)	
Number of positive node			
Mean (SD)	2.90 (2.89)	2.12 (2.99)	0.20*
Median (range)	2 (0-10)	1 (0-11)	
Number of node removed			
Median (range)	12 (1-29)	14 (6-33)	0.46
Metastases			
No	22 (100 %)	25 (100 %)	
Estrogen receptor			
Negative	7 (31.82%)	6 (24 %)	0.55
Positive	15 (68.18%)	19 (76 %)	
HER2			
Negative	8 (36.36%)	12 (48 %)	
Positive	3 (13.64%)	2 (8 %)	0.39
Unknown	11 (50 %)	9 (36 %)	
Not assessed	0 (0 %)	2 (8 %)	
Progesterone receptor			
Negative	6 (27.27%)	7 (28 %)	
Positive	13 (59.09%)	16 (64 %)	0.82
Unknown	3 (13.64%)	2 (8 %)	

t test was used for quantitative data and chi square was used for categorical data * Mann-Whitney test was used

Table 3. Comparison between Conventional and Hypofractionation group as treatment characteristics

	Conventional N=22	Hypofractionationb N=25	P value
Chemotherapy			
No	1 (4.55%)	0 (0 %)	
Pre-operative	1 (4.55%)	0 (0 %)	0.31
Yes	20 (90.91%)	25 (100 %)	
Type of chemotherapy			
CMF	2 (9.52%)	1 (4 %)	
CMF/Txl	1 (4.76%)	0 (0 %)	
FAC	12 (57.14%)	8 (32 %)	
FAC/Txl	0 (0 %)	1 (4 %)	
FEC	5 (23.81%)	13 (52 %)	0.22
FEC/Txl	0 (0 %)	1 (4 %)	
FEC/Txt	1 (4.76%)	0 (0 %)	
FEC/Txt-cisp	0 (0 %)	1 (4 %)	
Number of cycles			
4	0 (0.00%)	1 (4 %)	
5	1 (4.76%)	0 (0 %)	0.36
6	20 (95.24%)	24 (96 %)	
Regularity			
Yes	22 (100 %)	25 (100 %)	

Table 4. Comparison between Conventional and Hypofractionation group as regard Radiotherapy (continued)

	Conventional N=22	Hypofractionation N=25	P value
Radiotherapy			
Yes	22 (100 %)	25 (100 %)	
Total dose in cGy			
4272	0 (0 %)	25 (100)	<0.0001
5000	22 (100%)	0 (0 %)	
RT interruption by days			
Mean (SD)	6.2 (13.82)	1.2 (3.04)	0.21*
Median (range)	0 (0-45)	0 (0-12)	
Distance between RT field borders			
Mean (SD)	19.59 (1.87)	20.02 (1.83)	
Median (range)	20 (17-25)	20 (16-24)	0.43
RT time from MRM in days			
Mean (SD)	140.86 (54.40)	166.84 (28.58)	0.03*
Median (range)	147 (25-240)	170 (92-240)	
RT time from chemotherapy			
Mean (SD)	32.76 (27.39)	28.5 (23.97)	0.77*
Median (range)	20 (9-100)	24.5 (6-127)	
Acute toxicity			
No	20 (90.91%)	19 (76 %)	0.18
Skin (grade II dermatitis)	2 (9.09%)	6 (24 %)	
Chronic toxicity			
No	21 (95.45%)	22 (88 %)	0.36
Yes	1 (4.55%)	3 (12 %)	
Hormonal treatment			
No	6 (27.27%)	6 (24 %)	
Yes	15 (68.18%)	18 (72 %)	0.96
Unknown	1 (4.55%)	1 (4 %)	
Type of hormonal treatment			
AI	7 (46.67%)	8 (44.44%)	
TAM	7 (46.67%)	10 (55.56%)	0.51
TAM/AI	1 (6.67%)	0 (0 %)	
Regularity			
No	7 (31.82%)	7 (28 %)	0.78
Yes	15 (68.18%)	18 (72 %)	

t test was used for quantitative data and chi square was used for categorical data *Mann-Whitney test was used .

Analysis of Treatment Characteristics

Treatment analysis revealed only one patients in CF group did not receive any chemotherapy and one received pre-operative chemotherapy. The most frequent regimen used was FAC and FEC either alone or followed by taxanes with a courses of 6 to 8 cycles. As regard radiotherapy, no significant differences were found among patients receiving CF compared to HF with tissue separation as calculated at the beam entrance through chest wall (average 20 cm, and range was 17-25 cm for CF and 16-24 cm for HF). The median time from MRM until start of radiotherapy was 147 and 170 days for CF group and HF group, respectively (p value= 0.03), [Table 3, 4].

