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The Intensity Modulated Radiotherapy *vs.* the 3D-Conformal Radiotherapy Regarding Acute Radiation Skin Toxicity and Treatment-Related Lymphopenia in Early-Stage Breast Cancer Patients

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Abstract

Adjuvant radiotherapy is an integral part of breast cancer treatment, and there was a great evolution of radiotherapy techniques over the past few years. Intensity-modulated radiation therapy (IMRT) was developed in the 1990s as a modern technique aiming to spare normal tissues from toxic effects of radiotherapy. This study aimed at comparing the IMRT technique to the 3D-coformal radiotherapy technique (3D-CRT) in early breast cancer patients regarding the occurrence of acute skin toxicities and treatment-related lymphopenia (TRL). It is a prospective study conducted on 100 eligible patients who were divided equally between two groups; the first, are patients received adjuvant radiotherapy using IMRT technique and the second group were those who received 3D-CRT. Results showed that sever acute skin toxicity or moist desquamation in IMRT group was 6% *vs.* 18% in 3DCRT group (p<0.05). And, the sever TRL with IMRT technique was 9% compared 21% among those of the 3D-CRT group (p<0.05). The IMRT technique resulted in statistically significant lower incidence of sever acute skin toxicities as well as less sever TRL when compared with 3D-CRT technique.

Keywords: Breast cancer; Adjuvant radiotherapy; IMRT

Introduction

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females. In the United States, breast cancer is the most common female cancer, the second most common cause of cancer death in women, and the main cause of death in women ages 40 to 49 years. The lifetime probability of developing invasive breast cancer is one in eight [1].

Early-stage breast cancer is treated with a multi-modality post-surgical approach that can include chemotherapy, radiotherapy, targeted therapies and hormonal therapy. Radiotherapy, an integral part in the treatment of early breast cancer, can be toxic to circulating lymphocytes as one of its side effects. Radiotherapy can result in treatment-related lymphopenia [2].

Radiation for breast cancer is well tolerated in general by most patients and does not significantly impair their daily activities. Acute toxicities of radiotherapy are generally self-limiting, and resolve within 4-6 weeks after the treatment is completed. Skin reactions or acute radiation dermatitis and the constitutional symptom of fatigue are the most common early toxicities from irradiation in breast cancer patients. The acute radiation dermatitis is defined as a skin changes occurring within 30-90 days of radiation exposure. These skin reactions are ranging from erythema to wet desquamation or ulceration [3-5].

Intensity-modulated radiation therapy (IMRT) was developed in the 1990s as a modern technique aiming to spare normal tissues from toxic effects of radiotherapy. Its main goal is to allow for dose escalation to the tumor while limiting dose to adjacent normal tissues. There are many randomized trials compared the standard 2D radiotherapy *vs.* IMRT in early-stage breast cancer, one of those trials showed that Breast IMRT significantly reduced the occurrence of moist desquamation anywhere in the breast, with an absolute reduction of 16.6% (p=0.002), as well as moist desquamation in the inframammary fold by 17% (p=0.001) [6-8].

There is no study which compares the IMRT technique *vs.* the 3D-conformal radiotherapy technique (3D-CRT) regarding the incidence of acute skin toxicity, and on the TRL which has a proven prognostic impact.

Aim of the Work

The primary objective of this work was to Study the effect of a new radiotherapy technique, which is the Intensity Modulated Radiotherapy (IMRT) *vs.* the 3D-Conformal Radiotherapy (3D-CRT) technique on the occurrence and severity of acute treatment-related skin toxicities as well as treatment-related lymphopenia.

Patients and Methods

It is a Prospective study which compared two groups of patients regarding the severity of the acute skin toxicities and TRL. It included a group who were planned to receive their adjuvant radiotherapy using IMRT technique *vs.* another group who were receiving radiotherapy using 3D-CRT technique. It included 50 patients in each group.

Inclusion criteria

1) Female gender.

2) Aged 18 years or older.

3)   Stage I-IIIA breast cancer.

4)   Planned to receive adjuvant locoregional radiotherapy to the breast and/or chest wall.

5)   Have available total lymphocyte counts before and 1-2 months after starting radiotherapy.

Exclusion criteria

1)   Stage IV breast cancer.

2)   Simultaneous presence of other malignancy.

To assess the difference in severity of TRL among the two groups of patients, we was collect a venous blood sample from patients to carry a Complete Blood Count (CBC) test with differential cell counts using the Sysmex 5-part differential hematology analyser, before starting adjuvant radiotherapy and 1 month after the end of radiotherapy coarse. And, for more accuracy we are intending to send the collected peripheral blood samples for Flowcytometry to define the decrease in the CD4 counts in particular.

