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LOCOREGIONAL RECURRENCE IN PATIENTS WITH NODE NEGATIVE EARLY BREAST CANCER WHO RECEIVED ADJUVANT HYPOFRACTIONATED RADIOTHERAPY REGIMEN VS. CONVENTIONAL FRACTIONATION REGIMEN AFTER BREAST CONSERVATIVE SURGERY RETROSPECTIVE STUDY

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Keywords:

early breast cancer, hypofractionation, local recurrence.

Abstract

Objective: to retrospectively compare the risk of locoregional recurrence (LRR) in patients with node negative early breast cancer between patients who have been treated with adjuvant hypofractionated radiotherapy (HFRT) regimen to those who have been treated with adjuvant conventional fractionation regimen (CFRT).

Patients and methods: Medical records of 144 patients with stage I and II breast cancer with negative lymph nodes were reviewed retrospectively. Median follow up was 46 months (range 41.8-50.8)

Results:100 patients received adjuvant GFRT while 44 patients received CFRT. LRR rate was 4.9 %. No statistical significance (P-value 0.62) was found between both CFRT (95% CI 89-103) and HFRT (95% CI 107.4-117.4) regarding mean time to local failure. ER and HER2 receptor status and overall radiotherapy treatment time (OTT) were found to be correlated significantly with mean time to local failure.

Conclusion:HFRTis equivalent to alternative conventional technique for patients diagnosed with stage I, II node negative breast cancer regarding Locoregional control, disease free survival and overall survival.

Introduction

Worldwide, breast cancer is the most frequently diagnosed cancer **(1),**accounting for 1.67 million new cases diagnosed each year, approximately one new case diagnosed every 18 seconds **(2).**In Egypt, it comes as the second most common cancer after hepatic cancer representing 15.4 % of all diagnosed cancers**(3).** In Ain Shams University hospitals (El- Demerdash Hospital), breast cancer represented around 25 % of all cases that registered in the outpatient clinics in 2017 and 2018, in 2017 out of 2274 patients registered in the different outpatient clinics, 613 patients presented with breast cancer, while in 2018, 583 patients were presented with breast cancer out of 2452 patient with other diagnoses. a cooperation of a multidisciplinary team of surgical oncology, medical oncology and radiotherapy is needed for proper management as this cooperation showed a reduced breast cancer mortality **(4).** Replacement of mastectomy with breast conservative therapy (BCT) is one of the most advances in the management of breast cancer as the standard of care for patients with early breast cancer as it showed equivalent disease-free and overall survival (OS), and better cosmetic outcomes in comparison to mastectomy **(5)**. Adjuvant whole breast irradiation (WBI) has demonstrated in addition to its known benefits for local control, an overall survival (OS) benefits with a 15-years reduction in breast cancer mortality **(6).** American Society for Radiation Oncology (ASTRO) in its most recent guidelines encouraged hypofractionated adjuvant WBI with the regimen of 40 Gy in 15 fractions or 42,5 Gy in 16 fractions. **(7).** WBI may be associated with acute radiation toxicity such as skin reactions, and late ones, such as cardiotoxicity, pulmonary toxicity and secondary malignancies**(8)**

Methods

Study population

This is a retrospective study that included 144 patients who were diagnosed with invasive breast cancer proved by histopathology, presented to Ain Shams University hospital during the period from 1st of January 2008 till 31th of December 2017 and fulfilling the inclusion criteria, obtained from filing system. All of patients were > 18 years old**,**

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stage I, II breast cancer with node negative disease only, all patients underwent breast conservative surgery followed by adjuvant WBI +/- boost irradiation to tumor bed.

One hundred patients received adjuvant HFRT-WBI either 45.05 cGy in 17 fractions fractionsor 4005 cGy in 15 fractions +/- boost to the tumor bed. Forty-four patients received adjuvant CFRT (50 Gy in 25 fractions) +/- boost to the tumor bed.

Outcome measure
Local recurrence was defined as disease recurrence within the ipsilateral breast or chest wall. Regional Recurrence was defined as disease recurrence in the ipsilateral axillary nodes, internal mammary nodes, or supraclavicular nodes. Locoregional recurrence was assessed by regular clinical examination, yearly bilateral sonomammography, MRI breast if query local recurrence in sonomammogram, fine needle aspiration cytology (FNAC) or ultras-sound guided biopsy and subsequent histopathological examination if suspected malignant local recurrence. Time to local failure was calculated from the date of surgery to local relapse. Overall Survival was calculated from the date of surgery to the date of death or last follow up. Regular clinical follow up of symptoms and signs of either late pulmonary or cardiac toxicity, with further investigations if needed such as ECHO, CXR, and CT chest. The length of follow up was calculated from the date of surgery to the date of most recent imaging or clinical review in which disease status was recorded.

