Original Article

Late Toxicity of Hypofractionated Whole-Breast Radiotherapy in Early Breast Cancer Patients

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Abstract

Background: Adjuvant radiation therapy (RT) reduces risk of locoregional recurrence (LRR) and improves breast cancer-specific and overall survivals in the setting of whole-breast radiotherapy after breast-conserving surgery. in hypofractionated regimen 40-42.5 Gy in 15 -16 fractions or 45-50.4 Gy in 25 – 28 fractions with boost to tumor bed 10-16 Gy in 4-8 fractions. After BCS, radiation therapy in the form of Whole Breast Radiation Therapy (WBRT) is the standard adjuvant treatment, with 90–95 percent local control rates. The skin is especially sensitive to the toxic effects of radiation (ionizing radiation) due to its high cellular turnover rate. In fact, an estimated 74% to 100% of patients who receive RT for breast cancer will experience cutaneous toxicities. **Aim:** Evaluation of late skin toxicity of Adjuvant hypofractionated Radiotherapy in early breast cancer patients. **Subjects and Methods:** This retrospective study will be conducted in Clinical Oncology & Nuclear Medicine Department, Zagazig University Hospitals. Random selection of cases who treated at the department, who fulfilled the eligibility criteria and received HF Rth from (2018 -2021). data will be collected from patient files and follow up toxicity sheets. Late skin toxicity was assessed in all patients. **Results:** There is high significant correlation between , DM, HTN and late skin toxicity , , there is also significant correlation between chemotherapy and late skin toxciciy. Regimen of chemotherapy has no significant correlation. **Conclusion:** HF-WBI is feasible and safe, because of the low rate of moderate-high scores toxicity. Chemotherapy and DM had impact on late fibrosis .the rate of severe toxicity (> grade 2) was low even in these patients.

Keywords: Hypofractionated Whole-Breast Radiotherapy, Early Breast Cancer

INTRODUCTION

Breast cancer is a multi-factorial disease and various factors contribute to its occurrence. Although the disease occurs all over the world, its incidence, mortality, and survival rates vary considerably among different parts of the world, which could be due to many factors such as population structure, lifestyle, genetic factors, and environment. **(1).**

In Egypt, breast cancer is the most common malignancy in women, accounting for 38.8% of cancers in this population, with the estimated number of breast cancer cases nearly 22,700 in 2020 and forecasted to be approximately 46,000 in 2050**.** It is estimated that the breast cancer mortality rate is around 11%, being the second cause of cancer-related mortality after liver cancer ***(1)***

Adjuvant radiation therapy (RT) reduces risk of locoregional recurrence (LRR) and improves breast cancer-specific and overall survivals in the setting of whole-breast radiotherapy after breast-conserving surgery, regional nodal irradiation, and postmastectomy radiotherapy. in hypofractionated regimen 40-42.5 Gy in 15 -16 fractions or 45-50.4 Gy in 25 – 28 fractions with boost to tumor bed 10-16 Gy in 4-8 fractions **(2).**

The efficacy of breast-conserving treatment has been shown in several prospective randomized controlled trials. Patients who did not receive whole-breast radiation after breast conserving surgery had higher recurrence rates and a pattern of recurrences that occurred predominantly in the tumor bed in these randomized studies ***(2).***

Treatment acceleration (via hypofractionation), with an OTT of less than 6–7 weeks, may improve cure rates by reducing the period for proliferation and repopulation**.** Even when combined into a 3-week regimen, hypofractionated and conventional fractionation exhibited equivalent long-term efficacy, cosmetic effects, and delayed hazardous consequences **(3)**

Different hypofractionation schedules showed acceptable adverse reactions, good efficacy and aesthetic outcomes ***(4)***
The aim of this study was Evaluation of late skin toxicity of Adjuvant hypofractionated Radiotherapy in early breast cancer patients.