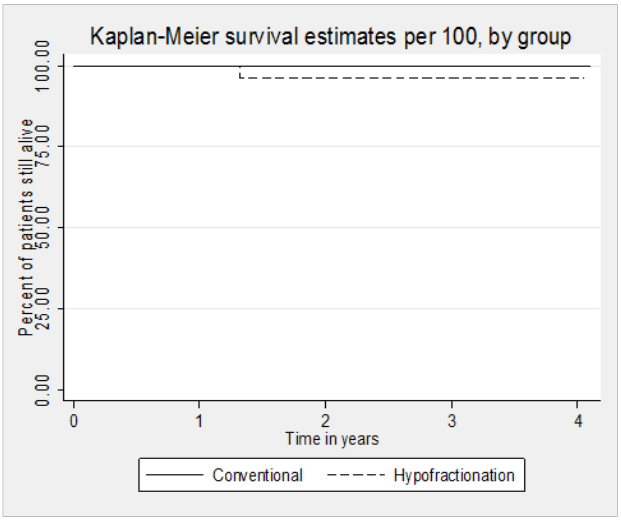

Figure 1. Kaplan-Meier plot of OAS.

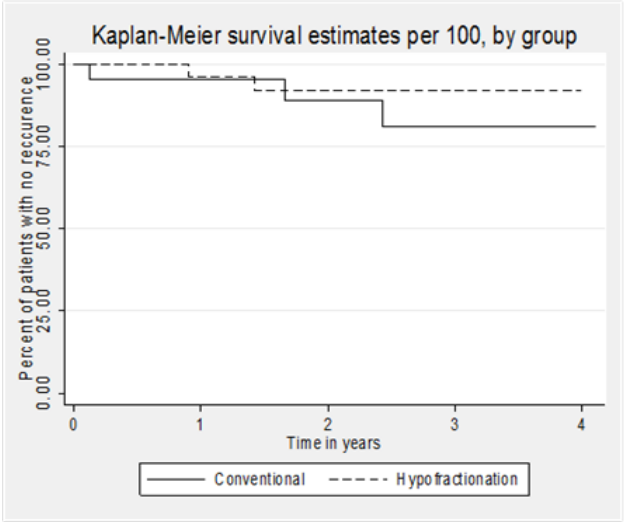

Figure 2. Kaplan-Meier plot of Proportion of patients with disease free survival during period of follow up

Survival and toxicity data analysis

After a median follow up of 34 months (range: 13 – 53 months). Four-year OAS rates for the both groups were 98 %(100% for CF group and 96% for HF group), and with no significant difference (P value= 0.37) [Figure 1]. The 4 year disease free survival rate for both were 87% (81% and 92% for CF group and HF group respectively) (p-value= 0.47) and HR= 0.52 (0.09-2.13). [Figure 2]

As regard treatment toxicity, the incidence of grade I dermatitis were 55% and 52% in patients with HF and CF, respectively and grade II dermatitis were 24% and 9,09%, respectively (p=0.18). Grade II radiation induced pneumonitis (12% versus 4.55, p=0.36) were comparable between HF and CF, respectively.

4. Discussion

Hypofractionation post-mastectomy radiotherapy offers local control and adverse effects comparable to the conventional fractionation with the advantage of reducing workload and cost of treatment. Theoretical and clinical evidence support the hypothesis that, a modest increase in the dose per fraction coupled with a modest decrease in the total dose can be safe and effective way to improve care as the CF [13, 14, 15]

The use of hypofractionated schedules for post mastectomy or regional nodal irradiation is controversial. This is commonly in the UK where there are constraints on budget. The randomized studies, which established the use of hypofractionated radiotherapy, were following breast-conserving therapy and the results may not be applicable to post-mastectomy patients. There have been four large RCTs assessing the outcome of hypofractionated versus standard fractionation RT following BCS, Canadian, START A, START B, Royal Marsden Hospital (RMH) and the Gloucestershire Oncology Centre (GOC) [11, 3, 14,15, 5]. The endpoints of these studies included both the rate of local recurrence, radiotherapy side effects and breast cosmoses, all four trials show that, the rates of local relapse were equivalent or better among patients treated with hypofractionated whole breast RT compared to 50 Gy in 25 fractions. A similar conclusion was reported by a Cochrane review [16].