Statistical analysis:
Data management and nalysis were performed using The Statistical Package for the Social Sciences (SPSS) version 14 (SPSS Inc., Chicago. IL). Categorical variables were presented as numbers and percentages and continuous variables as means and standard deviation. Survival analysis was performed using the Kaplan Meier method and the Log Rank test to determine the significance of difference in survival. The significance of difference in the frequency of categorical variables between groups was determined using Chi-square test or Fisher's exact test when appropriate. Statistical significance was assumed at $P < 0.05$.

Results

Patient's characteristics
The clinical and pathological characteristics were similar between both groups of HFRT and CFRT (table 1), median follow up time was 46 months (range 41.8-50.8)

table (1): summarize patient's characteristics:

		No of patients (No.=144)		**P-value**
		Convent (No.=44)	**HFRT (No.=100)**	
Age	< 45	13 (29.5)	31 (31.0)	1.0
	≥ 45	31 (70.5)	69 (69.0)	
	Range	30-70	25-81	
	Mean	49.14 (9.96)	49.97 (11.11)	0.66
	Median	47.50	50.00	0.7333

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Menopausal Status	Peri	1 (2.3)	5 (5.0)	0.626
	Pre	24 (54.5)	45 (45.0)	
	Post	19 (43.2)	50 (50.0)	
Family history (FH)	Breast cancer, 1st degree	3 (6.8)	9 (9.0)	0.803
	Breast cancer, 2nd degree	4 (9.1)	5 (5.0)	
	OTHER MALIGNANCY	2 (4.5)	4 (4.0)	
	No malignancy	35 (79.5)	82 (82.0)	
Histological Subtype	DCIS with microinvasion	1 (2.4)	1 (1.1)	0.572
	IDC	36 (87.8)	84 (92.3)	
	ILC	1 (2.4)	2 (2.2)	
	Invasive Medullary	1 (2.4)	3 (3.3)	
	Mucoid	1 (2.4)	1 (1.1)	
	Tubular	1 (2.4)	0 (0.0)	
	NA	3	9	
Histopathological Grade (G)	I	1 (2.8)	0 (0.0)	0.441
	II	33 (91.7)	78 (94.0)	
	III	2 (5.6)	5 (6.0)	
	NA	8	17	
Staging				
Tumor Size (T)	**T1**	17 (38.6)	35 (35.0)	0.879
	T2	26 (59.1)	62 (62.0)	
	T3	1 (2.3)	3 (3.0)	
Dissected lymph nodes (N)	<10	8 (18.6)	9 (9.0)	0.178
	≥ 10	35 (81.4)	91 (91.0)	
	NA	**1**		
IHC				
ER	Positive	14 (31.8)	25 (25.5)	0.565
	Negative	30 (68.2)	73 (74.5)	

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	NA	0	2	
PR	Positive	14 (31.8)	33 (33.7)	0.981
	Negative	30 (68.2)	65 (66.3)	
	NA		2	
HER2 Neu	Positive	37 (90.2)	75 (79.8)	0.212
	Negative	4 (9.8)	19 (20.2)	
	NA	3	6	
KI 67	**< 20 %**	6 (40.0)	29 (59.2)	0.313
	≥ 20 %	9 (60.0)	20 (40.8)	
	N/A	29	51	
PNI	Negative	10 (90.9)	35 (100.0)	
	Positive	1 (9.1)	0 (0.0)	0.239
	NA	33	65	
LVI	Negative	10 (90.9)	31 (88.6)	1.000
	Positive	1 (9.1)	4 (11.4)	
	NA	33	65	
Carcinoma in situ	Absent	10 (45.5)	13 (28.9)	0.286
	Present	12 (54.5)	32 (71.1)	
	NA	22	55	
Surgical Margin	Negative	36 (100.0)	81 (97.6)	1
	Positive	0 (0.0)	2 (2.4)	
	NA	8	17	
Surgery/RTH interval	≤ 6 months	20 (45.5)	36 (36.0)	0.375
	> 6 months	24 (54.5)	64 (64.0)	
RTH OTT delay	No delay	23 (52.3)	51 (51.0)	0.728
	Delay of 7 days	2 (4.5)	5 (5.0)	
	Delay 8-14 days	7 (15.9)	23 (23.0)	
	Delay>2 wks	12 (27.3)	21 (21.0)	
CTH	**No**	8 (18.2)	14 (14.0)	0.696
	Yes	36 (81.8)	86 (86.0)	
Trastuzumab in HER2 +ve patients (no.= 23)		**No.= 4**	**No.=19**	
	Yes	3 (75.0)	7 (36.8)	0.281
	No	1 (25.0)	12 (63.2)	