Subjects and Methods

This retrospective study will be conducted in Clinical Oncology & Nuclear Medicine Department, Zagazig University Hospitals. Random selection of cases who treated at the department, who fulfilled the eligibility criteria and received HF Rth from (2018 -2021). data will be collected from patient files and follow up toxicity sheets . **IRB Approval No. (#8051/14-9-2021).**

Eligibility Criteria:

Histologically confirmed innvasive duct carcinoma early breast carcinoma (Stages I-IIB).

- Underwent breast conservative surgery
- Negative margins (no tumor on ink).
- No previous radiotherapy.
- Hormone therapy was allowed.

-Exclusion criteria:

-Prior treatment for contralateral or synchronous breast cancer or if they had prior RT to the current breast.

- Synchronous second primary tumor
- Distant metastases
- Pregnancy
- Comorbid conditions: Paget's disease, Collagen vascular disease, Life expectancy <2 years secondary to comorbidities,

-Operational Design

Ealy breast cancer patients underwent breast conserving surgery, and HF Rth from 2018- 2021

-Study design

Retrospective (record based) cohort study

- Sample size

300 cases who fulfill the inclusion and exclusion criteria and received hypofractionated radiotherapy at clinical oncology department zagazig university hospitals during the study period from 2018 2021 will be included as a comprehensive sample

Study plan

Acute & late skin toxcicity that was previously assesd in all patients included in sample size with early breast cancer underwent breast conserving surgery, and HF Rth from 2018 2021.. from patient follow up toxicity sheets at which examination of patients was done weekly during radiotherapy delivery, after 3 monthes and 6 monthes to assess late toxcicity

For all study patients, the following data was recorded; personal &medical history, pathological data and details of treatment received (chemotherapy & radiotherapy)

Radiotherapy:

Dose of radiotherapy 40Gy/15Fr in 3weeks, 5 days a week by use of opposed tangential fields to the whole Breast +/- regional lymph nodes followed by Boost of 10Gy/5Fr given to the tumor bed.

Tumor bed was delineated using preoperative clinical data, cavity seroma or scar.

Treatment plan of radiotherapy:

Immobilization of all patients was done by using a breast board **followed** by CT scanning with slices thickness of 5mm start at 5 mm intervals from top of thyroid notch to 5 cm below contralateral infamammary fold. CT images then transferred to treatment planning system. Delineation and contouring included the GTV and relevant organs-at-risk (OARs) were according to the Radiation Therapy Oncology Group (RTOG) recommendations **(5)**

Tangential fields were designed upon planning target volume based on the delineated target volumes.

Dose-volume histogram was obtained to optimize the plan, also better dose homogeneity was achieved— dose in the target volume ranging from –5% to +7%, in accordance with the ICRU-50 recommendations. The entire breast was treated to a dose of 40 Gy in 15 fractions over 5 weeks, followed by a boost to the tumor bed to a dose of 10 Gy in 5 fractions

Treatment evaluation:

Radiotherapy Toxicity and tolerability was assessed weekly and at the end of treatment and every 3 months & 6 monthes according to follow up protocol of breast cancer.

- Breast cosmesis was assessed by the RTOG (**6)** and Harvard criteria (**7)** respectively. The cosmesis was assessed

before initiation of radiotherapy, weekly during radiotherapy, at end of radiotherapy then at 3&6 months. This was done by patient (subjective) and physician (objective) and by comparing it with the contralateral untreated breast. Breast size, shape, texture, scar was recorded

Results

*300*patients were involved in our study who were proved pathologically to have early stage breast cancer , underwent conservative breast surgery and received ad hypofractionated radiotherapy 40Gy/15Fr followed by Boost of 10Gy/5Fr given to the tumor bed.

