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Postmastectomy Hypofractionated Irradiation in Egyptian patients with Breast Cancer: Zagazig University Experience

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Abstract

Background: Hypofractionated regimen delivers greater than 2 Gy of radiation per fraction while reducing the total cumulative dose through reducing the number of treatment sessions. Radiobiologically, this approach appears to be as effective as the conventional schedule. Financially, this treatment method is useful in reducing breast cancer radiotherapy costs.

Purpose: To evaluate the efficacy and toxicities of postmastectomy hypofractionated schedule compared to conventional fractionated radiotherapy.

Methods: This study included one hundred and forty patients, they were randomly divided into two groups; *Treatment group* [hypofractionated radiotherapy group (N: 62)] received 40 Gy (2.67 Gy per fraction) over 3 weeks and *Control group* [conventional fractionated radiotherapy group (N: 78)] received 50 Gy (2 Gy per fraction) over 5 weeks, the radiation toxicities and local tumor control were compared in both groups.

Results: The local recurrence and distant metastasis in hypofractionated group was 3.2% and 1.6% respectively while in conventional group were 3.8% and 2.6% respectively, grade II acute radiation dermatitis was reported in 22.6% in hypofractionated group versus 7.7% for patients receiving conventional radiotherapy, also, there was increase in the incidence of subcutaneous fibrosis in hypofractionated group in which grade II was reported in 17.7% versus 3.8% in conventional group, otherwise, other toxicities were comparable in both groups.

Conclusion: Hypofractionated radiotherapy was tolerated and has comparable outcome compared to conventional fractionation regarding local tumor control and treatment toxicities.

Keywords: Breast cancer; Hypofractionation; Radiation toxicities

Introduction

Worldwide, breast cancer is increasingly recognized as the commonest cancer in females and a leading cause of cancer-related mortality in women in both developed and developing countries[1]. Radiotherapy is an important part of adjuvant management for large percentage of patients after mastectomy[2]. Conventional radiotherapy after breast surgery requires at least 5 weeks of daily treatment[3]. Treatment of patients with conventional fractionation resulted in 60 to 90% good cosmetic outcome[4]. Data from randomized trials showed that breast cancer tissue is probably similarly sensitive to fraction size as healthy tissue, this means that larger fractions could be safely delivered with better therapeutic outcome[5]. Therefore, this technique results in reduction of the treatment time from five weeks or more to three weeks or less with maintenance of both tumor control and cosmetic rates, also, it has advantage that it was more convenient to the patients and financially better, as it has lower costs due to fewer travels to radiotherapy centers compared with conventional radiotherapy[6]. Radiobiologically, the low α/β ratio which is close to that of late-responding normal tissues could be an indication towards hypofractionation[7-10]. Furthermore, 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, however, it was noted that the possibility of late normal tissue damage was increased with larger fractions of radiation[11,12].

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Patients and Methods

Eligibility

Patients with confirmed breast cancer (stage T3-4, N0-N1), underwent modified radical mastectomy and received adjuvant chemotherapy treatment. Other inclusion criteria include; Age > 30 years; ECOG performance status 0 - 2, separation (midline - mid-axillary line) < 25 cm. Patients were excluded if had non-epithelial breast malignancies (e.g., sarcoma or lymphoma), history of other diseases comorbidities (e.g., pulmonary or cardiovascular), also, patients with severe physical or mental disorder were excluded. Informed consent was given by every patient who participated in this study.

Pretreatment evaluation

Before treatment, patients were subjected to thorough medical history and physical examination, assessment of ECOG performance status, echocardiography for cases with left breast cancer, routine laboratory investigations (full blood count, liver and kidney functions, serum calcium), abdominal ultrasound, chest radiographs or computed tomography (CT) and bone scan.

Treatment schedule

The patients met the inclusion criteria were randomly divided into two groups; hypofractionated radiotherapy group (N: 62) receive 40 Gy (2.67 Gy per fraction) over three weeks and conventional fractionated radiotherapy group (N: 78) receive 50 Gy (2 Gy per fraction) over five weeks.

Endpoints

The primary endpoint was toxicities of radiotherapy in both groups, secondary endpoints were disease relapse and overall survival (OS).

