Adjuvant hypofractionated versus conventional fractionated radiotherapy in nodal positive breast cancer

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Abstract:

Background: For patients with breast cancer, radiation therapy (RT) is an effective treatment option. Locoregional RT is linked to significant decreases in local and regional recurrence, as well as modest gains in distant disease control and survival. Data analysis of multiple previous studies confirmed that hypofractionated (HF) breast RT has the same effect of conventional fractionation as regards controlling of the disease in node negative breast cancer. Concerns regarding side effects and a lack of data on the efficacy of hypofrationation for node-positive cases have limited the use of HF regional nodal RT

Patients and methods: This is a retrospective study assessed long-term, breast cancer-specific outcomes in node positive cases. 618 patients were included. And according to the radiotherapy protocol of treatment they divided into 2 groups; group 1 included 316 cases received conventional fractionation radiotherapy (50gy/25 ttt/5 weeks) and group 2 included 302 cases received hypofractionation radiotherapy (40gy/15 ttt/3 weeks). The 2 groups were compared regarding; time to develop local recurrence or distant metastasis, survival and toxicity.

Results: both groups were matched as regards clinicopathological fissures. The median follow up period was 113 months (ranged between 96 and 130 months). At the end of the study, 53 patient developed local recurrences (26 in group 1 and 27 in group 2) while 105 patients developed distant metastasis (54 in group1 and 51 in group2). 93 cases were died because of the disease (47 in group 1 and 46 in group 2). The results were matched between the 2 groups. Recurrence free survival for group 1 was 125.823 months compared to 125.922 for group 2. Distant metastasis free survival for group 1 was 124.063 while was 124.281 for group 2. The overall survival was 127.316 for group 1 compared to 126.967 for group 2. For all survival data there was no significant P value between the 2 groups. When considering sub-groups with higher risk for failure (G3, N2 or 3 and triple negative cases), also there was no significant P-value as regards survival data between both groups. Toxicity was so limited and comparable between both groups.

Conclusion: using hypofractionation was effective as conventional fractionation for patients with node-positive breast cancer. This model of therapy will be very helpful in developing countries with limited resources. However still more large studies are needed to confirm our results.

Keywords: breast cancer, radiotherapy, hypofractionation, conventional fractionatation.

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Introduction:

For patients with breast cancer, RT is an effective therapy option as regards local and regional control. It has also remarkable effect in decreasing the incidence of distant metastasis [1-4]. Data analysis of multiple previous studies confirmed that hypofractionated (HF) breast RT has the same effect of conventional fractionation as regards controlling of the disease, toxicity and cosmetic outcomes in patients with early node-negative breast cancer [5,6,7]. In this group of patients, involvement of regional lymph nodes in RTH is not advised.

Modest HF enhances patient convenience and lowering health-care expenditures and out-of-pocket expenses [8]. Furthermore, broad use of HF regimens

could boost patient throughput in a crowded RT department. This could be especially useful in developing countries where access to RT is limited [9]. Also, and in comparison, to CF RT, HF regional lymph nodes irradiation was not associated with high incidence of arm stiffness or lymphedema according to recent studies [12].

Despite these benefits, concerns regarding side effects, particularly brachial plexopathy [10], and a lack of data on the efficacy of hypofrationation for node-positive cases have limited the use of HF regional nodal RT. For those patients, conventional fractionation remains the standard therapy [11].

Aim of the work:

To assess the effect of hypofractionated radiotherapy for cases of node positive breast cancer compared to conventional fractionation as regards DFS, OAS and toxicity.