The radiotherapy dose and fractionation which was be received by the eligible patients was be 50 Gy at 2 Gy/fraction to whole breast in case of conservative breast surgery, or chest wall in case of postmastectomy irradiation, and 50 Gy at 2 Gy/fraction to supraclavicular fossa (when included).

Baseline total lymphocyte counts was be classified as normal (≥ 1000 cells/mm) or abnormal (<1000 cell/mm). After the initiation of radiotherapy, the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was be used to classify the severity of TLC. Total lymphocyte counts at 2 months, 6 months and 12 months after the initiation of radiotherapy was be dichotomized to CTCAE grade 0 to II *vs.* grade III to V for the relevant analyses.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative parametric data, while it was done for qualitative data as number and percentage.

Inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher's exact test for variables with small expected numbers, while correlations were done using Pearson's correlation for numerical parametric data. Linear regression model was used to find out independent factors affecting different scales.

The level of significance was taken at p value <0.050 is highly statistically significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

Results

Clinico-pathologic data

The patients' age: Table 1, shows comparison between the two studied groups regarding age. In group I (IMRT group), age ranged from 26-60 with mean value 46.2 ± 11.2 and in group II (3D-CRT group) ranged from 25-63 with mean value 47.2 ± 10.5. There was no

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT"	
Age	<50	No.	31	35	66
		%	62.00%	70.00%	66.00%
	>50	No.	19	15	34
		%	38.00%	30.00%	34.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
Min.–Max.			26-60	25-63	25-63
Mean ± SD			46.2 ± 11.2	47.2 ± 10.5	46.9 ± 10.6
Median			45	46	45.5
X^2			0.713		
p			0.263		

Table 1: Comparison between the two studied groups regarding age.

statistical significant difference between two studied groups regarding age (p>0.05). Patients below 50 years old constitute 62% in group I and 70% in group II. Whereas, patients above 50 constitutes the remaining (Figure 1).

The stage: Table 2, shows comparison between the two studied groups regarding stage. There was no statistical significant difference between the two studied groups regarding stage (p>0.05).

Tumor grade: Table 3, shows comparison between the two studied groups regarding grade. There was no statistical significant difference between the two studied groups regarding grade (p>0.05).

Lymphnode status: Table 4, shows comparison between the two studied groups regarding lymphnode (LN) involvement. There is 52% with positive LNs in the group I and 62% in the group II. There was no statistical significant difference between the two studied groups regarding LNs (p>0.05).

Hormonal receptors status: Table 5, shows comparison between the two studied groups regarding ER/PR. The ER/PR negative patients were 15% in the group I and 11% in the group II. There was no statistical significant difference between two studied groups regarding ER/PR (p>0.05).

Her2/neu over-expression by IHC: Table 6, shows comparison between the two studied groups regarding Her2. There is 11% of patients who were positive for Her2 by IHC in group I and 15% in group II. There was no statistical significant difference between the two studied groups regarding Her2 (p>0.05).

Radiotherapy toxicity

Treatment related lymphopenia (TRL): Table 7, shows comparison between the two studied groups regarding lymphopenia. 44% of patients developed TRL in the IMRT group and 38% developed TRL in the 3D-CRT group. There was no statistical significant difference between two studied groups regarding lymphopenia (p>0.05) (Figure 2).

Regarding the sever (<500) TRL, patients who received adjuvant radiotherapy with IMRT technique showed significantly less incidence of sever TRL (9%) compared to those on the 3D-CRT (21%). Table 8, shows comparison between the two studied groups regarding sever Lymphopenia. There was a significant increase in lymphopneia in group II (3D-CRT) more than group I (p>0.05).

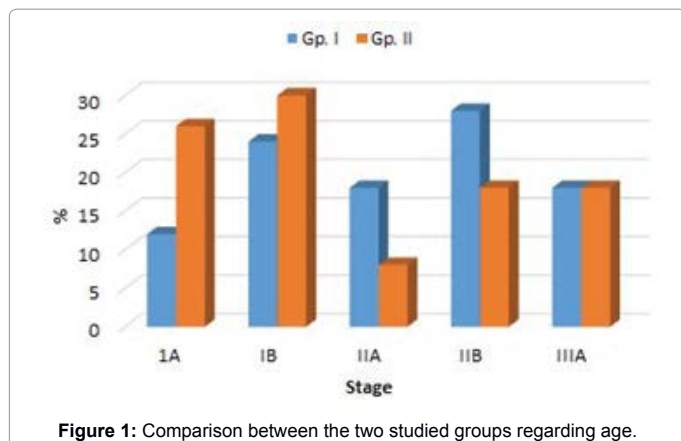**Skin toxicity:** There was significant difference in sever skin toxicity

Figure 1: Comparison between the two studied groups regarding age.