Treatment evaluation and patients' follow-up

Re-evaluation during radiotherapy every week for early toxicities then patients were re-evaluated every month, for late toxicities for at least one year. Skin, subcutaneous, and pulmonary complications were evaluated according to RTOG/EORTC Radiation Morbidity Scoring System[13]. Echocardiography for patients with left-sided breast cancer was done two months after radiotherapy. Disease free survival (DFS) was defined as the interval from enrollment of patients to the date of first event (local recurrence, metastasis) or to the date of the last follow-up. OS was defined as the interval from enrollment to the date of death or to the last follow-up.

Statistical analysis

Data were analyzed by SPSS for windows version 18.0 (SPSS Inc., Chicago, IL, USA) and Med Calc for windows version 13 (Med Calc Software bvba, Ostend, Belgium). Shapiro-Wilk test was used for continuous variables to check the normality while Mann-Whitney U was used to compare two groups of non-normally distributed data. Percent of categorical variables were compared using Chi-square test or Fischer's exact test when appropriate. All tests were two sided.

Results

This study included one hundred and forty patients with breast cancer (stage T3-4, N0-N1) referred to department of clinical oncology and nuclear medicine, faculty of medicine, Zagazig university Egypt, after surgery to receive adjuvant treatment.

Clinicopathological data

The mean age for hypofractionated group was 45.58 years (range 31 -72 years) and 48 years (range 31 -71 years) for conventional group, patients more than 50 years represented 22.6% of patients that received hypofractionated radiotherapy while in conventional group was 33.3% (p = 0.162). Premenopausal women represented 54.8% of hypofractionated group versus 38.5% for conventional group. The right breast was affected in 38.7% of patients in hypofractionated group and 30.8% in conventional group. The most prevalent histopathological grade in hypofractionated group was grade II (45.2%) and (56.4%) in conventional group. Fifty-six patients (90.3%) in hypofractionated group had T3 tumor and in conventional group was 97.4%. N1 (1 to 3 positive axillary lymph nodes) was reported in 38.7% of hypofractionated group and 46.2% in conventional group. Fifteen patients in hypofractionated group had negative hormonal receptor versus twenty-two in conventional group (Table 1).

Table 1: Clinicopathological data of studied groups.

Clinicopathological data	Group I HF (N = 62)		Group II CF (N = 78)		p-value
	No.	%	No.	%	
Age					
Mean ± SD	45.48 ± 10.83		48 ± 10.16		0.060•
Median (Range)	45 (31 – 72)		48 (31 – 71)		
< 50 years	48	77.4%	52	66.7%	0.162§
≥ 50 years	14	22.6%	26	33.3%	
Menopausal status					
Premenopausal	34	54.8%	30	38.5%	0.146§
Perimenopausal	14	22.6%	22	28.2%	
Postmenopausal	14	22.6%	26	33.3%	
Side of breast cancer					
Right breast	24	38.7%	24	30.8%	0.326§
Left breast	38	61.3%	54	69.2%	
Histopathological grade					
Grade I	12	19.4%	12	15.4%	0.417§
Grade II	28	45.2%	44	56.4%	
Grade III	22	35.5%	22	28.2%	
Tumor size (T)					
T3	56	90.3%	76	97.4%	0.139‡
T4	6	9.7%	2	2.6%	
Lymph node (N)					
N0	38	61.3%	42	53.8%	0.377§
N1	24	38.7%	36	46.2%	
TNM stage grouping					

Stage II	38	61.3%	42	53.8%	0.377§
Stage III	24	38.7%	36	46.2%	
Hormone receptor status					
Negative	15	24.2%	22	28.2%	0.593§
Positive	47	75.8%	56	71.8%	

• Mann Whitney U test, § Chi-square test, ‡ Fischer's exact test, p < 0.05 is significant

Systemic treatment

All studied patients received systemic treatment in the form of adjuvant chemotherapy. Most of the studied patients received FAC (5-fluoruracil, doxorubicin, cyclophosphamide) regimen, 71% in hypofractionated group and 66.7% in conventional group. After radiotherapy, most of the studied patients received tamoxifen, 64.5% in hypofractionated group and 60.3% in conventional group

Table 2: Systemic treatment.

