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Radiotherapy in Breast Cancer in Single Institute Study experience: comparing Extreme Hypofractionation to Moderate Hypofractionation

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Original Article

ABSTRACT

Background: *Breast carcinoma is a common malignancy in Iraq. Radiotherapy is an essential line of breast cancer treatment. Nationally, hypofractionation radiotherapy has successfully implemented in the management of breast cancer.* ***Aim of study:*** *To compare the efficacy and safety of extreme hypofractionation with moderate hypofractionation radiotherapy in breast cancer management.* ***Patients & Methods****: A retrospective review was conducted on medical records for one hundreds of women with breast cancers in different stages, whose treated with two different hypofractionated radiotherapy regimens in Zhianawa Cancer Center Sulaimani-Iraq between July 2015 and December, 2019. Fifty patients had taken for each treatment group. The patients followed up for four years through regular visits of patients to the Zhianawa cancer center or by phone call.****Results****: There was a significant difference between comparing groups regarding the utilization of boost ($p<0.001$), survival outcomes ($p=0.003$), and distant metastasis ($p=0.001$). The disease outcomes of patients managed by extreme hypofractionation protocol were close to those treated by moderate protocol. The higher death rate and distant metastasis in patients treated with extreme hypofractionation were substantially due to more advanced disease stages.* ***Conclusions:*** *The Extreme hypofractionation radiotherapy is an effective and safe treatment option for breast cancer. Although differences in survival outcome and distant metastasis, the extreme hypofractionation is non-inferior to moderate hypofractionation schedules in median survival, locoregional recurrence, and late side effects*

Keywords: *Breast Cancer, Hypofractionation Radiotherapy, Outcome*

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1. INTRODUCTION

Breast cancer is the predominant malignancy of women all over the world[1], constituting about 22.9% of all cancers [2]. The incidence of breast carcinoma is rising gradually in both poor and rich countries. Globally, breast cancer incidence is ranging from 19.3-89.7/100,000 women [3]. The incidence rate of breast cancer in Iraq had increased over the last two decades and became the leading cause of mortality for Iraqi women with higher recorded cases in Northern Iraq[4]. Common risk factors of breast cancer are including dietary factors (fatty diet, alcohol, and smoking), Obesity, age, and genetic mutations[5-8]. The survival of women with breast cancer depends mainly on the histology subtypes, disease stage, and access to treatment, ethnicity, and location of the patient. There are high survival rates observed in the western world in breast cancer cases compared to developing countries where survival rates are less[9]. However, the survival of women with breast cancer has shown 1.4% annual improvement in expanding screening, improvement of surgical and radiotherapy techniques, and inventing systemic therapy as well[10]. Treatment options for breast cancer consisted of a combination of surgery, systemic treatment, and radiotherapy. Breast cancer treatment was evaluated by integrating standard immunohistochemical markers and gene expression with information from anatomic imaging and targeted functional imaging [11]. Adding radiation for surgery in breast cancer treatment helps achieve a 90-95% local control rate within ten years following treatment[12, 13]. The standard fractionation radiotherapy, including 45–50 Gy in 25 fractions of 1.8 or 2 Gy/day, five days a week, for 33 days [14]. Many studies have shown lower local recurrence after applying radiotherapy, reaching 8%–10% compared to no radiotherapy implementation that reaches 25%–35%[10, 14, 15]. Nowadays, the American Society of Radiation Oncology (ASTRO) guidelines referring to hypofractionation radiotherapy for all women at any age, whether they had received chemotherapy or not[18]. The hypofractionation radiotherapy of whole-breast has developed as a standard treatment for post-lumpectomy radiation at early-stage breast carcinoma with favorable outcomes[18, 19]. It showed an equal 10-years local control and better cosmetic results and less adverse effects of hypofractionation. Recently, about 20% of breast cancer women are treated by WBI [20]. The hypofractionation radiotherapy recorded significant success in Iraq by reducing locoregional recurrence, distant metastasis, and mortality rates[21].