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT"	
Stage	1A	No.	6	13	19
		%	12.00%	26.00%	19.00%
	IB	No.	12	15	27
		%	24.00%	30.00%	27.00%
	IIA	No.	9	4	13
		%	18.00%	8.00%	13.00%
	IIB	No.	14	9	23
		%	28.00%	18.00%	23.00%
	IIIA	No.	9	9	18
		%	18.00%	18.00%	18.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X^2			5.922		
p			0.205		

Table 2: Comparison between the two studied groups regarding stage.

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT	
Grade	Unknown	No.	11	14	25
		%	22.00%	28.00%	25.00%
	I	No.	16	11	27
		%	32.00%	22.00%	27.00%
	II	No.	12	16	28
		%	24.00%	32.00%	28.00%
	III	No.	11	9	20
		%	22.00%	18.00%	20.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X^2			2.057		
p			0.561		

Table 3: Comparison between the two studied groups regarding grade.

		Group		Total
		Gp. I "IMRT"	Gp. II "3DCRT"	
LNs	-ve No.	24	19	43
	%	48.00%	38.00%	43.00%
	+ve No.	26	31	57
	%	52.00%	62.00%	57.00%
Total	No.	50	50	100
	%	100.00%	100.00%	100.00%
X^2		1.02		
p		0.21		

Table 4: Comparison between the two studied groups regarding LNs.

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT"	
ER/PR	ER/PR +ve	No.	9	10	19
		%	18.00%	20.00%	19.00%
	ER/PR -ve	No.	15	11	26
		%	30.00%	22.00%	26.00%
	ER+/PR-	No.	5	10	15
		%	10.00%	20.00%	15.00%
	ER-/PR+	No.	11	7	18
		%	22.00%	14.00%	18.00%
	NA	No.	10	12	22
		%	20.00%	24.00%	22.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X^2			3.405		
P			0.492		

Table 5: Comparison between the two studied groups regarding ER/PR.

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT"	
Her2	NA	No.	14	13	27
		%	28.00%	26.00%	27.00%
	+ve	No.	11	15	26
		%	22.00%	30.00%	26.00%
	-ve	No.	11	12	23
		%	22.00%	24.00%	23.00%
	Equivocal	No.	14	10	24
		%	28.00%	20.00%	24.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X^2			1.363		
p			0.714		

Table 6: Comparison between the two studied groups regarding Her2.

Multi-variant analysis

Using Cox Regression analysis, the patient's age was an independent prognostic variable in correlation to the severity of skin toxicity resulted from radiotherapy. As patients who aged more than 50 years were significantly prone to more sever skin toxicity from radiotherapy. Also, the tumor stage was found to be a prognostic variable that appears to be independently correlated to TRL occurrence. As, stages II-B and III-A were found to be significantly associated with more sever TRL in both groups.

Discussion

The primary objective of this work is to Study the effect of a new

between the two groups, where the IMRT group showed less sever skin toxicity incidence (3 patients) compared to 24 patients in the 3D-CRT group.

Table 9, shows comparison between the two studied groups regarding sever skin toxicity or moist desquamation. In IMRT group the toxicity was 6.0% in the patients, while in 3DCRT (group II), there were 48.0% of the patients had severe skin toxicity. There was statistical significant increase in the number of patients had sever skin toxicity in group II more than group I (p<0.05).

			Group		Total
			Gp. I "IMRT"	Gp. II "3DCRT	
Lymphopenia	Yes	No.	22	19	41
		%	44.00%	38.00%	41.00%
	No	No.	28	31	59
		%	56.00%	62.00%	59.00%
Total		No.	50	50	100
		%	100.00%	100.00%	100.00%
X^2			372		
p			0.342		

Table 7: Comparison between the two studied groups regarding lymphopenia.
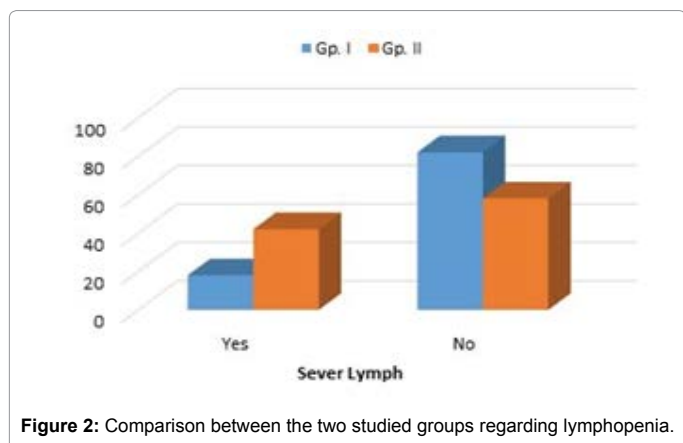
Figure 2: Comparison between the two studied groups regarding lymphopenia.