Systemic treatment	Group I HF (N = 62)		Group II CF (N = 78)		p-value
	No.	%	No.	%	
Chemotherapy regimen					
FAC	44	71%	52	66.7%	0.857§
FEC	8	12.9%	12	15.4%	
AC-Taxol	10	16.1%	14	17.9%	
Hormonal treatment					
Not received	15	24.2%	22	28.2%	0.593§
Received	47	75.8%	56	71.8%	
Tamoxifen	40	64.5%	47	60.3%	0.869§
AI	7	11.3%	9	11.5%	

Acute radiation dermatitis was noted in hypofractionated group, where, grade II was reported in 22.6% versus 7.7% for patients receiving conventional radiotherapy (p < 0.001). Only one patient in hypofractionated group had grade II acute pneumonitis while three patients in conventional group with statistically insignificant difference (p = 0.088)

Table 3: Acute radiation complications.

Acute radiation complications	Group I HF (N = 62)		Group II CF (N = 78)		p-value
	No.	%	No.	%	
Acute dermatitis					
G0	10	16.1%	58	74.4%	< 0.001§
GI	38	61.3%	14	17.9%	
GII	14	22.6%	6	7.7%	
Acute pneumonitis					
G0	54	87.1%	73	93.6%	0.088§
GI	7	11.3%	2	2.6%	
GII	1	1.6%	3	3.8%	

Chronic radiation complications

Grade II chronic radiation dermatitis in hypofractionated group versus conventional group was 1.6% versus 2.6% respectively (p = 0.792). Grade II chronic pneumonitis had not occurred in any patients received hypofractionated radiotherapy versus one patient in conventional group. There was a significant difference between hypofractionated group and conventional group regarding subcutaneous fibrosis, as grade II reported in 17.7% versus 3.8% respectively (p = 0.007). Regarding cardiac toxicities, there is statistically insignificant difference between the two groups (p = 0.840).

Table 4: Chronic radiation complications.

Chronic radiation complications	Group I HF (N = 62)		Group II CF (N = 78)		p-value
	No.	%	No.	%	
Chronic dermatitis					
G0	59	95.2%	72	92.3%	0.792§
GI	2	3.2%	4	5.1%	
GII	1	1.6%	2	2.6%	
Chronic pneumonitis					
G0	58	93.5%	75	96.2%	0.361§
GI	4	6.5%	2	2.6%	
GII	0	0%	1	1.3%	
Subcutaneous fibrosis					
G0	43	69.4%	70	89.7%	0.007§
GI	8	12.9%	5	6.4%	
GII	11	17.7%	3	3.8%	
Cardiac toxicities	**(N = 38)**		**(N = 54)**		
No	34	89.5%	49	90.7%	0.840§
Yes	4	10.5%	5	9.3%	

Pattern of failure

Local recurrence occurred in two patients (3.2%) at the site of the scar and distant metastasis in one patient (1.6%) in hypofractionated group, three local recurrences (3.8%) occurred and two patients (2.6%) with distant metastases among conventional group

Table 5: Local recurrence and distant metastasis.

Local recurrence and distant metastasis	Group I HF (N = 62)		Group II CF (N = 78)		p-value
	No.	%	No.	%	
Local recurrence	2	3.2%	3	3.8%	0.908§
Distant metastasis	1	1.6%	2	2.6%	
Disease free	59	95.2%	73	93.6%	

Survival

After a median follow-up of 30 months (range: 12 – 45 months), three-years (OS) rates were 95.1% for hypofractionated radiotherapy group and 98.7% for conventional radiotherapy group, with no significant difference (p-value = 0.759). The 3 years disease free survival (DFS) rate was 95.2% for treatment group and 93.6% for control group (p-value = 0.908)[14].