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FH= Family History, RTH= Radiotherapy, OTT= overall treatment time, DCIS= ductal carcinoma in situ, IHC = Immune Histochemistry, ER= Estrogen Receptor, PR= Progestron Receptor, PNI= Perineural invasion, LVI= lymphovascular invasion.

Treatment outcomes

locoregional control

Median TLC failure was not reached, the overall mean TLC failure was 112.4 months (95 CI 107.4-117.4), with 96 months (95% CI 89-103) for patients treated with CFRT and 111.9 months (95% CI 107.4-117.4) for those treated with HFRT without statistical significance between them. (P value=0.62)

Table (2): Comparison between patients who received CFRT vs. HFRT regarding TLC failure:

arm	Mean(a)			Chi-square test	P-value
	Estimate	95% Confidence Interval			
		Lower Bound	Upper Bound		
CFRT	96.051	89.036	103.066	.237	.627
HFRT	111.968	104.092	119.844		
Overall	112.461	107.476	117.446		

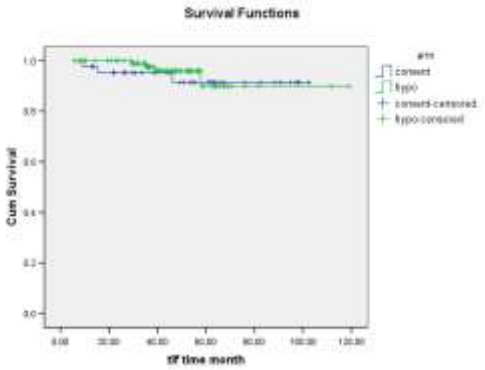

Fig (1): survival curves of TLC between patients received CFRT (blue) vs. HFRT (green)

Diseasefree survival

Median disease free survival was not reached, mean disease free survival was 107.6 months, 107 months for patients who received HFRT regimen, while it was 91.6 months for patients who received CFRT without statistical significance (P value 0.5)

Table (3): Comparison between patients who received CFRT vs. HFRT regarding disease free survival:

arm	Mean(a)			Chi	P-
	Estimate		95% Confidence Interval		

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			Lower Bound	Upper Bound	- Square	value
CFRT	91.626		82.77	100.474		
HFRT	107.01		97.49	116.533	0.33	0.562
Overall	107.68		101.36	114.002		

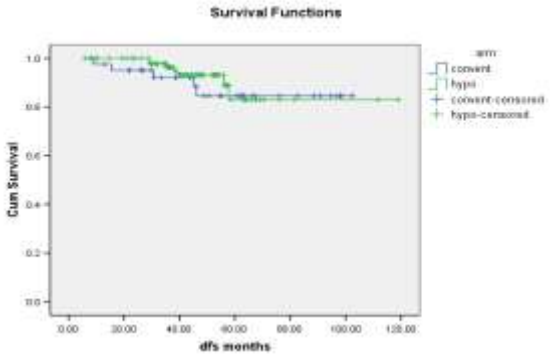

Fig (2): survival curves of DFS between patients received CFRT (blue) vs. HFRT (green)

2.2.3. Overall survival

Five cases were reported to die from breast cancer after reported multiple distant metastasis, 4 patients received HFRT, while one case received CFRT. Median overall survival was not reached, overall mean survival was 113 months for all cases (CI 95% 107.862-118.308), 100 months (CI 95% 95.968-104.550) for patients who received CFRT, 110 months (CI 95% 101.351-119.457) for patients who received HFRT without statistical significance between both groups.

