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ORIGINAL ARTICLE

Retrospective Study Comparing Two Palliative Hypofraction Radiotherapy Protocols to Advanced Breast Cancer

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ABSTRACT

Background: Breast cancer is the most common malignancy in women in the world. Metastatic breast cancer (MBC) still remains incurable, and despite the many advances that have been achieved, the prognosis for those patients remains poor. Palliative RT is an efficacious treatment for ulcerative breast cancer with minimal toxicity. **Aim of work**: The aim of this study to retrospectively evaluate the outcomes of the 20Gy in 5 fractions and 30Gy in 10 fractions regimes in patients with advanced or metastatic breast cancer at Zagazig University. **Patients and methods:** This is a retrospective study on 20 patients with advanced breast cancer treated by palliative hypofraction radiotherapy at Clinical Oncology and Nuclear Medicine Department in Zagazig University Hospitals last 5 years. Data were collected retrospectively from records in last 5 years. **Results:** Majority of our studied groups were positive regard ER and PR, HER 2 were positive in only 12.5% and 33.3% respectively and Ki 67 were not done in majority of both groups. The local progression free survival (PFS) was not statistically significant between the two groups. The 30 Gy group received a higher equivalent dose compared to the 20 Gy group. ER status was a significant prognostic factor. This could be due to the added benefit of hormonal treatment in local control. **Conclusion:** The 20 Gy regime is a reasonable alternative for local control to the 30Gy regime in patients with locally advanced breast cancer.

Keywords: Breast cancer, Palliative hypofraction radiotherapy**,** Advanced Breast Cancer

INTRODUCTION

Breast cancer is the most common malignancy in women in the world **[1].** In Egypt, breast cancer represents 38.8% of total cancer incidence. In 2013, the estimated number of cases in Egypt was 17905 case and was expected to be triple by 2050**.** In America, it is estimated that 30% of all new cancer cases (252.710) among women are breast cancer in 2017**[2].** Radiotherapy has been used for palliating symptoms of cancer since its discovery in the 1800's. It can relieve symptoms due to either primary or metastatic tumors, including common manifestations of cancer such as pain, obstruction, bleeding, and neurologic symptoms. While the complexity of palliative radiotherapy has increased with that advent of newer technologies and the need to collaborate with other involved specialties, the common sense goals of its delivery remain a good chance for symptom relief with a limited risk of side effects **[3]**. The late responding tissues have lower alpha/beta ratios than early responding tissues **Hall and Amato [4]**. They are therefore more sensitive to dose per fraction. Breast cancers respond to radiotherapy similarly to late responding tissues, therefore, they are more sensitive to dose per fraction. This is at the risk of more late effects, but as these patients are for palliative intent, they

may not live long enough for those long terms effects to manifest.

In the metastatic setting, it is used for effective palliation of symptomatic metastases. Advances in tumor biology and immunology have led some to suggest a role for radiotherapy in the metastatic setting to augment traditional systemic therapies such as chemotherapy or immune-modulating agents. While a period of ten years of research have demonstrated that a major component of local tumr control is mediated by irreparable damage to the DNA of malignant cells resulting in cell death **[5].** The palliative RT (≥30 Gy) is an effective treatment for ulcerative breast cancer with minimal toxicity **Vempati et al.,[6]**. Prior RT should not be a contraindication, as patients with previous history of RT have similar low toxicity rates compared to RT-naïve patients. The aim of this study is to retrospectively evaluatethe outcomes of the 20Gy in 5 fractions and 30Gy in 10 fractions regimes for local treatment in patients with advanced or metastatic breast cancer at zagazig university.

PATIENTS AND METHODS

Assuming that attendance rate of cases with advanced breast cancer treated by palliative hypofraction radiotherapy in clinical oncology and nuclear medicine in zagazig university hospital was 4 ber year and data will be collected retrospectively from records in last 5 years so sample size will be 20 patients. **Inclusion criteria:** Patients 18 years and older. They should have proven and documented evidence of advanced or metastatic breast cancer clinically and radiologically. Patients should have either been treated with the palliative regime of either 20Gy or 30Gy. They may have had previous chemotherapy with minimal or no clinical response. Patients who are oestrogen receptor and progesterone receptor positive or negative included. **Exclusion criteria:** Chest wall irradiation postmastectomy or breast irradiation postlumpectomy.

