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ORIGINAL ARTICLE

Comparing Late Toxicity of Conventional versus Hypofractionated Postmastectomy Radiotherapy: Retrospective Analysis

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ABSTRACT

Background: Breast cancer (BC) is predicted to be the most common malignancy for Egyptian women, representing 37.7% of all cancers in females and 29.1% of cancer-related mortality. The present work aims to compare the late toxicity of conventional versus hypofractionated postmastectomy radiotherapy.

Methods: This retrospective randomized cross-section investigation was conducted on 154 cases who received hypofractionated (HF) and conventional fractionated (CF) radiotherapy (RT) at the Clinical Oncology Department of Zagazig University Hospitals. Data was obtained from patients' files and follow-up toxicity sheets; time of follow up from January 2018 to March 2021. The studied cases were divided into Group I: 64 cases received conventional radiotherapy. Group II: 90 cases received hypofractionated radiotherapy.

Results: There was no substantial variance between the studied groups in the number of dissected lymph nodes, frequency, neoadjuvant or adjuvant chemotherapy, frequency of Herceptin intake, or frequency and type of hormonal therapy. There was a remarkable elevation in the degree of skin, subcutaneous, and lung among HF- the postmastectomy RT (HF-PMRT) group compared to the CF-PMRT group. At the same time, Brachial plexopathy showed a statistically significant increase in its degree among the CF-PMRT group compared to the HF-PMRT group.

Conclusions: Our research indicated that HFRT therapy is comparable to CFRT without evidence of inferior local tumor control or increased side effects. It is possible to recommend HFRT as an alternative to HFRT for PM chest wall RT because it is both safe and effective.

Keywords: Late Toxicity ;Hypofractionated; Postmastectomy ;Radiotherapy

INTRODUCTION

Breast cancer (BC) has the most significant prevalence and comes second in cancers with a high mortality rate in women, based on the United States cancer statistics [1].

BC is the most common malignancy for Egyptian women, representing 37.7% of all cancers in females and 29.1% of cancer-related mortality [2]. The term "early BC" refers to a stage of cancer that is potentially curable. Long-term survivors of early BC who had systemic therapy (chemotherapy, hormonal, targeted therapy, and local radiation) following surgery account for roughly 80% of cases [3]. Adjuvant radiation therapy (RT) is a significant part of the multimodal therapy of BC cases. Early-stage patients are frequently managed with breast-conserving surgery (BCS), then adjuvant RT, with systemic medications [4]. It is widely acknowledged that postmastectomy RT (PMRT) enhances long-term results by lowering local recurrence and death rates from BC [5]. Hypofractionated RT (HFRT) schemes with fraction sizes greater than 2Gy have been employed in the management of breast cancer since the 2000s. Although this radiation regimen has

the advantage of cutting treatment duration in half, late toxicity (LT) is worse following radiobiological evidence; the normal breast and underlying tissues are susceptible to the fraction size, total dose given, and volume irradiated [6]. After breast-conserving surgery (BCS), a 42.5Gy in 16 fractions regimen improves locoregional control, overall survival (OS), and cosmetic results for early-stage BC cases. Historically, the standard RT dose for PMRT is 50 Gy divided into 2 Gy daily portions over five weeks [7].

As a result, even slightly greater fractional radiation doses can cause significant late damage. Considering worries regarding LT, numerous major studies have shown that HFRT following BCS is entirely safe; at a 10-year follow-up, the updated findings of a landmark Canadian experiment showed that outcomes were comparable to the usual radiation regimen [8].

The present work aims to achieve better treatment with the least dose of radiotherapy.

METHODS

Patients: This retrospective randomized cross-section study was conducted on 154 cases who received HFRT and conventional fractionated (CF) RT (CFRT) at the Clinical Oncology Department of Zagazig University Hospitals during the study period (2018-2021) were included in a comprehensive sample. Data was received from case files and follow-up toxicity sheets. The studied cases were divided into Group I: 64 cases received conventional radiotherapy. Group II: 90 cases received hypofractionated radiotherapy. Verbal and written informed consent was collected from all instances after explaining the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB#9476/17-4-2022).