Clinic pathological features in patients in our study: (Table 1 & 2)

The age ranged between 31 and 74 years and the median age of patients was 52 years. 78% of patients (234 patients) are obese , 11.7% (35 patients) are overweight and only 9% (27 patients) are average weight, 36% of patients (108 patients) are diabetic and 28.3 % (85 patients) are hypertensive, 62% (186) patients had right breast cancer while 38% (114) patients had left sided cancer. 57.7% (173 patients) of breast cancer lesions detected were in upper outer quadrant, The majority of patients 233 patients (77.7%) were IDC and 67 patients(22.3%) were ILC, Grade II tumors were the predominant representing 66.7% (200 patients), GradeIII were 23.7% (71 patients) and GradeI were 9.7 % (29 patients), The number of patients had T1 tumor was 170 patients (56.7%) ,T2 were 97 patients (32.3%) and the remaining 33 patients (11%) had T3, 57.7% of patients (173 patients) had stage II breast cancer while the remaining 42.3% (127 patients) had stage I . (ER) Hormonal positive patients in our study represented 54.7% (164 patients) and remaining 45.3 % (136 patients) were ER negative .PR hormonal positive patients were 123 patients (41%) while the remaining 59% (177 patients) were PR negative. Lymph node positive patients were 93 patients (31%), while Lymph node negative patients were 207 patients (69%).

Table (1): Basic characteristics of the studied breast cancer patients (N=300).

	All studied patients (N=300)	
Basic characteristics	No.	%
Age (years)		
Mean±SD	51.28	±11.85
Median (Range)	52	(31 – 74)
BMI		
Underweight	4	1.3%
Average weight	27	9%
Overweight	35	11.7%
Obese	234	78%
Hypertension		
Absent	215	71.7%
Present	85	28.3%
Diabetes		
Absent	192	64%
Present	108	36%
Laterality		
Right	186	62%
Left	114	38%
Site of tumor		
UOQ	173	57.7%
UIQ	44	14.7%
LOQ	26	8.7%
LIQ	55	18.3%
Central	2	0.7%

Table (2): Pathological findings and IHC staining of the studied breast cancer patients (N=300).

Pathological findings and IHC staining	All studied patients (N=300)	
	No.	%

Pathology		
IDC NOS	233	77.7%
ILC	67	22.3%
Grade		
Grade I	29	9.7%
Grade II	200	66.7%
Grade III	71	23.7%
LVI		
Absent	201	67%
Present	99	33%
EIC		
Absent	229	76.3%
Present	71	23.7%
pT		
pT1	170	56.7%
pT2	97	32.3%
pT3	33	11%
pN		
pN0	207	69%
pN1	93	31%
Pathological AJCC stage		
Stage I	127	42.3%
Stage IA	127	42.3%
Stage IB	0	0%
Stage II	173	57.7%
Stage IIA	93	31%
Stage IIB	80	26.7%
ER		
Negative	136	45.3%
Positive	164	54.7%
PR		
Negative	177	59%
Positive	123	41%

Late toxcicity was also asssed and the result shows:
67.3% of patients (202 patients) had G0 late skin toxicity
31 % had G2 , 1% (3 patients) had G3 and only 0.7% (2 patients) had G3 late skin toxcicity

Table (3): Radiotherapy induced late skin toxicity among the studied breast cancer patients (N=300).

	All studied patients (N=300)	
Radiotherapy induced skin toxicity	No.	%
Late skin toxicity (at 6th month)		
G0	202	67.3%
G1	93	31%
G2	3	1%
G3	2	0.7%

175 patients (58.3 %) reported good cosmotic outcome at 6 monthes after receiving radiotherapy ,16.3 % of patients reported excellent cosmotic outcome but only 4.3% of patients (13 patients) reported poor outcome . (table 6)
Objective cosmotic outcome at 6 monthes was also assesd and the majority of patients (56.3 %) had good cosmotic outcome but only 5.3% of patients (16 patients) had poor cosmotic outcome. (Table 4)

Table (4): Cosmetic outcome of the studied breast cancer patients (N=300).

	All studied patients (N=300)	
Cosmetic outcome (at 6th month)	No.	%
By patient		
Poor	13	4.3%

Fair	63	21%
Good	175	58.3%
Excellent	49	16.3%
By physician		
Poor	16	5.3%
Fair	65	21.7%
Good	169	56.3%
Excellent	50	16.7%

Categorical variables were expressed as number (percentage).