Methods:

All the patients included in the study will be followed up for the following: Demographic features of the patients. The tumor characteristics at the time of breast cancer diagnosis as tumor size, nodal status, grade and histological type. Estrogen Receptor (ER) / Progesterone Receptor (PR) status. Hormonal and chemotherapy received. Radiotherapy (RT) regimen received and compliance to RT. Time of local progression and cause of death. Date of diagnosis. Treatment modalities that the patient will receive for the tumor. The standard palliative regimen used for patients with relatively good performance status, will be a total of 20Gy to whole breast (4Gy dialy for five fractions). The equivalent dose in 2Gy per fraction (EQD2) will be 26.67Gy, using an α/β of four for late effects. Patients will receive a total of 30Gy to the whole breast (one fraction daily, 5 days per week for 2weeks i.e.10 fractions,3Gy per fraction). The EQD2 for early response is 32.5Gy,and for late response is 35Gy, once again using an α/β of four for late effects. The time factor will be not taken into account. The local skin effects will be documented according to the Radiation Therapy Oncology Group (RTOG) Skin Toxicity Guidelines.

Outcome of treatment regards: Overall survival. Progression free survival.

Ethical Clearance: Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from Clinical Oncology and Nuclear Medicine Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approva. The work has been carried out in accordance with the code of ethics of the world medical association (Decleration of Helsinki) for studies involving humans.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference

and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test survival by Kaplan Meier. P value was set at <0.05 for significant results and <0.001 for high significant result.

RESULTS

There was no significant difference between groups regard any items, as IDC was largest in both groups, grade II represent 87.5% and 58.3% in both groups respectively, T4 represent 100% in both groups, regarding N: N3 represent 75% in both groups, M1 100% in both groups, stage IV 75% and 100% respectively **(Table 1)**.

This study found two groups were positive regard ER in 20Gy group 100% & 30Gy group 83.3% and PR in 20Gy group 87.5% and 30Gy group 91.7%, HER 2 in 20Gy group 12.5% & 30Gy group 33.3% and Ki 67 were not done in high of both groups **(Table 2)**.

There was no significant difference between groups regard skin reaction as largest of both groups had skin reaction varied from G1 to G3, regarding Loco regional progression Loco regional progression all 1st group had it and 83.3% from 2nd group with no significant difference or association **(Table 3)**.

This study that mean of survival among 20Gy Group was 5.861 and median was 1 and among 30Gy Group mean was 7.75 and median was 2. **Table (4)**

This study that mean of survival among 20Gy Group was 21.3 and median was 15 and among 30Gy Group mean was 22.2 and median was 20. **Table (5)**

Table (1): Tumor characters distribution between groups.

			Group		Total	X^2	P
			20Gy Group	30Gy Group			
Histology	**IDC**	**N**	8	11	19	0.702	0.402
		%	100.0%	91.7%	95.0%		
	Mixed	**N**	0	1	1		
		%	0.0%	8.3%	5.0%		
Grade	**G2**	**N**	7	7	14	1.94	0.16
		%	87.5%	58.3%	70.0%		
	G3	**N**	1	5	6		
		%	12.5%	41.7%	30.0%		
T	**T4**	**N**	8	12	10	-	-
		%	100.0%	100.0%	100.0%		
N	**N2**	**N**	2	3	5	-	-
		%	25.0%	25.0%	25.0%		
	N3	**N**	6	9	15		
		%	75.0%	75.0%	75.0%		
M	**M1**	**N**	8	12	20	-	-
		%	100.0%	100.0%	100.0%		
Stage	**Stage III**	**N**	2	0	2	3.33	0.068
		%	25.0%	0.0%	10.0%		
	Stage IV	**N**	6	12	18		
		%	75.0%	100.0%	90.0%		
Total		**N**	8	12	20		
		%	100.0%	100.0%	100.0%		

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Table (2): ER status, PR status, Her 2 status and Ki 67 distribution between groups.

			Group		Total	X^2	P
			20Gy Group	30Gy Group			
ER status	**-VE**	**N**	0	2	2	1.48	0.22
		%	0.0%	16.7%	10.0%		
	+VE	**N**	8	10	18		
		%	100.0%	83.3%	90.0%		
PR status	**-VE**	**N**	1	1	2	0.093	0.76
		%	12.5%	8.3%	10.0%		
	+VE	**N**	7	11	18		
		%	87.5%	91.7%	90.0%		
Her_2_status	**-VE**	**N**	2	3	5	1.25	0.53
		%	25.0%	25.0%	25.0%		
	+VE	**N**	1	4	5		
		%	12.5%	33.3%	25.0%		
	Not done	**N**	5	5	10		
		%	62.5%	41.7%	50.0%		
Ki_67	**Low**	**N**	0	1	1	0.7	0.4
		%	0.0%	8.3%	5.0%		
	Not done	**N**	8	11	19		
		%	100.0%	91.7%	95.0%		
Total		**N**	8	12	20		
		%	100.0%	100.0%	100.0%		