Cases with the following criteria were included: female patient, age > 18 years of age, with invasive carcinoma of the breast, PM, early stage, and locally advanced disease.

Cases with the following characteristics were excluded: cases with positive margins, previous cancer, distant metastases, and BCS.

Methods: The following variables were anonymously extracted from the patient medical record and then transcribed into an Excel spreadsheet. LT was assessed according to The RT Oncology Group (RTOG) [9]/ European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema for skin, subcutaneous tissue, lung, and heart for all: G0-No symptom to G5 –Death. ***Time of follow up***: from January 2018 to March 2021.

Skin: Was evaluated at least six months after the end of RT. The evaluations were conducted by visual inspection and palpation of the chest wall associated with the operation scar, and the findings varied from grade 0 (no reaction) to grade 4 (severe reaction) (G0-4). G1: little atrophy, pigmentation alterations, and little hair loss. G2: patchy atrophy, moderate telangiectasia, and complete hair loss. G3: significant atrophy and severe telangiectasia. G4: Ulceration.

Subcutaneous tissue: LT was evaluated at least six months after the end of RT. The evaluations were performed by observing and palpating the chest wall near the operation scar, and the findings varied from grade 0 (no reaction) to grade 4 (severe reaction). G1: mild ulceration (fibrosis), subcutaneous fat loss. G2: asymptomatic moderate fibrosis. G3: severe induration with subcutaneous tissue loss. G4: necrosis.

Heart: The degree of cardiac toxicity ranges from asymptomatic or mild symptoms to severe heart failure. In our investigation, all cases received echocardiography (ECG) before and after RTH. Cases with an ejection fraction (EF) of less than 55% were eliminated. G1: symptoms are either asymptomatic or mild. At rest, transient T wave inversion and an ST sinus tachy of 110. G2: Moderate angina with exertion, normal heart size, minor pericarditis, persistent aberrant Twave and ST alterations, and low ORS. G3: pericardial effusion, severe angina, constrictive pericarditis, moderate heart failure (HF), and severe constrictive pericarditis. G4: tamponade, severe HF, and severe constrictive pericarditis.

Lung: The severity of radiation pneumonitis (RP) ranges from a radiographic result with no clinical symptoms to a life-threatening condition necessitating hospitalization. Therefore, a CT lung scan was conducted before treatment and six months after RT. G1: Asymptomatic or moderate symptoms (dry cough with a modest radiographic appearance). G2: Moderate symptomatic fibrosis or pneumonitis, low-grade fever, patchy radiographic appearance. G3: Severe symptomatic fibrosis or pneumonitis with extensive radiographic abnormalities. G4: Severe respiratory insufficiency; maintain oxygen-assisted breathing.

Arm lymphedema: Lymphedema staging was done according to the International Society of

Lymphology (ISL) [10]. Stage 0 is subclinical, with no visible edema despite alterations in the lymphatic system. Stage 1 is the initial stage of swelling. Stage 2 has persistent swelling. Stage 3 involves hard, fibrotic tissue with concomitant skin abnormalities.

Brachial plexopathy: The severity of brachial plexus injuries can be evaluated by the patient's symptoms and by physical examination. The intensity varies from mild sensory defect to incapacitation. This was assessed by modified LENT SOMA scales [11]. G1: mild sensory deficiency, no pain, no therapy needed. G2: Moderate sensory deficiency, bearable pain, and mild arm weakness. G3: Continuous parathesis with partial paresis; medication for pain is needed. G4: Complete paresis, severe pain, and muscular atrophy necessitating daily pain treatment.

Rib fraction: Yes or No.

Shoulder stiffness: Yes or No.