Patients and Methods:

This is a retrospective study for patients diagnosed with node positive breast cancer referred to clinical oncology and nuclear medicine department, faculty of medicine, Mansoura university hospital to receive radiotherapy after surgery in the period between 2009 and 2012. Patients were included if it's their 1st breast cancer diagnosis, have positive lymph nodes confirmed pathologically, female, operated by conservative or radical surgery with axillary dissection, did not receive neoadjuvat therapy and have no distant metastasis. All cases received radiotherapy either conventional or hypofractionation. Demographic, tumor and treatment characteristics were collected from patients' files. Patients were under follow up after the end of treatment monthly by physical examination and every 3 months by radiological examination for one year, every 6 months in 2nd year then annually. They were examined for development of local recurrence or distant metastasis. The period of follow up ranged between 8 and 10 years till patient last visit or lost follow up and survival data were recorded. At the end of the study, 618 patients were included. And according to the radiotherapy protocol of treatment they divided into 2 groups; group 1 included 316 cases received conventional fractionation radiotherapy (50gy/25 ttt/5 weeks) and group 2 included 302 cases received hypofractionation radiotherapy (40gy/15 ttt/3 weeks). The 2 groups were compared regarding; time to develop local recurrence or distant metastasis, survival and toxicity.

Results:

Table 1 show clinicopathological and treatment characteristics of both groups. The mean age for group 1 was 50.78 and for group 2 were 50.23. According to menopausal status of the cases; 115 cases were premenopausal in group 1 compared to 114 in group 2. As regards the stage of the disease at presentation also both groups were matched. Early disease (T1, T2) were presented in 186 cases of group 1 compared to 179 cases in group 2, and advanced disease (T3, T4) were diagnosed in 130 cases of group 1 compared to 123 cases in group 2. Also, cases with N1 disease were 129 in group 1 compared to 118 in group 2, while N2 and N3 cases were 187 in group 1 and 184 in group 2. Low grad disease (G1, 2) were presented in 261 cases of group 1 and 252 cases of group 2, while high grad (G3) were diagnosed in 55 cases of gruop1 and 50 cases of group 2. Most of cases were hormonal positive (263 in group 1 and 253 in group 2). As regards HER2 status, also majority of cases were positive (186 and 180 in both groups respectively). 71 cases were diagnosed with triple negative disease, 36 in group 1 and 35 in group 2. All cases were undergoing surgery before RTH, 142 cases of group 1 were underwent conservative surgery compared to 136 in group 2. While 174 cases in group 1 were operated with radical surgery compared to 166 cases in group 2. For all previous parameters, both groups were matched with no significant P value.

After the end of RTH, all cases were under follow up. The median follow up period was 113 months (ranged between 96 and 130 months). Patients were examined for detection of development of local or distant failure with recording of date of failure if happened. At the end of the study, 53 patient developed local recurrences (26 in group 1 and 27 in group 2) while 105 patients developed distant metastasis (54 in group1 and 51 in group2). 93 cases died because of the disease (47 in group 1 and 46 in group 2). For all previous data the results were matched between the 2 groups as shown in table (1).

Table (2) shows the survival data for both groups at the end of the study. Recurrence free survival for group 1 was 125.823 months compared to 125.922 for group 2. Distant metastasis free survival for group 1 was 124.063 while was 124.281 for group 2. The overall survival was 127.316 for group 1 compared to 126.967 for group 2. For all survival data there was no significant P value between the 2 groups.

Kaplan-Meier curves for overall, recurrence free and distant metastasis free survival are illustrated in figure 1, 2 and 3. The 2 curves for both groups look so near to each other with no remarkable difference.