Considering late skin toxicity , ,There is high significant correlation between , DM, HTN and late skin toxicity .(p value <0.001) No statistical difference between late toxcicity and age, BMI ,or site of tumor. (table 5)

Table (5): Relationship between basic charactertics and late skin toxicity (at 6th month)

Basic charactertics	N	Late skin toxicity (at 6th month)				Test	p-value (Sig.)
		Absent (N=202)		Present (N=98)			
		No.	%	No.	%		
Age (years)							
Mean±SD		51.61	±11.95	50.59	±11.65	-0.750[d]	0.453
Median (Range)		52	(31 – 72)	52	(31 – 74)		(NS)
BMI							
Underweight	4	4	100%	0	0%	0.502[c]	0.479
Average weight	27	15	55.6%	12	44.4%		(NS)
Overweight	35	22	62.9%	13	37.1%		
Obese	234	161	68.8%	73	31.2%		
Hypertension							
Absent	215	160	74.4%	55	25.6%	17.319[b]	<0.001
Present	85	42	49.4%	43	50.6%		(HS)
Diabetes							
Absent	192	161	83.9%	31	16.1%	66.180[b]	<0.001
Present	108	41	38%	67	62%		(HS)
Laterality							
Right	186	124	66.7%	62	33.3%	0.099[b]	0.753
Left	114	77	68.4%	36	31.6%		(NS)
Site of tumor							
UOQ	173	123	71.1%	50	28.9%	11.575[b]	0.021
UIQ	44	26	59.1%	18	40.9%		(S)
LOQ	26	11	42.3%	15	57.7%		
LIQ	55	40	72.7%	15	27.3%		
Central	2	2	100%	0	0%		

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); b: Chi-square test; c: Chi-square test for trend; d: Mann Whitney U test; p-value< 0.05 is significant; Sig.: Significance.

Another significant correlation between late skin toxciciy and chemotherapyp value (0.002) . Regimen of chemotherapy has no significant correlation. P value 0.065 (Table 6)

Table (6): Relationship between adjuvant chemotherapy and late skin toxicity (at 6th month).

Adjuvant chemotherapy	N	Late skin toxicity (at 6th month)				Test	p-value (Sig.)
		Absent (N=202)		Present (N=98)			
		No.	%	No.	%		
Chemotherapy							
No	58	49	84.5%	9	15.5%	9.614[b]	0.002
Yes	242	153	63.2%	89	36.8%		(S)
Regimen							
No	58	49	84.5%	9	15.5%	10.401[b]	0.065
CAF	21	13	61.9%	8	38.1%		(NS)
AC-Taxol	131	85	64.9%	46	35.1%		
AC-Docetaxel	39	25	64.1%	14	35.9%		
EC-Taxol	35	20	57.1%	15	42.9%		
EC-Docetaxel	16	10	62.5%	6	37.5%		

Categorical variables were expressed as number (percentage); b: Chi-square test; p-value< 0.05 is significant; Sig.: Significance

Statistical analysis of data revealed that no significant difference between late toxicity and energy used , irradiated breast& boost volume nor lymph node irradiation .There is only significant difference with bolus use (p value <0.001)

Table (7): Relationship between adjuvant radiotherapy and late skin toxicity (at 6th month).