Table (3): Outcome distribution between studied groups

			Group		Total	X^2	P
			20Gy Group	30Gy Group			
Skin reaction	**G0**	**N**	0	2	2	3.96	0.26
		%	0.0%	16.7%	10.0%		
	G1	**N**	3	4	7		
		%	37.5%	33.3%	35.0%		
	G2	**N**	4	2	6		
		%	50.0%	16.7%	30.0%		
	G3	**N**	1	4	5		
		%	12.5%	33.3%	25.0%		
Loco regional progression	**No**	**N**	0	2	2	1.48	0.22
		%	0.0%	16.7%	10.0%		
	Yes	**N**	8	10	18		
		%	100.0%	83.3%	90.0%		
Total		**N**	8	12	20		
		%	100.0%	100.0%	100.0%		

Table (4): Kaplan Meier survival curve for progression free survival regard time of treatment beginning.

Group	Mean	Median
20Gy Group	5.861	1.000
30Gy Group	7.754	2.000
Overall	6.767	2.000

P =0.09 no significant difference regard median of survival

Table (5): Kaplan Meier survival curve for overall survival regard time of diagnosis.

Group	Mean	Median
20Gy Group	21.250	15.000
30Gy Group	22.306	20.000
Overall	21.450	20.000

P =0.07 no significant difference regard median of survival.

DISCUSSION

Breast cancer is one of most common cancer in women, in both the developing and developed countries **[7]**. Locally advanced breast cancer (LABC), defined as primary tumor greater than 5cm, with or without nodal involvement, only occurs in 5% to 10% of cases in developed countries. However, these numbers are much higher in the developing world due to lack of adequate screening, awareness, and accessibility to healthcare resources **[8]**.

According to the ESO-ESMO guidelines, the treatment of locally advanced disease involves multiple modalities. The aim is to downstage the tumour using neo-adjuvant chemotherapy or using hormonal treatment where appropriate, followed by surgery and adjuvant radiotherapy and biological agents. For metastatic disease, there is a lack of evidence on how to locally palliate the disease **[9]**.

Within the palliative realm, there are treatments ranging from aggressive surgical intervention and intra-arterial chemotherapy to topical palliative emollients. Radiation therapy (RT) has been and continues to be used in patients with ulcerative breast lesions to reduce tumor burden, provide symptomatic relief, and improve quality of life (QoL) **[10]**.

Fakie [7] evaluated and compared the loco-regional progression free survival (PFS), overall survival (OS) and acute effects of the two breast palliative regimes used in patients with locally advanced or metastatic breast cancer. There were 43 patients who received radiotherapy, with palliative intent, to their whole breast. Fourteen patients received a total dose of 20Gy (regimen 1) and 29 patients received a total dose of 36Gy (regimen 2). The median age was 66 years (range, 36-78 years) in the 20Gy group versus 63 years (range 36-86 years) in the 36Gy group (p=0.28).

Regarding histology, there was no significant difference between groups regard tumor character distribution, as IDC was largest in both groups, grade II represent 87.5% and 58.3% in both groups respectively. **Elston and Ellis [11]** studied 1831 patients and showed a very strong correlation with prognosis, patients with grade I and II tumors have a significantly better survival than those with grade III tumors (p=0.0001)**.**

In our study, T4 represent 100% in both groups. **El Gantiry [12]** revised 1208 premenopausal women treated between 1980 and 1989 and reported 4%, 45%, 38.5% and 15% in T1, T2, T3 and T4 respectively.

Regarding N, N3 represents 75% in both groups, M1 100% in both groups, stage IV 75% and 100% respectively. **Fakie [7]** found that the disease stage at presentation was not statistically significant between the two

groups. In the 20Gy group, (64% vs 66% in regimen 2) of the patients presented with inoperable, locally advanced disease (Stage 3) and (36% vs 34% in 36Gy group) presented with locally advanced disease, as well as distant metastasis (Stage 4).

This study found two groups were positive regard ER and PR, HER 2 were positive in only 12.5% and 33.3% respectively and Ki 67 were not done in largest of both groups. **Faki [7]** showed that ER status was a statistically significant prognostic factor (p=0.01). In the 20Gy group, 71% (n=10) of the patients died due to progression of local disease, two patients due to visceral metastasis and one patient died secondary to brain metastasis. Conversely, in the 36Gy group, only 14% (n=4) died due to local progression, nine patients due to distant metastasis, and four patients due to medical comorbidities. Of the 14 patients that progressed locally, 80% was Stage 3 in the 20Gy group (compared to 75% in the 36Gy group) and 20% Stage 4 (compared to 25% in the 36Gy group). In the 20Gy group, 60% were ER negative compared to 50% in the 36Gy group.