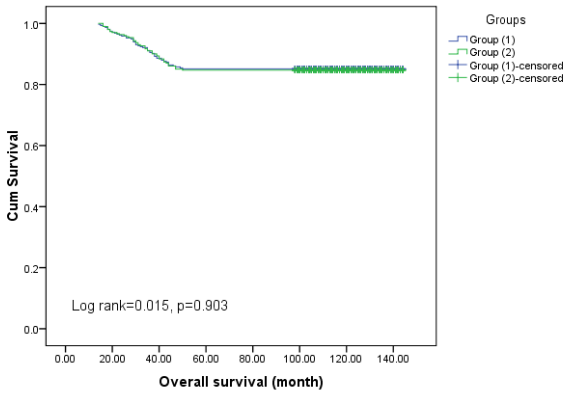

Figure 1

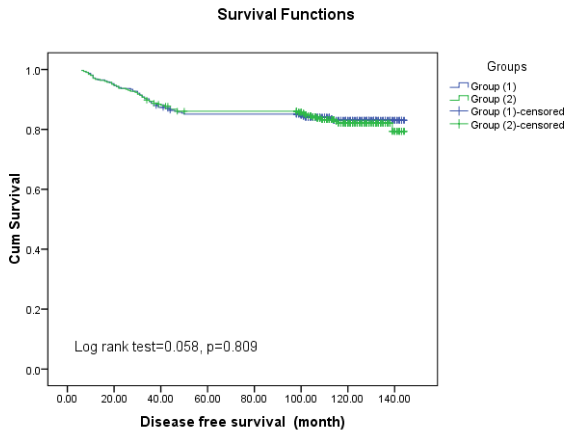

Figure 2

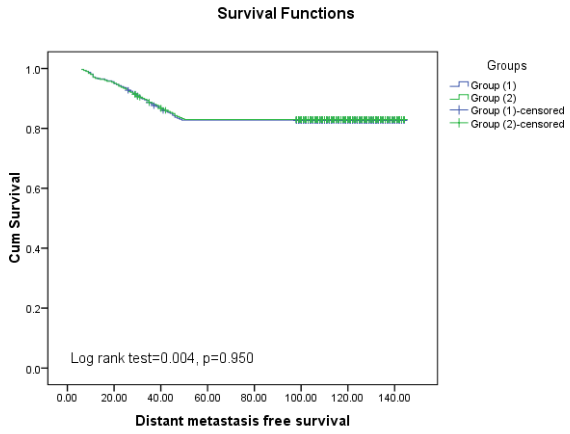

Figure 3

To asses if there are sub-groups of patients whom could not have benefits of hypofractionation, we performed Multivariable analysis for patients with high risk factors. We consider G3, N2 or 3 and triple negative cases as sub-groups with higher risk for recurrence.

Considering G3 disease, there was 105 cases in the cohort, 55 in group 1 and 50 in group 2. Local recurrence was noticed in 28 cases in group 1 compared to 33 cases in group 2. Distant metastasis happened in 28 cases of 1st group and 29 cases in the 2nd. At the end of the study, 24 cases died in group 1 compared to 30 cases in group 2. For all previous data, there was no significant difference as shown in table 3.

Table 4 demonstrates the survival data for this sub-group. Recurrence free survival, distant metastasis free survival and overall survival were comparable between the 2 groups with no significant P value as shown in table 4.

As regards cases with advanced nodal disease (N 2, 3), 187 cases were diagnosed in group 1 compared to 184 cases in group 2. Local recurrence was detected in 33 cases in 1st group compared to 46 cases in the 2nd. Distant metastasis diagnosed in 34 cases in group 1 compared to 42 cases in group 2. The number of deaths was 31 and 40 respectively with no significant difference between the 2 groups as described in table 5.

Table 6 illustrates the survival data for that sub-group which is also comparable with no significant P value as regards recurrence free, distant metastasis free and overall survival.

Triple negative cases were diagnosed in only 71 cases of our examined patients. This sub-group of patients is expected to have worse prognosis with high risk of recurrence and developing distant metastasis. 36 cases were diagnosed in group 1 compared to 35 cases in group 2. The number of cases developed local recurrence was high as expected (44 cases, 62%) but it was comparable between the 2 groups (22 cases in each group). Also, distant metastasis was noticed in 43 cases (20 in group 1 and 23 in group 2). The number of died cases was 24 in group 1 and 29 in group 2. No significant difference was recorded as table 7 shows.