Adjuvant radiotherapy	N	Late skin toxicity (at 6th month)				Test	p-value (Sig.)
		Absent (N=202)		Present (N=98)			
		No.	%	No.	%		
Energy							
Cobalt-60	15	14	93.3%	1	6.7%	6.025[b]	0.110
6MV	6	5	83.3%	1	16.7%		(NS)
15MV	271	177	65.3%	94	34.7%		
6 & 15MV	8	6	75%	2	25%		
Breast volume (cc)							
Mean±SD		1447.16 ±502.28		1405.28 ±485.22		-0.761[d]	0.446
Median		1412.60		1297.70			(NS)
(Range)		(125.60-2906.60)		(514.30-3001.10)			
Boost volume (cc)							
Mean±SD		108.79 ±45.42		112.75 ±44.87		-0.756[d]	0.450
Median		105.60		106.40			(NS)
(Range)		(15.90-198.60)		(29.50-199.50)			
Boost type							
Photon	256	170	66.4%	86	33.6%	0.682[b]	0.409
Electron	44	32	72.7%	12	27.3%		(NS)
Bolus use							
No	271	191	70.5%	80	29.5%	12.618[b]	<0.001
Yes	29	11	37.9%	18	62.1%		(HS)
LN irradiation							
No	200	133	66.5%	67	33.5%	0.189[b]	0.663
Yes	100	69	69%	31	31%		(NS)

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); b: Chi-square test; d: Mann Whitney U test; p-value< 0.05 is significant; Sig.: Significance.

According to subjective comotic outcome at 6 monthes , there is significant correlation between it and DM (p value <0.001), HTN (p value 0.002) No significance detected between it and age ,BMI nor tumor location. (Table 8)

Table (8): Relationship between basic charactertics and cosmetic at 6month by patient.

Basic charactertics	N	Cosmetic at 6month by patient				Test	p-value (Sig.)
		Poor - Fair (N=76)		Good - Excellent (N=224)			
		No.	%	No.	%		
Age (years)							
Mean±SD		50.21 ±11.81		51.64 ±11.86		-0.930[d]	0.353

Median (Range)			53 (31 – 73)		52 (31 – 74)		(NS)
BMI							
Underweight	4	0	0%	4	100%	1.065[c]	0.302
Average weight	27	9	33.3%	18	66.7%		(NS)
Overweight	35	13	37.1%	22	62.9%		
Obese	234	54	23.1%	180	76.9%		
Hypertension							
Absent	215	44	20.5%	171	79.5%	9.507[b]	0.002
Present	85	32	37.6%	53	62.4%		(S)
Diabetes							
Absent	192	32	16.7%	160	83.3%	21.178[b]	<0.001
Present	108	44	40.7%	64	59.3%		(HS)
Laterality							
Right	186	52	28%	134	72%	1.781[b]	0.182
Left	114	24	21.1%	90	78.9%		(NS)
Site of tumor							
UOQ	173	39	22.5%	134	77.5%	9.668[b]	0.046
UIQ	44	16	36.4%	28	63.6%		(S)
LOQ	26	11	42.3%	15	57.7%		
LIQ	55	10	18.2%	45	81.8%		
Central	2	0	0%	2	100%		

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); b: Chi-square test; c: Chi-square test for trend; d: Mann Whitney U test; p-value< 0.05 is significant; Sig.: Significance.

There is also significant correlation between cosmetic outcome at 6month by patient and chemotherapy (p value 0.024). Regimen of chemotherapy has no significant correlation. (Table 9)

Table (9): Relationship between adjuvant chemotherapy and cosmetic at 6month by patient.

	N	Cosmetic at 6month by patient				Test	p-value (Sig.)
		Poor - Fair (N=76)		Good - Excellent (N=224)			
Adjuvant chemotherapy		No.	%	No.	%		
Chemotherapy							
No	58	8	13.8%	50	86.2%	5.062[b]	0.024
Yes	242	68	28.1%	174	71.9%		(S)
Regimen							
No	58	8	13.8%	50	86.2%	6.336[b]	0.275
CAF	21	6	28.6%	15	71.4%		(NS)
AC-Taxol	131	34	26%	97	74%		
AC-Docetaxel	39	11	28.2%	28	71.8%		
EC-Taxol	35	11	31.4%	24	68.6%		
EC-Docetaxel	16	6	37.5%	10	62.5%		

Categorical variables were expressed as number (percentage); b: Chi-square test; p-value< 0.05 is significant; Sig.: Significance.