Sever Lymphopenia		Group		Total
		Gp. I "IMRT"	Gp. II "3DCRT	
Yes	No.	9	21	30
	%	18.00%	42.00%	30.00%
No	No.	41	29	70
	%	82.00%	58.00%	70.00%
Total	No.	50	50	100
	%	100.00%	100.00%	100.00%
X^2		4.852		
p		0.0211*		

Table 8: Comparison between the two studied groups regarding sever lymphopenia.

Sever skin toxicity or moist desquamation		Group		Total
		Gp. I "IMRT"	Gp. II "3DCRT	
Yes	No.	3	24	27
	%	6.00%	48.00%	27.00%
No	tNo.	47	26	73
	%	94.00%	52.00%	73.00%
Total	No.	50	50	100
	%	100.00%	100.00%	100.00%
X^2		11.52		
p		0.001*		

Table 9: Comparison between the two studied groups regarding Sever skin toxicity or moist desquamation.

radiotherapy technique, which is the Intensity Modulated Radiotherapy (IMRT) *vs.* the 3D-Conformal Radiotherapy (3D-CRT) technique on the occurrence and severity of acute skin toxicities and lymphopenia.

It was a prospective study which was carried out on 100 patients and different variables and data was collected, in chosen the patients was considered that the patients in the two groups be matched as match

as possible to eliminate the basic demographic and clinical data to effect on the net results.

Regarding the age of the patients, the mean age in group I and II was matched, in group I the mean age was 46.2 ± 11.2, while in group II was 47.2 ± 10.5 years and median age for all groups was 48.0 years, there was no significant difference between the two groups regarding age. In agreement without study Nagia et al., selected their patients in the same age group to compare between IMRT and 3DCRT the mean age for all patients show a median 52.0 years [9].

In our study the pathological data of the two groups show insignificant difference, regarding stage from IA to IIIA in both groups, without significant difference, also the grade and positive lymph nodes show insignificant difference between the two groups. In agreement without study, may studies show insignificant difference between the two compared groups regarding pathological and clinical data to eliminate the effect on the net results of the study [10,11].

In our study the hormonal receptors of the patients show an increasing in ER/PR –ve receptors more than the other types of ER/PR results, on comparing the two groups regarding hormonal receptors it was found that there was no significant difference, the Her2 show insignificant difference between the two studied groups. In agreement with our results, the study of Clarke et al., which showed similar results regarding the ER/PR and Her2 results [12].

In this study the skin side effect shown as sever skin toxicity or moist desquamation. In IMRT group the toxicity was 6.0% in the patients, while in 3DCRT (gp II), there were 18.0% of the patients had severe skin toxicity. There was statistical significant increase in the number of patients had severe skin toxicity in group II more than group I (p<0.05).

Pignol et al., reported the results of a Canadian multicenter randomized control trial evaluating the occurrence of acute skin toxicity in 331 patients using either IMRT or non-IMRT wedge RT. All patients were randomized to receive whole breast treatment to a total dose of 50 Gy in 2.5 Gy fractions. The study reported an overall reduction of approximately 17% in the rate of occurrence of moist desquamation, and on multivariate analysis reported that smaller breast size and treatment technique (IMRT) were significantly associated with a decreased risk occurrence of moist desquamation. The results of the present meta-analysis support those of the Pignol et al., in that the authors report a protective association between moist desquamation and IMRT [7].

The incidence of lymphopenia was found in IMRT to be 18.0%, while in 3DCRT it was 42.0% this difference was statistically significant with P value less than 0.05. Regarding the sever (<500) TRL, patients who received adjuvant radiotherapy with IMRT technique showed significantly less incidence of sever TRL (9%) compared to those in the 3D-CRT group (21%).

Conclusion

The IMRT technique resulted in less incidence of acute skin toxicities as well as less sever TRL when compared with 3D-CRT technique. However, larger number of patients should be studies to validate these results and to reach a statistical power which could be a practice changing guide.

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