This study found there was no significant difference between groups regard skin reaction as largest of both groups had skin reaction varied from G1 to G3, regarding Loco regional progression all 1st group had it and 83.3% from 2nd group with no significant difference or association.

Kirova et al. [13] compared normofractionated radiotherapy to hypo-fractionated radiotherapy in the postoperative setting. The main concern with hypofractionation is the increased incidence of late effects, with fibrosis occurring in 39% of patients according to the studies done in elderly. Results were similar between the two groups, except that there was a higher rate of late effects (33%) in the hypofractionated regimen.

However, due to the palliative intent of our treatment, the late complication risk was accepted. Skin necrosis and rib fractures were not reported in patient folders but this non-reporting may be due to patients not surviving a long period of time in which to experience late effects. **Fakie [7]** found that in the 20Gy group, 71% had RTOG Grade 1 acute skin effects, 21% had Grade 2 effects, and 8% had Grade 3 effects. Similarly, in the 36Gy group, 62% had grade 1 effects, 24% had Grade 2 effects and 14% had grade 3 effects. In both groups, grade 4 effects were not evident.

The local progression free survival (PFS) was not statistically significant between the two groups. This may be due to the study being underpowered. The 30 Gy group received a higher equivalent dose compared to the 20 Gy group. Therefore, it was hypothesised that they would have a better PFS. The results found that ER status was a significant prognostic factor. This could be due to the added benefit of hormonal treatment in local control. The overall survival was also not statistically significant between the two groups.

Fakie [7] found a statistically significant difference in survival between the two groups. In the 20Gy group 92% of the patients had died at the end of the follow up period compared to 58% in the 36Gy group. The cohort follow up period was 25 months (range 3.1 to 83.2 months). The median overall survival (OS) was 29.1 months (range 19.35 to 44.81 months) for the cohort. The median OS in the 20Gy group was 25.8 months (range 11.56 - 43.03 months) and 29.6 months (range 25.62 - 44.81 months) in the 36Gy group. The overall median progression free survival (PFS) was 5.1 months (range 3.44 - 10.61). In the 20Gy group PFS was 4.5 months (range 3.61-5.81) and 7.7 months (range 3.44-19.81) in the 36Gy group.

A limited number of studies were performed examining hypo-fractionation in the palliative setting. There are studies and retrospective reviews that have been published using the once weekly hypofractionated radiotherapy regime. However, it was investigated in the elderly population as definitive radiotherapy or as adjuvant treatment post mastectomy. These trials looked at the incidence of acute and late side effects of hypofractionated radiotherapy, tolerance and compliance to radiotherapy, the local control rate, disease free survival, cause specific survival and overall survival.

Hall and Amato [4] have shown that late responding tissues have lower alpha/beta ratios than early responding tissues. They are therefore more sensitive to dose per fraction. Breast cancers respond to radiotherapy similarly to late responding tissues, therefore, they are more sensitive to dose per fraction. This is at the risk of more late effects, but as these patients are for palliative intent, they may not live long enough forthose long terms effects to manifest.

Vempati et al. [6] suggested that palliative RT (≥30 Gy) is an efficacious treatment for ulcerative breast cancer with minimal toxicity. Prior RT should not be a contraindication, as patients with previous history of RT have similar low toxicity rates compared to RT-naïve patients. **Fakie [7]** did not show a statistically significant difference in terms of PFS and OS between the two radiotherapy regimes. They both remain reasonable options in local palliation in patients with locally advanced breast cancer.

There were a number of limitations in this study. Firstly, the cohort reported on was small. Secondly, since the study was retrospective, patient records were heavily relied upon. However, these records did not adequately document patient and treatment characteristics such as performance status, quality of life, early and late effects of radiotherapy and cosmesis. In addition, skin reactions were not graded according to the RTOG skin toxicity guidelines, making grading susceptible to observer bias. It should be noted that T3 and T4 patients are difficult to grade due to the presence of ulceration and bleeding, secondary to disease. Late effects were not well recorded, but it was not of great concern as these were palliative patients with limited life span and the benefit of local control outweighed the risk of late effects due to higher overall dose.

CONCLUSION

The 20 Gy regime is a reasonable alternative for local control to the 30Gy regime in patients with locally advanced breast cancer. There is no statistically significant difference between the two regimens in term of overall survival, progression free survival and acute skin effects.

RECOMMENDATIONS

Previous trials have shown promising results using a once weekly hypo-fractionated regime in palliative setting. However, trials need to be performed in the palliative setting to assess its clinical effectiveness in terms of local control and to assess its impact on the quality of life of the patients compared to daily doses.

Conflict of Interest:

No any financial or personal relationships with other people or organizations that could inappropriately influence the current study.

Financial Disclosures:

No any specific financial interests, relationship and affiliations relevant to the subject of the manuscript.

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