Statistical analysis of data revealed that there is also no significant difference between subjective cosmotic outcome and energy used , irradiated breast& boost volume nor lymph node irradiation .There is only significant difference with bolus use (p value 0.011) (Table 10)

Table (10): Relationship between adjuvant radiotherapy and cosmetic at 6month by patient.

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	N	Cosmetic at 6month by patient		Test	p-value (Sig.)
Adjuvant radiotherapy		Poor - Fair (N=76)	Good – Excellent (N=224)		

		No.	%	No.	%		
Energy							
Cobalt-60	15	0	0%	15	100%	6.582[b]	0.086
6MV	6	1	16.7%	5	83.3%		(NS)
15MV	271	74	27.3%	197	72.7%		
6 & 15MV	8	1	12.5%	7	87.5%		
Breast volume (cc)							
Mean±SD		1431.70 ±502.33		1434.08 ±495.44		-0.361[d]	0.718
Median		1297.70		1412.60			(NS)
(Range)		(685.70-3001.10)		(125.60-2096.60)			
Boost volume (cc)							
Mean±SD		110.33 ±47.44		110.01 ±44.53		-0.105[d]	0.916
Median		103.95		105.60			(NS)
(Range)		(15.90-199.50)		(15.90-198.60)			
Boost type							
Photon	256	65	25.4%	191	74.6%	0.003[b]	0.956
Electron	44	11	25%	33	75%		(NS)
Bolus use							
No	271	63	23.2%	208	76.8%	6.450[b]	0.011
Yes	29	13	44.8%	16	55.2%		(S)
LN irradiation							
No	200	54	27%	146	73%	0.881[b]	0.348
Yes	100	22	22%	78	78%		(NS)

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); b: Chi-square test; d: Mann Whitney U test; p-value< 0.05 is significant; Sig.: Significance.

Analysis of data also revealed significant correlation between objective cosmetic outcome by at 6 monthes and DM (p value 0.001) & HTN (p value 0.0210) No statistical difference was detected between it and age , BMI nor tumor localization . (Table 10)

Table (10): Relationship between basic charactertics and cosmetic at 6 month by physician.

Basic charactertics	N	Cosmetic at 6 month by physician								Test	p-value (Sig.)
		Poor (N=16)		Fair (N=65)		Good (N=169)		Excellent (N=50)			
		No.	%	No.	%	No.	%	No.	%		
Age (years)											
Mean±SD		50.06	±13.34	51.95	±11.32	51.26	±12.01	50.86	±11.80	0.503[a]	0.918
Median (Range)		53.50	(31 – 73)	56	(31 – 74)	52	(31 – 71)	52	(31 – 72)		(NS)
BMI											
Underweight	4	0	0%	0	0%	2	50%	2	50%	0.407[c]	0.523
Average weight	27	1	3.7%	7	25.9%	12	44.4%	7	25.9%		(NS)
Overweight	35	2	5.7%	10	28.6%	21	60%	2	5.7%		
Obese	234	13	5.6%	48	20.5%	134	57.3%	39	16.7%		
Hypertension											
Absent	215	11	5.1%	37	17.2%	127	59.1%	40	18.6%	9.744[b]	0.021
Present	85	5	5.9%	28	32.9%	42	49.4%	10	11.8%		(S)
Diabetes											
Absent	192	6	3.1%	31	16.1%	120	62.5%	35	18.2%	16.761[b]	0.001
Present	108	10	9.3%	34	31.5%	49	45.4%	15	13.9%		(S)
Laterality											
Right	186	11	5.9%	45	24.2%	102	55.8%	28	15.1%	2.710[b]	0.439
Left	114	5	4.4%	20	17.5%	67	58.8%	22	19.3%		(NS)
Site of tumor											
UOQ	173	8	4.6%	38	22%	97	56.1%	30	17.3%	10.099[b]	0.607

UIQ	44	1	2.3%	12	27.3%	25	56.8%	6	13.6%	(NS)
LOQ	26	3	11.5%	8	30.8%	12	46.2%	3	11.5%	
LIQ	55	4	7.3%	7	12.7%	13	60%	11	20%	
Central	1	0	0%	0	0%	1	100%	0	0%	

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); a: Kruskal Wallis H test; b: Chi-square test; c: Chi-square test for trend; p-value< 0.05 is significant; Sig.: Significance

Finally , no significance was detected between objective cosmotic outcome at 6 monthes and adjuvant chemotherapy (p value 0.301) (Table 11)

Table (11): Relationship between adjuvant chemotherapy and cosmetic at 6 month by physician.