Discussion

For patients with breast cancer underwent total mastectomy, there are several studies demonstrated that postmastecto-

my radiotherapy reduced locoregional recurrence (LR) as well as improved disease-free survival (DFS) and overall survival (OS)[15,16]. Hypofractionation was considered in several randomized trials to be as safe and effective as conventional fractionation with therapeutic and financial advantages[17]. In the current study, the median age was 45 years in treatment arm and 48 years in control arm (p = 0.060). This results are in agreement with Kumbhaj *et al* study in which the median age was 47 years, Ali and Abd AlMageed study in which the median age was 46.6 years in conventional arm and 55 years in hypofractionation arm[18,24]. Regarding menopausal status, premenopausal women represented 54.8% of hypofractionated group versus 38.5% for conventional group, these results were slightly different from Ali and Abd AlMageed study where premenopausal patients represented 20% of hypofractionation arm and 45% of conventional arm while postmenopausal patients were 76% and 45% in both groups respectively, these results were different from that in Kumbhaj *et al* study, in which postmenopausal women represented 60% and 56% in hypofractionation and conventional arms respectively, also, 75.8% of hypofractionated group had positive hormonal receptor versus 71.8% in conventional group, this is in agreement with Ali and Abd AlMageed study where hormone positive patients represented 76% in hypofractionation arm and 68% in conventional arm. Fifty-six patients (90.3%) in hypofractionated group had T3 tumor and in conventional group was 97.4%. From 1 to 3 positive axillary lymph nodes was reported in 38.7% of hypofractionated group and 46.2% in conventional group. The three-years OS rates was 95.1% in hypofractionated radiotherapy group and 98.7% in conventional radiotherapy group, with insignificant difference (p-value = 0.759). Also, three-years DFS rate was 95.2% and 93.6% for conventional radiotherapy group and hypofractionation radiotherapy group, respectively with insignificant difference (p-value = 0.908). Treatment toxicities were comparable between both groups, these results are the same as that of Whelan *et al* who reported that there was no statistically significant difference in OS between hypofractionated and conventional group and that of Canadian trial update[19]. The same results were achieved in START A, B trials[7,8] and Spooner study[20] in which there was no evidence that hypofractionated regimens were associated with a worse overall survival rate. The incidence of recurrence was 3.2% in hpofractionated group and 3.8% in conventional one, (p = 0.908), but, three-years DFS rate were 95.2% and 93.6% for treatment group and control group respectively (p-value= 0.908), these results are the same as that obtained by Eldeep et al and Shaltout and Abd El Razek, who reported in their studies that there was statistically insignificant difference between the two groups regarding DFS and local control[21,22]. In our study, acute radiation dermatitis was higher in hypofractionated group, as grade II was reported in 22.6% versus 7.7% for patient receiving conventional radiotherapy (p < 0.001), this results was in accordance with Kumbhaj *et al* study, who reported that grade I, II and III reactions were 20%, 50% and 20% respectively in hypofractionation arm versus 30%, 45% and 5% in conventional fractionation arm respectively with no significant difference between both arms, however, Ali and Abd AlMageed in their study showed significant difference between both arms regarding skin toxicity in favor of hypofractionated arm. Only one patients in hypofractionated group had grade 2 acute pneumonitis while three patients in conventional group with non-significant difference (p = 0.088). In Ali and Abd AlMageed study, grade 0 radiation induced pneumonitis was 87.8% in treatment arm vs 81.5% in control arm while grade 1 was 9.4% vs 11.1% respectively with no significant difference between both arms. Grade II chronic radiation dermatitis in hypofractionated group was 1.6% versus 2.6% in conventional group respectively (p = 0.792). Grade II chronic pneumonitis had not occurred in any patients received hypofractionated radiotherapy versus one patient in conventional group, there was a significant difference between hypofractionated group and conventional group regarding subcutaneous fibrosis where grade II was reported in 17.7% versus 3.8% respectively (p = 0.007), these finding are reported also in Pinipatcharalert *et al* and Shaltout and Abd El Razek studies[21,23].

Conclusion and Recommendation

Post mastectomy hypofractionated radiotherapy is well tolerated and has local tumor control, DFS and OS rates comparable to conventional fractionation without evidence of higher adverse effects. So, hypofractionated radiotherapy can be considered as safe and effective alternative to conventional fractionation for patients with breast cancer and this should confirmed in meta analysis and phase III future studies.

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