The overall survival was very low in this sub-group of patients (63 months in group 1 and 48 months in group 2) compared to the whole study group and other subgroups. Also, the recurrence free and distant metastases free survival. But it was also comparable between the 2 groups as shown in table 8.

As regards toxicity, table 9 illustrates the incidence of expected complications between the 2 groups. Of course, lymphedema was the most common complication after surgery and radiotherapy (29 cases in group 1 and 28 cases in group 2). Affection of shoulder mobility was documented in 17 cases in both groups. Brachial plexopathy was recorded in very small number in both groups (7 and 5 respectively). No significant difference was detected for all those items between the 2 groups.

Table 1:

	Group (1) (no=316)	Group (2) (no=302)	Test of significance (p value)
Age/ years			
Mean ± SD	50.78±8.34	50.23±8.04	t=0.834
≤50 y	115 (36.4%)	114 (37.7%)	P=0.405
>50 y	201 (63.6%)	188 (62.3%)	
Menopausal status			
Premenopausal	115 (36.4%)	114 (37.7%)	$\chi2$ =0.122
Postmenopausal	201 (63.6%)	188 (62.3%)	P=0.727
T			
T1, T2	186 (58.9%)	179 (59.3%)	$\chi2$ =0.011
T3, T4	130 (41.1%)	123 (40.7%)	P=0.917
N			
N1	129 (40.8%)	118 (39.1%)	$\chi2$ =0.197
N2, N3	187 (59.2%)	184 (60.9%)	P=0.657
Grade of the tumor G1, G2	261 (82.6%)	252 (83.4%)	$\chi2$ =0.079
G3	55 (17.4%)	50 (16.6%)	P=0.779
Hormonal status			
Hormonal positive	263 (83.2%)	253 (83.8%)	$\chi2$ =0.034
Hormonal negative	53 (16.8%)	49 (16.2%)	P=0.855
Her2 status			
Her2 positive	186 (58.9%)	180 (59.6%)	$\chi2$ =0.035
Her2 negative	130 (41.1%)	122 (40.4%)	P=0.851
Triple negative			
Yes	36 (11.4%)	35 (11.6%)	$\chi2$ =0.006
No	280 (88.6%)	267 (88.4%)	P=0.939
LV			
Positive invasion	155 (49.1%)	150 (49.7%)	$\chi2$ =0.024
Negative invasion	161 (50.9%)	152 (50.3%)	P=0.878
Type of surgery			
Conservative surgery	142 (44.9%)	136 (45.0%)	$\chi2$ =0.001
Radical surgery	174 (55.1%)	166 (55.0%)	P=0.981
Local recurrence			
Yes	26 (8.2%)	27 (8.9%)	$\chi2$ =0.100
No	290 (91.8%)	275 (91.1%)	P=0.752
Distant metastasis			
Yes	54 (17.1%)	51 (16.9%)	$\chi2$ =0.004
No	262 (82.9%)	251 (83.1%)	P=0.947
Mortality			
Survived	269 (85.1%)	256 (84.8%)	$\chi2$ =0.016
Died	47 (14.9%)	46 (15.2%)	P=0.901

Table (2): Kaplan-Meier overall survival (Month), disease free survival (Month) and distant metastasis free survival

	Median Survival time	Std. Error	95% CI Lower	95% CI Upper	Log Rank test	P – value
Overall survival						
Group (1)	127.316	2.256	122.896	131.737	0.015	0.903
Group (2)	126.967	2.322	122.416	131.518		
Disease free survival						
Group (1)	125.823	2.366	121.186	130.460	0.058	0.809
Group (2)	125.922	2.388	121.241	130.604		
Distant metastasis free survival						
Group (1)	124.063	2.484	119.195	128.932	0.004	0.950
Group (2)	124.281	2.532	119.318	129.243		

Log Rank (Mantel-Cox) was used, CI: confidence interval, *significant p≤0.05

Table (3):