STATISTICAL ANALYSIS

Data was analyzed statistically with IIBM SPSS, version 24.0 (IBM Corporation, Armonk, New York). Quantitative data were described utilizing the mean, standard deviation, and range, while qualitative data were expressed using the number and percentage. The t-test was used to compare two groups of normally distributed variables. When applicable, the Mann–Whitney U test was used when comparing two means (for abnormally distributed data). The Chi-square test was employed to compare percentages of categorical variables. A p-value < 0.05 is considered significant.

RESULTS

The mean age of the cases was 54.23±10.28 years. According to the type of radiotherapy, the studied cases were divided into two groups: Group I: 64 cases received conventional radiotherapy. Group II: 90 cases received hypofractionated radiotherapy. Table (1) shows that females who received HF radiotherapy are older and more frequently postmenopausal but without statistical significance differences versus CF-received females. The groups had non-remarkable variance concerning histopathology, laterality, and extravascular or lympho-vascular invasion.

There were no substantial variances between the groups in ER, PR, or HER-2 receptors, but there was a statistically significant increase in KI67 among HF-PMRT cases compared to CF-PMRT cases (Table 2). Concerning tumor characteristics, there were no statistically significant differences between the studied groups in grades, stage, size, or LN (Table 3). Regarding treatment options, there were no statistically significant differences between the studied groups in the number of dissected lymph nodes (LN), frequency and neoadjuvant or adjuvant chemotherapy, frequency of Herceptin intake, or frequency and type of hormonal therapy (Table 4).

There was no substantial variance between the studied groups at the site of radiotherapy (Table 5).

Table (6) shows no remarkable variation between the studied groups in heart toxicity and arm lymphedema. No cases were reported, including rib fracture and shoulder stiffness. There was a substantial elevation in the degree of skin, subcutaneous, and lung among the HF-PMRT group compared to the CF-PMRT group. At the same time, Brachial plexopathy showed a statistically significant increase in its degree among the CF-PMRT group compared to the HF-PMRT group.

Table (1): Age group and tumor data of the studied cases

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
		No	%	No	%		
Age group:	< 35 years	2	3.1	0	0		
	35-50 years	30	46.9	35	38.9	4.2	0.12
	>50 years	32	50	55	61.1		
Menopause:	Pre	26	40.6	27	30	1.87	0.17
	Post	38	59.4	63	70		
Histopathology:	IDCA	62	96.9	82	91.1	3.69	0.30
	ILCA	0	0	4	4.4		
	Mixed	2	3.1	3	3.3		
	Other	0	0	1	1.1		

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
Laterality:	Right Left	22 42	34.4 65.6	45 45	50 50	3.72	0.053
Extracapsular invasion:	No Yes	41 23	64.1 35.9	52 38	57.8 42.2	0.62	0.43
Lympho-vascular invasion	No Yes	27 37	42.2 57.8	39 51	43.3 56.7	0.02	0.89

χ^2:Chi square test

Table (2): Receptors examination results among the studied groups

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
		No	%	No	%		
ER:	-ve +ve	14 50	21.9 78.1	17 73	18.9 81.1	0.21	0.65
PR:	-ve +ve	22 42	34.4 65.6	27 63	30 70	0.33	0.57
HER-2:	No Yes	43 21	67.2 32.8	70 20	77.8 22.2	2.15	0.14
KI67:	Median Range	14 2-50		27 1-62		**MW** **2.01**	**0.04***

χ^2:Chi square test MW: Mann Whitney test *: Significant (P<0.05)

Table (3): Tumor characters among the studied groups

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
		No	%	No	%		
Grade:	G1 G2 G3	2 36 26	3.1 56.3 40.6	1 48 41	1.1 53.3 45.6	1.05	0.60
Stage:	Stage 1 Stage 2 Stage 3	3 23 38	4.7 35.9 59.4	8 31 51	8.9 34.4 56.7	1	0.61
Size:	T1 T2 T3 T4	4 49 8 3	6.3 76.6 12.5 4.7	15 52 19 4	16.7 57.8 21.1 4.4	6.89	0.08
LN:	N0 N1 N2 N3	7 15 15 27	10.9 23.4 23.4 42.2	20 20 18 32	22.2 22.2 20 35.6	3.38	0.34