2. PATIENTS and METHODS

The study is a retrospective review performed for one hundred women with a diagnosis of breast cancer treated by hypofractionated radiotherapy at Zhianawa Cancer Center between July 2015 and December, 2019. Zhianawa Cancer Center (ZCC) is a tertiary radiotherapy center in Sulaimani, Iraq, and equipped with two LINAC machines and one HDR brachytherapy unit. Being an adult (age ≥18 years) with confirmed invasive breast carcinoma by histopathology, axillary lymph nodes assessed either by dissection or sentinel biopsy, Karnofsky Performance Score ≥70, undergone excision of primary breast tumor (Conservative surgery or mastectomy) and managed by hypofractionation radiotherapy all were inclusion criteria. The exclusion criteria included age less than 18 years, evidence of arm lymphedema, previous thoracic radiotherapy, and pregnant women. Variables including general characteristics (age, pathology, grading, laterality, and staging), types of treatment (Surgery, chemotherapy, and radiotherapy) and treatment outcomes (survival outcomes, and distant metastasis) and complication were all reviewed. The patients are evaluated and managed by a multidisciplinary team (Radiologist, Surgeon, Pathologist, Medical oncologist & Radiation oncologist). The data of fifty patients for each protocols had reviewed. The study's approval had obtained from the ethical board of the Kurdistan Board for medical specialty and local ZCC board review. Written informed consent had taken from all patients.

Radiotherapy Treatment protocols

The regimen for moderate hypofractionation is 4005 cGY/15 fractions (267cGY / fraction) within three weeks (5 days per week) to the chest wall or whole breast, with or without regional lymph nodes. In contrast, extreme hypofractionation is 2700 cGY/5 fractions (540c GY/fraction) in a week to the chest wall or whole breast with or without regional lymph nodes. A sequential tumor bed radiotherapy boost applied for patients underwent conservative breast surgery, and the dose was ranged from 10-16Gy for patients with age< 50 years or high-grade disease regardless of age. The radiotherapy started 4-6 weeks from the last chemotherapy session or 12 weeks from surgery date for those not received chemotherapy.

Before treatment, all patients underwent CT-simulation, and volumes (targets and organs at risk) were delineated. The Clinical Target Volume (CTV) for the whole breast includes soft tissues from 5 mm below the skin surface to the deep fascia while chest wall (CTV) includes skin flaps and underlying soft tissue to deep fascia; both excluded muscle and rib cage. The Planning Target Volume (PTV) was created by adding 7 mm to CTV of the chest wall or whole breast, and 5 mm to CTV of Lymph nodes.

The two tangential opposing beams covered the whole breast or chest wall PTV to minimize the ipsilateral lung and heart exposure. During plan assessment always tried to cover PTV with a minimum of 95% with maximum dose point not beyond 110% of prescribed dose and respect dose tolerance for critical organs (for moderate hypofractionation V12 of ipsilateral lung ≤17% and heart V2≤ 30% or V10 ≤5%, while extreme group; V8 of ipsilateral lung ≤ 17 and V1.5 of heart ≤30%, or V7 is less than 5%) however; some deviation were allowed due to anatomical variation in the chest wall. Planning different photon energies (6, 10, and 18 MV) for locoregional coverage and variable electron energies (6-18 MeV) has utilized to boost area. The patient's data for that four-year duration was available in ZCC's registry system, recorded during their visits, or taken through phone calls. The data collected were analyzed statistically by the Statistical Package of Social Sciences software version 22. The Chi-square test and Fischer's exact test applied for analyzing the data is suitable. The level of significance (p-value) was regarded as statistically significant if it was 0.05 or less.

3. RESULTS

This study included 100 women with breast cancer managed by two radiotherapy protocols (50) patients with extreme hypofractionation, and the other 50 patients with moderate hypofractionation). The comparison of the two groups showed no significant difference regarding age (p=0.060, pathology (p=0.6), laterality (p=0.3), disease stages (p=0.3), and primary surgery (p=0.1). However, the moderate hypofractionation group had more higher grade of disease (p=0.009) (**Table 1**).