The current study is prospective in nature, and the two groups (CF and HF) had almost even in distribution of their tumor and clinical characteristics [Table 1, 2], it confirmed the feasibility of hypofractionated radiotherapy in breast cancer patients and comparability in terms of local control, toxicities and OS. Most of breast cancer patients in the CF group were ≥ 35 years of age, while all of HF group, except one were above 45 years of age. Fifty-three% of CF group had stage II and 30% had stage III disease, while 56% of HF group had stage II and 36% had stage III disease. With a median follow up of 34 months (range: 13 – 53 months), four-year OS rates for the both groups were 98 % (100% for CF and 96% for HF group), and with no significant difference (P value= 0.37). The 4 year disease free survival rate for both were 87% (81% and 92% for CF and HF), respectively (p-value= 0.47) and HR= 0.52 (0.09-2.13). Treatment toxicities were comparable between HF and CF

group.

The present study showed that, HF group had comparable 4-year OAS rate with CF group (96% versus 100%, p=0.37). This result is agreement with Whelan, et al 2002 who reported that, there was no statistically significant difference in OAS between HF and CF group [3]. An update of the Canadian trial showed that, results have not changed after a 10- year follow up, when the probability of OAS was similar in HF and CF group (p=0.79) [17]. The START A trial [14], START B trial [15], and Spooner [18], reported also that, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate.

The British Columbia randomized trial of post-mastectomy RT (PMRT) has reported 20-year follow-up among 318 pre- menopausal women with node-positive breast cancer treated with modified radical mastectomy and adjuvant CMF chemotherapy who were randomized to receive loco-regional RT or no further treatment. Patients randomized to PMRT received 37.5 Gy in 16 fractions to the chest wall and 35 Gy in 16 fractions to the regional nodes including a direct field to treat both internal mammary node chains. Initial Ragaz et al. 1997 and their updated analyses have confirmed a significant 10% overall survival advantage for subjects who received PMRT. At a median follow-up of 20.8 years, subjects treated with hypofractionated RT had 16% fewer isolated loco-regional recurrences (74% vs. 90%, p= 0.002) [19].

In the current study, we used HF dose 42.72 Gy with 2.67 Gy per fraction, which is matched with the recommended biologically equivalent dose to 40-60 Gy in 2 Gy per fraction. The loco-regional outcome and survival were comparable to that of CF, the overall incidence of death/100patients =2.13 and incidence of death/100patients in CF= 0 and HF= 4 with P value=0.34. In addition, as regard the loco-regional control, overall incidence of recurrence/100 patients=10.64, with an incidence of recurrence /100 patients in CF=13.64 and HF=8, P value=0.53 and HR = 0.52 (0.09-2.13). None of both groups relapsed locally and the three cases relapsed remotely in either group, (lung, liver and bone for HF group while lung and bone for CF group).

In our study the 4-years DFS rate for both group were 87%, (81% and 92% for CF and HF, respectively p=0.47). Our result is agreement with Shaltout and Abd El Razek 2012, and Eldeep, et al 2012, who reported that, there was no statistically significant difference between the two groups regarding to local control or DFS [20, 21].

In our work, patients with hypofractionated radiation was safe and showed acceptable toxicity rate with 24% incidence of grade II dermatitis and resulted in only 1 week treatment interruption compared with 9% in CF with 10 days interrupted treatment. Grade II radiation induced pneumonitis was found in 12% of HF group and in 4.55% of CF group (p= 0.36). These finding are agreement with Pinipatcharalert, et al 2011 and Shaltout and Abd El Razek 2012, who reported that, acute and late toxicities were comparable in both groups [12, 20].

This study contains small number of patients and comparatively short period of follow up that represent major limitation for the conclusion. Finally, this short (hypofractionated) radiotherapy schedule would be more convenient for patients (especially those coming from remote areas to radiotherapy departments) and for health care providers, as it would increase the turnover in RT departments. The use of a 16-fractions, instead of a 25-fractions regime, would save 900 treatment sessions per 100 patients (2500 - 1600 = 900). This corresponds to an additional 56 (900:16) patients who could be treated with the same number of fractions. This would result in substantial economic benefit as breast cancer patients represent the majority of patients treated in radiotherapy departments [22].

6. Conclusions and Recommendations

Recent randomized trials justify the routine use of HF for adjuvant radiotherapy in women with breast cancer. Post-mastectomy still an open area for extensive research, our study showed that hypofractionated radiation therapy is comparable to that of CF without evidence of inferior local tumor control or higher adverse effects. Hypofractionated radiation therapy can be recommended as safe and effective alternatives to CF for post-mastectomy chest wall radiotherapy. These results need to be evaluated with multicenter and larger sample size.

Conflict of Interests

The authors declare that they have no conflict of interests.

Abbreviations

BCS: breast conservative surgery
CF: conventional fractionated radiotherapy
HF: hypofractionated radiotherapy
OAS: overall survival
DFS: disease free survival
PMRT: post-mastectomy radiotherapy

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