χ^2:Chi square test

Table (4): Treatment data among the studied groups

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		t	P
Number of dissected LN:	Mean ± Sd Range	19.55±5.58 8 - 35		18.7 ± 7.04 3 - 38		0.80	0.43
Variable		**No**	**%**	**No**	**%**	χ^2	**P**
NA chemotherapy:	No AC + Taxol	57 7	89.1 10.9	83 7	92.2 7.8	0.45	0.50
Adj chemotherapy:	No Anthracyclin AC + taxol	7 2 55	10.9 3.1 85.9	9 1 80	10 1.1 88.9	0.85	0.66
Herceptin:	No Yes	44 20	68.8 31.3	70 20	77.8 22.2	1.59	0.21
Hormonal:	No Tam AI TAM+Zoladex	14 14 29 7	21.9 21.9 45.3 10.9	17 18 47 8	18.9 20 52.2 8.9	0.75	0.86

SD: Standard deviation t: Independent t test χ^2:Chi square test

Table (5): Radiotherapy data among the studied groups

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
		No	**%**	**No**	**%**		
Site:	**Chest wall** **CW+SC** **CW+SC+Axilla**	4 54 6	6.3 84.4 9.4	8 77 5	8.9 85.6 5.6	1.1	0.58

χ^2:Chi square test

Table (6): Late toxicity among the studied groups

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
		No	**%**	**No**	**%**		
Skin:	G1 G2 G3	24 39 1	37.5 60.9 1.6	28 50 12	31.1 55.6 13.3	**6.78**	**0.03**
Subcutaneous tissues:	G 1 G 2	27 37	42.2 57.8	23 67	25.6 74.4	**4.72**	**0.03**
Lung:	G 1 G 2	53 11	82.8 17.2	59 31	65.6 34.4	**5.62**	**0.02**
Heart:	G 1 G 2	49 15	76.6 23.4	75 15	83.3 16.7	1.09	0.30
Arm lymphedema:	Mild Moderate Marked	33 29 2	51.6 45.3 3.1	34 49 7	37.8 54.4 7.8	3.64	0.16
Brachial plexopathy:	G 0 G1 G2 G3	7 32 18 7	10.9 50 27.7 10.9	6 53 31 0	6.7 58.9 34.4 0	**11.66**	**0.009**

Variable		Group I (CF-PMRT) (n=64)		Group II (HF-PMRT) (n=90)		χ^2	P
Rib fracture:	No Yes	64 0	100 0	90 0	100 0	--	---
Shoulder stiffness:	No Yes	64 0	100 0	90 0	100 0	--	---
χ^2:Chi square test							

DISCUSSION

BC has the highest prevalence rate and is responsible for the second-largest number of fatalities among all cancers that affect women in the United States, according to cancer statistics from 2019 [12].

It is common knowledge that postmastectomy radiation, also known as PMRT, improves long-term results in BC cases who had mastectomy by lowering the risk of local recurrence and overall cancer mortality. The lower total dosage administered in a smaller fraction number could potentially yield rates of tumor control and healthy tissue damage that are comparable to those achieved using a typical fractionation schedule.

Our investigation was conducted on 154 females with BC coming to the Oncology department from 2018 to 2022 to receive post-mastectomy radiotherapy. The mean age of the cases was 54.23±10.28 years. According to the type of radiotherapy, the studied cases were divided into two groups: Group I: 64 cases received conventional radiotherapy. Group II: 90 cases received hypofractionated radiotherapy.