Regarding adjuvant hormonal or biological therapy usage, there were no significant differences between the two treated groups (p=0.6), But in terms of chemotherapy administration, patients in moderate protocol administered more chemotherapy in comparison to those managed by extreme hypofractionation (p=0.01). (**Table 2**).

Regarding adding of boost to lumpectomy bed, statistically significant numbers (52%) of patients treated with extreme hypofractionation had a boost in comparison to those in moderate fractionation (8%) (p<0.001). About the late complications, there were no statistically significant differences between the two groups (p=0.5). There were better survival outcomes (p=0.003) observed, and lower distant metastases (p=0.001) occurred in patients treated with moderate protocols in comparison to those treated by extreme hypofractionation (**Table 3**).

As shown in (**Figure 1**), the median survival for all patients treated with hypofractionation radiotherapy was (38 months), While in (**Figure 2**), the median survival of patients treated with extreme Group shows as (36 months) and survival of patients treated with the moderate group as

(39 months). Among patients managed by extreme hypofractionation grading of disease (I-III) exhibited no statistically significant impacts on survival outcomes (p=0.4) and distant metastasis (p=0.2), while initial patient presentation with higher disease stages had more late distant metastases (p=0.03) and disease-specific mortality (p=0.02). (**Tables 4&5**)

Table 1. Distribution of patients, disease, and treatment characteristics depending on hypofractionation protocols.

Variable		Hypofractionation radiotherapy				*P. value*
		Extreme		Moderate		
		No.	%	No.	%	
Age	<50 years	23	46.0	30	60.0	0.06 NS
	≥50 years	27	54.0	20	40.0	
Pathology	Invasive	47	94.0	49	98.0	0.6 NS
	Non-invasive	3	6.0	1	2.0	
Grade	I	7	14.0	5	10.0	0.009 S
	II	30	60.0	17	34.0	
	III	13	26.0	28	56.0	
Laterality	Right side	29	58.0	24	48.0	0.3 NS
	Left side	21	42.0	26	52.0	
Staging	0	3	6.0	1	2.0	0.3NS
	I	10	20.0	6	12.0	
	II	22	44.0	27	54.0	
	III	13	26.0	16	32.0	
	IV	2	4.0	0	0.0	
Surgery primary	BCS	26	52.0	34	68.0	0.1NS
	MRM	24	48.0	16	32.0	

NS=Not significant, S=Significant.

Table 2. Types of systemic treatment according to hypofractionation radiotherapy protocols.

Systemic therapy		Total hypofractionation radiotherapy				*P. value*
		Extreme		Moderate		
		No.	%	No.	%	
Hormonal/Biological therapy	Yes	2	4	5	10	0.6 NS
	No	48	96	45	90	
Chemotherapy	Yes	9	18	1	2	0.01S
	No	41	82	49	98	

NS: Not significant, S: Significant.

Table 3. Distribution of adding boost and treatment outcomes according to among both treated groups

Variable		Total hypofractionation radiotherapy				P
		Extreme		Moderate		
		No.	%	No.	%	
Boost	Yes	26	52	4	8	<0.001[S]
	No	24	48	46	92	
Late side effects	Yes	8	16	6	12	0.5 NS
	No	42	84	44	88	
Type of late side effects	Shoulder pain/stiffness	3	37.5	2	33.3	0.5 NS
	Telangiectasia	1	12.5	1	16.7	
	Lymphedema	4	50	3	50	
Survival outcome	Alive	42	84	50	100	0.003[S]
	Dead	8	16	0	0	
	Yes	10	20	0	0	

NS: Not significant, S: Significant.