Table (4): Comparison between patients who received CFRT vs. HFRT regarding overall survival:

	arm	Mean(a)					
		Estimate		95% Confidence Interval		Chi-Square	P-value
				Lower Bound	Upper Bound		
	CFRT	100.25		95.968	104.550		
	HFRT	110.40		101.351	119.457	1.004	0.316
	Overall	113.85		107.862	118.308		

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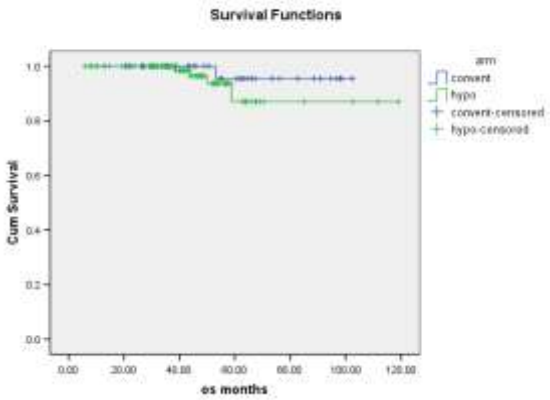

Fig (3): survival curves of OS between patients received CFRT (blue) vs. HFRT (green)

Only two patients were found to have non-clinically significant radiological evidence of pulmonary toxicity, one patient was presented with non-specific interstitial pneumonitis and the other patient was presented with reactionary minimal pleural thickening (table 5), and none of the patients had cardiac toxicity.

Table (5): Radiotherapy pulmonary toxicity between CFRT & HFRT:

RTH pulmonary toxicity		**CFRT (no.= 44)**	HFRT (no.=100)	**P-value**
	yes	43 (97.7)	99 (99.0)	0.519
	No	1 (2.3)	1 (1.0)	

correlation between time to local failure and other factors

Many factors were tested to find out if they can potentially influence time to local failure. (table 6)

Out of all of these factors, 3 factors were found to be significantly correlated to TLC failure which are ER receptor status (fig. 4), hER 2 neu receptor status (fig. 5) and overall radiotherapy treatment time gap (fig. 6), while all other factors were found to be of no statistical significance.

Table (6): correlation between time to local failure and other factors:

	Total N	TLC (months)	95% Confidence Interval		Log rank test	
		mean	Lower Bound	Upper Bound	X^2	P-value
Age (yrs)						
< 45	44	94.41	89.01	99.792	0.03	0.9
≥ 45	100	112.3	106.2	118.43		
Menopausal						
postmenopause	69	114.5	109.5	119.58	0.62	0.4

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premenopause	75	84.84	78.77	90.919		
ER						
+ve	103	114.5	109.1	119.81	4.64	0
-ve	39	91.56	81.59	101.52		
PR						
+ve	95	112.9	106.8	119.07	0.56	0.5
-ve	47	92.26	85.57	98.939		
Her2						
+ve	23	51.78	46.67	56.894	6.1	0.1
-ve	112	113.9	108.7	119.09		
T stage						
1	52	93.93	88	99.852	0.31	0.6
2,3	92	112.8	107.5	118.15		
Grade						
I, II	112	111.8	105.9	117.64	1.67	0.2
III	7	48.76	41.7	55.814		
LVI						
+ve	5	51.67	37.64	65.702	2.54	0.1
-ve	41	84.27	77.11	91.438		
In situ component						
present	44	93.23	84.69	101.76	0.04	0.8
absent	23	101.9	89.13	114.71		
Surgery/RTH interval						
≤ 6 months	58	114.9	109.1	120.63	0.55	0.5
> 6 months	86	95.83	89.86	101.8		
RTH OTT delay						
1 (no or 7days	81	101.3	98.99	103.62	10.4	0
2 (7 to 14 d)	30	110.9	99.96	121.8		
3 (>2w)	33	66.26	57.51	75.005		
FH						
+ve FH		94.64	87.63	101.64	0.1	0.8
-ve FH		111.9	106	117.74		
LN excised						
< 10		97.06	86.73	107.39	.03	0.9
≥ 10		112.3	106.8	117.87		
Ki 67						

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< 20 % ≥ 20%	No statistics are computed because all cases are censored.					
CTH						
yes	122	107.1	100.2	113.99	0.2	0.7
No	22	84.31	76.39	92.231		
Trastuzumab	23					
yes	13	51.91	46.11	57.721	0.39	0.5
no	10	44.38	35.73	53.021		