The current study illustrated that females who received HF radiotherapy are older and more frequently post-menopausal, but without statistical significance differences versus CF-received females. Rastogi et al. [12] reported that most cases were < 50 years old, had ECOG PS 1, and came from an urban background. In disagreement with our results, Chitapanarux et al. [13] assessed the long-term outcomes of CF and HF PMRT in terms of disease-free survival (DFS), local recurrence-free survival (LRRFS), and overall survival (OS). When comparing the two timelines, the cases in the HF-PMRT group were much younger. In a study by Abo Agag et al. [14], 47 females were first treated with Modified radical mastectomy (MRM), then systemic medication, and then allocated and randomized. The evaluation of case data demonstrated that HF cases had a higher average age (55 years HF; 46.5 years CF; with no remarkable variance (p = 0.16)).

The present investigation showed no substantial variances between the groups in histopathology, laterality, extravascular, or lympho-vascular invasion. This study demonstrated no remarkable variations between ER, PR, or HER-2 receptor groups. However, there was a statistically significant increase in KI67 among HF-PMRT cases compared to CF-PMRT cases. According to the findings of Rastogi et al. [12], there were no statistically significant variations in ER, PR, or HER-2 receptors between the investigated groups.

This study illustrated no substantial variations between the grades, stage, size, and LN groups.

In both groups, Rastogi et al. [12] revealed that most of the tumors were G3 infiltrating ductal carcinomas in the upper outer quadrant. The median number of LN dissected in the CF group was 14 and 15 in the HF group, respectively, with a median of 2 positive LN in both groups. Stage IIB cancers of the left breast were more prevalent in the CF group than in the HF group.

Chitapanarux et al. [13] revealed that the HFPMRT group was much younger (stages I and II), had less chemotherapy, had less regional nodal irradiation, and received a higher RT dose than the CF-PMRT group.

Regarding disease characteristics, Abo Agag et al. [14] showed that individuals who received HF had smaller tumors, had less probability of having positive LNs, and were a high probability of having the correct BC; however, these changes were not remarkable. Invasive ductal carcinoma was the most common histopathological form in CF (95%) and HF (88%). Stage II disease had the highest prevalence in CF (53%) and HF (56%), followed by stage III (30% and 36% for CF and HF, respectively). Cases receiving HF had a higher probability of having positive hormone receptors (68%) than CF (54.4%), although this was not substantial.

Respecting treatment options, there were no statistically significant differences between the studied groups in the number of dissected lymph nodes (LN), frequency and neoadjuvant (NA) or

adjuvant chemotherapy (ACT), frequency of Herceptin intake or frequency and type of hormonal therapy.

Regarding treatment protocol, Rastogi et al. [12] revealed that the supraclavicular fossa was irradiated in 84% of individuals with CF and 86% in cases with HF. NACT, ACT, and hormonal therapy were provided to 58%, 96%, and 58% of cases with CF and 52%, 98%, and 54% of cases with HF, respectively.

In a study by Abo Agag et al. [14], only one CF case did not receive CT, and one had it before surgery. The most commonly utilized regimen was FAC and FEC, either alone or combined with taxanes during a six-cycle period. There were no remarkable changes between the cases who had radiation. Tissue separation at the beam passage through the deep chest wall was used to compare CF with HF (CF and HF averaged 20 cm, with CF ranging from 17 to 25 cm and HF from 16 to 24 cm). There was a remarkable variance in the time duration from MRM to RT, with median times of 147 and 170 days ($p = 0.03$).

The current study reported that all the studied cases received 2D-RT. In addition, there was no remarkable variance between the studied groups at the site of radiotherapy.

Our study showed no substantial variation between the groups in heart toxicity and arm lymphedema. No cases were reported with 2ry malignancy, rib fracture, and shoulder stiffness. There was a substantial elevation in the degree of skin, subcutaneous, and lung among the HF-PMRT group compared to the CF-PMRT group. At the same time, Brachial plexopathy showed a statistically significant increase in its degree among the CF-PMRT group compared to the HF-PMRT group. LT is a concern even though this radiation regimen halves the total time needed for therapy. According to the radiobiological findings, healthy breast tissue and the tissues that comprise the underlying structure are sensitive to the fraction size, irradiation volume, and total received RT dosage [15].