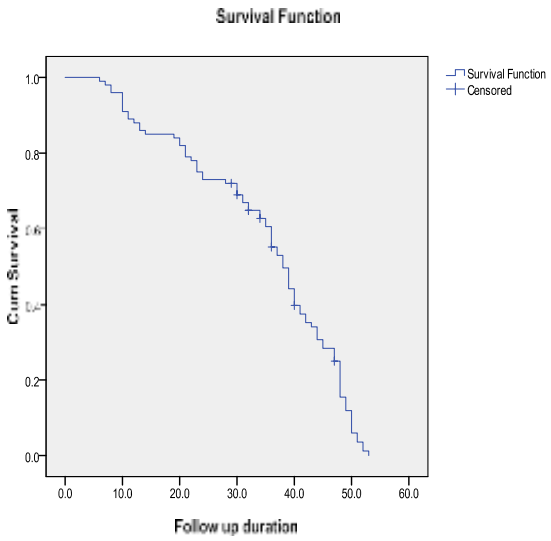

Figure 1

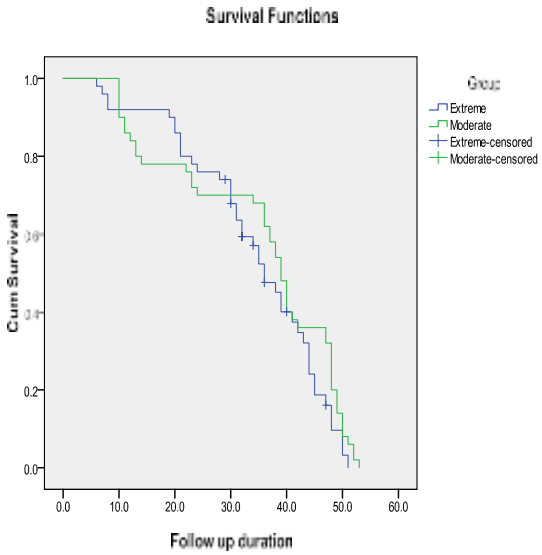

Figure 2

Figure 1. Kaplan Meier curve for the survival of all patients treated with both protocols

Figure 2. Kaplan Meier curve for the survival of patients according to radiotherapy treated groups.

Table 4. Patients survival outcomes according to the grading of disease and presenting stages of disease.

Variable		Survival outcome				*P. value*
		Alive		Dead		
		No.	%	No.	%	
Grading	**I**	7	16.7	0	0	
	II	25	59.5	5	62.5	0.4 NS
	III	10	23.8	3	37.5	
Staging	**0**	3	7.1	0	0	
	I	10	23.8	0	0	
	II	20	47.7	2	25.0	0.02 S
	III	9	21.4	4	50.0	
	IV	0	0	2	25.0	

NS: Not significant, S: Significant.

Table 5. Distribution of breast cancer metastases depending on the grading and staging of disease.

Variable		Distant metastasis				*P. value*
		Positive		Negative		
		No.	%	No.	%	
Grading	**I**	0	0	7	17.5	
	II	6	60	24	60	0.2 NS
	III	4	40	9	22.5	
Staging	**0**	0	0	3	7.5	
	I	0	0	10	25	
	II	4	40	18	45	0.03 S
	III	4	40	9	22.5	
	IV	2	20	0	0	

NS: Not significant, S: Significant.

4. DISCUSSION

Breast cancer is a high incident among Iraqi Kurdish young women[22]. The radiotherapy is essential as adjuvant treatment following lumpectomy or mastectomy and provides better local-regional control and survival outcomes[23, 24]. Advancement in radiotherapy techniques is continuous to be more convenient for patients and providers[25].