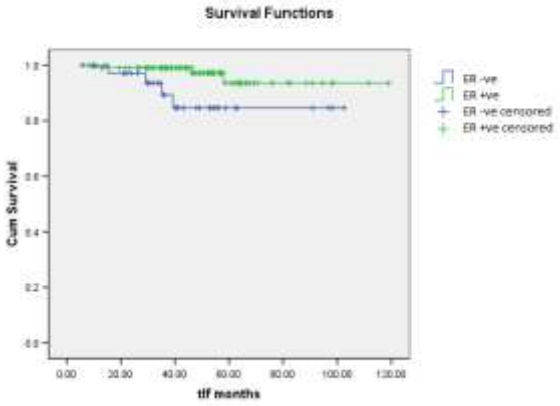

Figure (4): survival curves of TLC failure between patients with +ve ER receptors (green) vs. –ve ER receptors (blue)

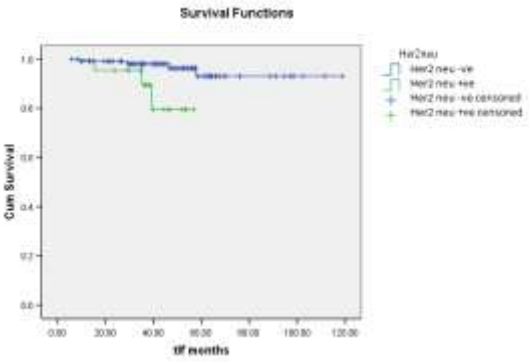

Figure (5): survival curves of TLC failure between patients with +ve Her2-neu receptors (green) vs. –ve Her2-neu receptors (blue)

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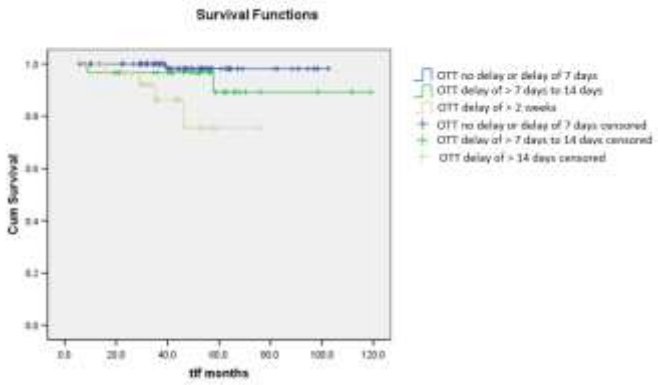

Figure (6): survival curves of TLC between patients with no delay or 7 days delay (blue) vs. OTT delay of > 7-14 delay (green) vs. OTT > 2 weeks (orange)

Discussion

In our study, patients were not equally distributed between the two fractionation arms where most of patients, 100 patients (69.4 %) received HRT, while only 44 patients (30.6%) received CRT, this is can be attributed to preference of hypofractionation technique for patients with early stage node negative breast cancer as this treatment technique was supported by the early promising results of START A and B trials **(9,10).**

In our study, LRR was 4.9 % which corresponds to the 10 years' local failure from the National Surgical Adjuvant Breast and Bowel Project which was 5.2 % in node negative breast cancer who underwent BCT and adjuvant systemic therapy **(11),** but it's lower than the local recurrence reported in the International Breast Cancer Study Group Trials I to V where local recurrence was 10. 2 % after 24 year follow up of 4,105 patients between 1978 and 1985 **(12),** and this can be attributed to the discrepancy in the period of follow up, 48 months in our study vs. 24 years in the other study and also due to different treatment approaches used currently such as chemotherapy protocols, radiotherapy techniques, adjuvant hormonal therapies and eventually monoclonal antibodies that used in HER2 receptor positive breast cancer.