Chitapanarux et al. [13] revealed that toxicity evaluations were assessed entirely in up to 98% of the second case-cohort for each therapy group.

The LT findings for all 1640 cases acquired from their records are summarized in Chitapanarux et al. [13] study. They revealed that the HF-PMRT group had considerably more LT in the skin, lung, and subcutaneous tissue than the CF-PMRT group. The prevalence of LT in LN and heart was comparable between the two therapeutic regimes. They then noticed LT in the second cohort of 937 eligible BC cases assessed for LT after a median follow-up time of 106.3 months.

Chitapanarux et al. [13] showed that the rate of severe LT (G2 or higher) was meager in both regimens. The study demonstrated remarkable variances in late RTOG $G \geq 2$ skin (4% vs. 1%) and subcutaneous tissue (7% vs. 2%) between the HFPMRT and CF-PMRT groups. In both groups, the prevalence of G2 late RTOG lung toxicity (persistent symptoms needing symptomatic therapy) was 1% or less. While EORTC lung LT was measured using imaging, the prevalence of $G \geq 2$ was elevated in the CF-PMRT group. The Egyptian study by Eldeeb et al. [15] reported $G \geq 2$ skin fibrosis in 17% of the CFRT group, 33% in the 45 Gy in the 17 fractions group, and 37% in the 40 Gy in the 15 fractions group.

Conversely, Kouloulias et al. [16] reported no $G \geq 2$ skin LT cases in either the HF-PMRT or CF-PMRT groups. Wang et al. [17] revealed that G3 skin LT was reported in fewer than 1% of the HF-PMRT group and 0% in the CF-PMRT group. Rastogi et al. [12] revealed that CF-PMRT and HF-CRT had a 4% risk of chronic dermatitis $G \geq 2$.

None of these investigations revealed a remarkable variation between the groups. A previous report by Pinitpatcharalert et al. [18] showed that $G \geq 2$ skin LT of 9% in the CF-PMRT group and 10% in the HF-PMRT group, concluding that skin LT was equivalent between two therapeutic arms.

Furthermore, the prevalence of $G \geq 2$lymphedema was over 25% in the three distinctive HFPMRT regimens Shahid et al. [19] study. The trial in Morocco by Bellefqih et al. [20] showed that only 5.8% of cases were evaluated for $G \geq 2$arm edema. Khan et al. [21] reported that a prospective evaluation of 69 cases employing 3.3 Gy with 11 fractions via 3D conformal RT (CRT) revealed that 4.5% of cases experienced $G \geq 2$arm edema. Eldeeb et al. [16] also showed that grade 2 or > two lymphedema was observed in the CF and two HF groups at 15, 17, and 17%, with no remarkable variance. Kouloulias et al. [17] showed that neither the CF nor the HF groups developed grade 2 lymphedema during the research duration. In addition, there was a remarkable variation for grade 1-3 lymphedema, which was 21 and 20% in the CF and HF groups, respectively. Rastogi et al. [12] also reported no substantial variation in the rate of $G \geq 2$ greater lymphedema between CFRT and HFRT. The prevalence of $G \geq 2$ lymphedema was extremely rare in the cases from Greece by Kouloulias et al. [17], in

which 15% of cases received sentinel LN biopsy and in the study by Khan et al. [21], which avoided level I axillary RT.

Rastogi et al. [12] revealed that the locoregional outcome and survival rates were comparable across groups. The LN recurrence location was the supraclavicular LN, while distant metastatic sites included the brain (3%), lung, bone, and liver (1%). Neither of the cases acquired a secondary cancer, including cancer of the opposite breast. No deaths were detected until the last follow-up in all groups.

CONCLUSIONS

Recent randomized trials support the practice of using HF as a routine adjuvant RT treatment in BC cases who are female. Our research indicated that HFRT is comparable to CFRT without evidence of inferior local tumor control or increased side effects. It is possible to recommend HFRT as an alternative to HFRT for PM chest wall RT because it is both safe and effective.

Conflict of Interest: None**.**

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