The current study showed a higher mortality in patients treated with the extreme hypofractionation protocol with no reported mortality for women in a moderate group. This finding is consistent with the results of Budach et al. [26] studies in Germany, which stated that moderately hypofractionation radiotherapy using 40 Gy in 15 fractions within three weeks for breast cancer is safe and accompanied with lower mortality. However, our study finding regarding survival outcome is inconsistent with results of Brunt et al. [27] studies in the UK, which reported no difference between patients treated with 26 Gy in one week and patients treated with 40 Gy in 3 weeks regarding mortality, local control, and safety. This inconsistency might be attributed to differences in sample size, short follow up duration, and health care quality between different medical centers. In our study, 52% of patients treated with extreme hypofractionated therapy significantly needed boost, while boost was offered only in 8% of patients treated with moderate fractionated radiotherapy.

Similarly, Dragun et al. [28] found that twenty-eight (18%) women treated with hypofractionation radiotherapy needed a once-weekly needed boost with a dose of 5.7 or 6 Gy depending on their previous schedule compared to patients treated daily with hypofractionation radiotherapy. The distant metastasis in the current study has significantly occurred among breast cancer women treated with extreme hypofractionation radiotherapy (80% free from distant metastasis). This finding is inconsistent with the results of FAST trials in the UK, which reported that metastasis-free survival for breast cancer women treated with extreme hypofractionation radiotherapy was 98.04%[17, 18]. This inconsistency may be because all FAST trial patients were stage I or II of breast tumor [17, 18]. In the current study, higher mortality and distant metastasis in patients treated with extreme hypofractionation might be due to lower systemic therapy administration and higher stage of disease at presentation. The present study revealed that median survival for breast cancer women treated with hypofractionation radiotherapy was thirty-eight months. This median survival is close to the results of Al-Naqqash et al. [23] studies in Iraq, which reported a median survival of 35 months for women with breast cancer treated with adjuvant radiotherapy. However, the current

study's median survival is lower than that of 52.4 months reported by Hashemi et al. [29] study in Iran. This difference might be due to the shorter duration of follow up in our research. In further analyses of this study, the median survival of patients treated with extreme hypofractionated protocols was thirty-six months, close to the median survival of patients treated with moderate hypofractionation radiotherapy (39 months). These findings are in agreement with the results of two studies published by Rivera and Hannoun-Lèvi in France [30] and Brunt et al. [29] in the UK, which all showed no differences in survival of women with breast cancer after treatment with extreme or moderate hypofractionation radiotherapy. Many authors documented that moderate hypofractionation radiation, including 15–16 fractions, is commonly accompanied by similar long-term findings better than conventional radiotherapy [17, 18]. In the UK, moderate hypofractionation radiotherapy, including fifteen fractions, is now the standard of care in early breast cancer [31]. However, the American Society for Radiation Oncology until now not indicating the regional hypofractionation radiation [16].

The current study showed that a higher death rate or distant metastasis in patients treated with extreme hypofractionation therapy were significantly associated with advanced breast cancer staging. This finding coincides with Gupta et al. [32] studies in the USA, which found that extreme hypofractionation radiotherapy applied for the advanced staging of breast cancers is commonly related to higher mortality or distant metastasis. Moreover, the current study showed no significant differences between extreme and moderate hypofractionation regarding the late side effects. This finding is consistent with the FAST-FORWARD trail in the UK, which revealed no significant differences between 27 GY compared with 40 GY for late side effects[33].

Our study concluded that Extreme hypofractionation radiotherapy is an effective and safe treatment choice for breast cancer, particularly for early stages. Although differences in survival outcome, and distant metastases, the extreme hypofractionation is non-inferior to moderate hypofractionation radiotherapy regarding median survival, locoregional recurrences, and late side effects.

5.CONCLUSIONS

The Extreme hypofractionation radiotherapy is an effective and safe treatment option for breast cancer. Although differences in survival outcome and distant metastasis, the extreme hypofractionation is non-inferior to moderate hypofractionation schedules in median survival, locoregional recurrence, and late side effects

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Ethical Clearance

Ethical clearance and approval of the study are ascertain by the authors, study protocol was approved by the Scientific Council of KRG-Iraq. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches. All official agreements were obtained accordingly.

Conflict of interest: *None declared by the authors*

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