LRR was similar between both groups of fractionation schedules and this is consistent with the 10 years results of Ontario Clinical Oncology Group Trial that have the same patients characteristics as our study that included 1234 patients all T1, T2 with node negative disease and the risk of local recurrence at 10 years was similar for both fractionation schedules**(13)** and was furtherly confirmed in the 12 years results update analysis **(14),** our results is also consistent with 10 years results of START A trial 10-year where rates of local-regional relapse did not differ significantly between the 41.6 Gy and 50 Gy regimen groups or the 39 Gy group **(9)**, and also with the results from START-B where the proportion of patients with local-regional relapse at 10 years did not differ significantly between the 40 Gy group and the 50 Gy group **(10)**

In our study neither DFS nor Overall survival were significantly different between both fractionation schedules and these results are consistent with results from START-A trial, and also from Ontario Clinical Oncology Group Trial where no significant overall survival difference between the two treatment groups at a median follow-up of 10 and 12 years and also it's the same results from meta-analysis of 6593 patients from 4 randomized controlled trials that showed no significant difference between arms of HFRT and CFRT **(15).**

In all of the large randomized trials latecardiopulmonary toxicity were similar between both fractionation schedules but it couldn't be assessed properly in our study as only 2 patients had late pulmonary toxicity, one of them received HFRT-WBI while the other received CFRT, and none had cardiological toxicity.

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Our study found that patients with ER negative receptors, Her 2 neu +ve receptors were correlated with statistically significant higher risk for local recurrence.

These results are consistent with results from a retrospective multi-center American study, where Her-2 neu and basal subtypes were associated with higher local recurrence rates **(16)** and also from the Danish study **(17)** and also with results from British Colombia Cancer Agency study where rates of local and regional recurrence were higher in patients HER2-enriched subtypes in comparison to patients with luminal A tumors **(18),** also a large data analysis of 14,595 patient showed matched data that HER2 enriched and TNBC were the subtypes associated with increased rate of local and regional recurrence followed by luminal/HER2 subtypes while the luminal A and B subtypes showed lower local and locoregional recurrence and also showed statistically significant better DFS **(19)**.

Also many in vitro Studies confirm these clinical results, where Her2 over expression modulates radiation resistance in breast cancer cells **(20)** the over-expression of HER2 is the main factor for low radiosebnsetivity due to different molecular mechanisms that regulate cell invasion and proliferation, also other studies suggest that the activation of focal adhesion Kinase (Fak) through the reduction of apoptosis and anoikis**(21),** another suggested mechanism is the modulation of FAS death receptor, a cell surface receptor that contains intracellular "death domain" that affects initiation of the apoptotic cell death after anticancer treatment **(22)**, Lack of Er receptors is associated with modification of the cell cycle distribution and the reduction of the radiation induced autophagy **(23).**

In our study radiotherapy overall treatment time (OTT) delay i.e. treatment interruption of 2 weeks or more was significantly correlated with higher risk of local recurrence, while paradoxically treatment delay of less than two weeks had a longer mean time for local control than patients who have no delay, but it didn't reach any statistical significance and this may be attributed to small sample size. in a study by Bese and her colleagues reported deleterious effect on both local control and even survival if treatment delay exceeds 7 days in the conventional regimen, while a gap of seven days had a non-statistically significant poorer local control than patients who have been treated with a less time gap **(24).**

From a radiobiological point of view, it is difficult to explain why the extension of the interruption to less than 2 weeks did not detectably influence the local control as the potential doubling times (Tpot) of breast cancers measured by cell flow cytometry do not reflect clinical volume doubling times and Tpot of breast tumors which has a wide spectrum, ranging from 1 week to 90 days **(25).** The mechanism may be repopulation of tumor clonogens due to either a de novo high proliferation fraction or accelerated repopulation that occurs in response to anti-neoplastic treatment which affect the Tumor Control Probability (TCP) **(26).** Although biological effective dose time charts are applied to correct interruptions, it is evident that adequate compensation is difficult for long time gaps **(27).**

The main strength of this study includes the homogenous study cohort, all patients had T1, T2, or T3, all with node negative disease.

We recognize limitations with this study including its retrospective nature, need for longer follow up period, low statistical power due to small population sample size, small number of patients in the conventional group but we addressed the rational cause for that result earlier in the discussion, also some files have been lost which added to this problem, lost data also was one of the limitations such as lost surgical pathology reports so we have to continue the lost data from the filing system which may lead to some inaccuracy of data, also a lot of patients were only referred to receive radiotherapy at the demerdash hospital so there were not enough data about their whole treatment plan and might lead to inhomogeneous treatment and follow up strategy.

Conclusion

WBI delivered over a shorter period of time as hypofractionation technique is found to be non-inferior to alternative conventional technique for patients diagnosed with stage I, II node negative breast cancer as it has a comparable local control, disease free survival, overall survival with conventional radiotherapy, cost-effective for health care facilities and more convenient for patients and their families.

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