Adjuvant chemotherapy	N	Cosmetic at 6 month by physician								Test	p-value (Sig.)
		Poor (N=16)		Fair (N=65)		Good (N=169)		Excellent (N=50)			
		No.	%	No.	%	No.	%	No.	%		
Chemotherapy											
No	58	2	3.4%	8	13.8%	36	62.1%	12	20.7%	3.654[b]	0.301
Yes	242	14	5.8%	57	23.6%	133	55%	38	15.7%		(NS)
Regimen											
No	58	2	3.4%	8	13.8%	36	62.1%	12	20.7%	18.636[b]	0.231
CAF	21	0	0%	3	14.3%	16	76.2%	2	9.5%		(NS)
AC-Taxol	131	7	5.3%	34	26%	71	54.2%	19	14.5%		
AC-Docetaxel	39	2	5.1%	11	28.2%	17	43.6%	9	23.1%		
EC-Taxol	35	2	5.7%	7	20%	19	54.3%	7	20%		
EC-Docetaxel	16	3	18.8%	2	12.5%	10	62.5%	1	6.2%		

Categorical variables were expressed as number (percentage); b: Chi-square test; p-value< 0.05 is significant; Sig.: Significance.

Discussion

WBRT alone reduces the 10-year risk of recurrence (including locoregional and distant) by 15% and the 15-year risk of breast cancer-related mortality by 4% [7]. Radiation boost gives a further 50% RR reduction and is indicated for most patients who have unfavourable risk factors for local control such as age<50 years, grade 3 tumors, presence of lymphovascular invasion, hormone receptor negativity or extensive intraductal component and non-radical tumor excision (focally—otherwise further surgery should be advocated).(**8).** Reactions occur within 1–4 weeks of treatment and range from erythema to dry or wet desquamation; ulceration may occur in more severe cases. Skin toxicity may affect women for a long time post-treatment **Whelan et al. (9).** RT-induced skin toxicity is a prominent clinical problem affecting the majority of breast cancer patients receiving adjuvant RT and can lead to temporary or permanent cessation of treatment. Severe skin reactions may be painful, lead to localized or occasionally systemic infection, and cause permanent scarring. The incidence of RT-related toxicity may be reduced by refinements in radiation techniques, such as improving dose conformity and dose homogeneity within the irradiated area. **Whelan et al. (9).**

Considering late skin toxicity, In the current study we observed high significant correlation between , DM &chemotherapy and late skin toxcicity.

Similar results in Ciammella , et al. (10) that Diabetes and chemotherapy were found to be statistically significant on the occurrence of late fibrosis**.**

The current study showed there is statical significance between late skin toxcicity and hypertention which was against results of **and Ciammella , et al. (11)** As hypertension didn't show any statistical difference

and Ciammella , et al. (11) results aslo showed that there is statical significance between late skin toxcicity and boost administration which wasn't found in the current study as all patients received boost dose .

The current study results revealed that no significant difference between late toxicity and energy used , irradiated breast& boost volume nor lymph node irradiation . this was confirmed also by **Ciammella , et al. (10) and Morsy, et al.(11)**

The main goals of BCT in early stage breast cancer are to provide primary tumor control comparable to mastectomy and to preserve an acceptable cosmetic appearance of the breast. An unsatisfactory cosmetic outcome should be considered as a potential late toxicity. Studies that include patient-rated cosmetic evaluations demonstrate good concordance with physician-rated cosmesis and satisfaction with a range of cosmetic outcomes **(12).**