	Grade (3)		Test of significance (p value)
	Group (1) (no=55)	Group (2) (no=50)	
Local recurrence			
Yes	28 (50.9%)	33 (66.0%)	$\chi2$ =2.45 P=0.118
No	27 (49.1%)	17 (34.0%)	
Distant metastasis			
Yes	28 (50.9%)	29 (58.0%)	$\chi2$ =0.531 P=0.466
No	27 (49.1%)	21 (42.0%)	
Mortality			
Survived	31 (56.4%)	20 (40.0%)	$\chi2$ =2.81 P=0.094
Died	24 (43.6%)	30 (60.0%)	

Table (4): Kaplan-Meier overall survival (Month), disease free survival (Month) and distant metastasis free survival in grade 3

Grade (3)	Median Survival time	Std. Error	95% CI		Log Rank test	P - value
			Lower	Upper		
Overall survival						
Group (1)	91.327	7.804	76.031	106.623	2.266	0.132
Group (2)	62.735	6.154	50.674	74.796		
Disease free survival						
Group (1)	83.052	8.166	67.046	99.057	2.10	0.147
Group (2)	67.543	8.138	51.591	83.494		
Distant metastasis free survival						
Group (1)	78.411	8.239	62.262	94.559	0.902	0.342
Group (2)	58.337	6.715	45.175	71.498		

Table (5):

	N2 or N3		Test of significance (p value)
	Group (1) (no=187)	Group (2) (no=184)	
Local recurrence			
Yes	33 (17.6%)	46 (25.0%)	$\chi2$ =2.99 P=0.084
No	154 (82.4%)	138 (75.0%)	
Distant metastasis			
Yes	34 (18.2%)	42 (22.8%)	$\chi2$ =1.23 P=0.268
No	153 (81.8%)	142 (77.2%)	
Mortality			
Survived	156 (83.4%)	144 (78.3%)	$\chi2$ =1.59 P=0.206
Died	31 (16.6%)	40 (21.7%)	

Table (6): Kaplan-Meier overall survival (Month), disease free survival (Month) and distant metastasis free survival in N2, N3

N2 or N3	Median Survival time	Std. Error	95% CI		Log Rank test	P – value
			Lower	Upper		
Overall survival						
Group (1)	124.818	3.157	118.630	118.630	1.406	0.236
Group (2)	119.519	3.439	112.779	112.779		
Disease free survival						
Group (1)	123.937	3.270	117.528	117.528	2.770	0.096
Group (2)	117.288	3.569	110.292	110.292		
Distant metastasis free survival						
Group (1)	122.335	3.381	115.708	128.963	1.223	0.269
Group (2)	116.942	3.686	109.718	124.166		

Table (7):

	Triple negative cases		Test of significance (p value)
	Group (1) (no=36)	Group (2) (no=35)	
Local recurrence			$\chi2$ =0.023 P=0.88
Yes	22 (61.1%)	22 (62.9%)	
No	14 (38.9%)	13 (37.1%)	
Distant metastasis			$\chi2$ =0.767 P=0.381
Yes	20 (55.6%)	23 (65.7%)	
No	16 (44.4%)	12 (34.3%)	
Mortality			$\chi2$ =2.46 P=0.117
Survived	12 (33.3%)	6 (17.1%)	
Died	24 (66.7%)	29 (82.9%)	

Table (8): Kaplan-Meier overall survival (Month), disease free survival (Month) and distant metastasis free survival in triple negative

Triple negative cases	Median Survival time	Std. Error	95% CI		Log Rank test	P – value
			Lower	Upper		
Overall survival						
Group (1)	63.278	8.887	45.860	80.696	1.06	0.304
Group (2)	48.000	7.237	33.815	62.185		
Disease free survival						
Group (1)	58.111	9.518	39.456	76.766	1.052	0.305
Group (2)	42.400	7.764	27.183	57.617		
Distant metastasis free survival						
Group (1)	58.710	9.420	40.247	77.173	1.692	.193
Group (2)	39.221	7.081	25.343			