The principal long-term effects that impair cosmeses are telangiectasia, fibrosis and atrophy of the breast. Fibrosis and atrophy are the result of specific responses of fibrocytes to irradiation. Fibrosis represents a proliferative response of the surviving fibrocytes to growth factors released by injury, and atrophy reflects both loss of fibrocytes and collagen reabsorption (**14).**
The present study showed There is significant correlation between, DM, HTN and comotic outcome by patients at 6 months , there is also significant correlation between chemotherapy and cosmetic at 6month by patient.
In Ragaz J, et al.(14) study, Seventeen patients (59%) got unsatisfactory results (11, and 6 patients in conventional and hypofractionation group, respectively). The ratio between lumpectomy volume to the remaining irradiated breast volume was the most sensitive predictor to the cosmetic outcome. Those with satisfactory results had a lower ratio of 0.3±0.2 compared to their counterpart who had a ratio of .5±0.2 (p=0.02)
In a prospective assessment of late changes in breast appearance in 559 patients (all treated with conventional fractionation), **Moody et al. (15**) noted a strong association with breast size. Only 6% of patients with small breasts developed moderate or severe late changes compared with 22% with medium sized breasts and 39% of patients with large breasts ($p<0.001$). To explore the reason, radiation dose distributions were assessed in three-level transverse CT images of the breast. There was a significant relation between breast size and dose inhomogeneity, which may account for the marked changes in breast appearance reported in women with large breasts.
Washington University found that the percentage of excellent/good cosmetic outcomes decreased with the use of more than 2 fields ($P = 0.034$), and increasing radiation dose to the entire breast ($P = 0.024$). With increasing separations at the central axis, a relative deterioration occurred in excellent/good ratings, especially with the use of lower energy, 4 MV photons. This is inferred to be from the dose inhomogeneity that occurs with the larger chest-wall separation. The effect of dose homogeneity on cosmetic outcome is again demonstrated in this study by a significantly higher frequency of excellent/good cosmetic scores (82%) that occurred with the use of compensating filters compared with no use of compensating filters (59%) ($P = 0.002$). Daily fraction size (1.8 vs. 2.0 Gy), boost versus no boost, and the type of boost did not influence cosmetic outcome in this series. **(12).**
Other studies have confirmed the influence of radiation therapy factors on cosmetic outcomes. For instance, **Ryoo et al.** (**16**) reported that the use of a wedge in the breast tangents was a significant factor for obtaining a good cosmetic result. (**16).**
Wazer et al (18), demonstrated an increase in fair/poor cosmetic outcomes with larger chest-wall separations (24 cm mean) and greater maximal dose inhomogeneity (13% mean) at the central axis. The use of a boost and a supraclavicular and/or axillary field were the other factors associated with a higher proportion of fair/poor cosmetic outcomes. In this study, an electron boost, but not an interstitial implant boost, was associated with the decline in cosmetic outcome. (**17)**

In an attempt to objectively measure cosmetic outcome, **Pezner et al**. **(18)** developed a Breast Retraction Assessment that quantified the amount of retraction of the treated breast in comparison to the untreated one by measuring the lateral and vertical displacement of the nipple. On multivariate analysis in order of descending importance, patient age > 60, extensive breast resection, patient weight > 150 pounds, and upper quadrant primary site were the most significant factors related to breast retraction after BCT. None of the RT parameters studied were associated with breast retraction. Subset analysis related that the volume of the boost had some relation to retraction, but did not reach statistical significance. (**18)**

It has been demonstrated in many studies that surgical factors associated with bad cosmesis including the extent or volume of surgical resection and scar orientation have the largest impact on breast appearance and the cosmetic outcome. The use of chemotherapy and patient factors such as breast size, older age, and race have also been associated with more frequent cosmetic failures (**17)**

Conclusion

HF-WBI is feasible and safe, because of the low rate of moderate-high scores toxicity. Chemotherapy and DM had impact on late fibrosis .the rate of severe toxicity (> grade 2) was low even in these patients

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