Table (9): TOXICITY

Toxicity	Group (1) (no=316)	Group (2) (no=302)	Test of significance (p value)
Lymphedema	29 (9.2%)	28 (9.3%)	$\chi2$ =0.002 P=0.967
Shoulder immobility	17 (5.4%)	17 (5.6%)	$\chi2$ =0.018 P=0.891
Brachial plexopathy	7 (2.2%)	5 (1.7%)	$\chi2$ =0.25 P=0.614

Discussion:

Conventional fractionation RTH is still the standard of treatment after surgery for cases with node positive breast cancer. But due to the overcrowded machines especially in developing countries, many centers try to study the efficacy of hypofractionated RTH for those group of patients aiming to solve this problem.

The debate about that technique of treatment is if it achieves the same results achieved by the conventional fractionation or if its associated with lower effects as regards local and distant control.

Our center started to use hypofractionation for node positive breast cancer disease since 2008with agreement of many members of our staff and disagreement of others. After about 12 years of that date, assessment of that issue was needed.

Our retrospective study was done over 618 cases, 316 received conventional fractionation and 302 received hypofractionation. And at the end of the study, the results are comparable between both groups.

Conventional RT is still recommended by Polish national guidelines, but HF is also acceptable as long as the dose given to the heart is kept to a minimum [13]. It was also endorsed in a recent Polish proclamation on breast cancer diagnosis and treatment issued by the Ministry of Health [14].

In our study, the survival data for both groups was matched with no statistically difference in clinicopathological parameters and patients' criteria. loco-regional recurrence was detected in 8.2 % in the 1st group and 8.9% in 2nd group with no statistically significant P=0.752. The values were mostly similar to those reported by Wang et al., (8.3% (90% CI 5.8-10.7) in HFRT group and 8.1% (90% CI 5.4-10.6) in CFRT group (absolute difference 0.2%, 90% CI -3.0 to 2.6; HR 1.10, 90% CI 0.72 to 1.69) [15] but higher than reported by Tovanabutra et al., which was 3.89% (95% CI, 1.81-5.98) in HFRT group and 3.91% (95% CI,0.50-7.3) in CFRT group [16].

As regards DFS In our study, it was 125.823, 125.922 Ms. respectively in both groups with its p value 0.809, which is similar to Pinitpatcharalert et al., who found that 5-year DFS in two groups was not significantly different, with 62.7 percent in the CFRT group and 69.6 percent in the HFRT group (p=0.136) [17].

The OAS it was 127.316, 126.967 in both groups respectively with no statistically significance (p=0.903). Pinitpatcharalert et al., found that the difference between CFRT and HFRT in terms of 5-year overall survival (62.7 percent vs. 73.0 percent) was substantially higher in the hypofractionated group (p=0.048) [17]. Unlike Wang et al., who found that 5-year overall survival was similar in both groups, with 86 percent in CFRT and 84 percent in HFRT (p=0.526).

In our study, the complication of radiotherapy was mostly similar in both groups; lymphedema was developed in 9.2% in group 1 and 9.3% in group 2, affection of shoulder mobility was documented in 5.4% and 5.6% in both groups and Brachial plexopathy was recorded in very small number in both groups (7 and 5 cases respectively). Wang et al. detected same incidence of lymphedema and arm stiffness when comparing HF to CF [15]. Similarly, a phase II trial using hypofrationation for 67 women after surgery reported low incidence of lymphedema (only 1.5 percent) [18]. Also, the UK START studies found a rare incidence of toxicities when utilizing hypofrationation [6].

Conclusion:

We concluded that using hypofractionation was as effective as conventional fractionation for patients with node-positive breast cancer as regards efficacy and toxicity. The same was noticed in sub-groups with high-risk features. This model of therapy will be very helpful in developing countries with limited resources. However still more large studies are needed to confirm our results.

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