A Comparative Study of Cardiac Toxicity Analysis in Hypo-Fractionated Vs Conventionalfractionated Adjuvant Radiotherapy in Post-Mastectomy Leftbreast Carcinoma

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Abstract:

Background: Post-mastectomy adjuvant radiotherapy improves long-term survival by reducing the risk of loco-regional recurrence in breast cancer patients with high-risk features. Considering radiation therapy to the left sided chest wall heart is an important organ at risk. Hypo-fractionated radiotherapy is increasingly being used due to involvement of fewer treatment sessions and is almost radio-biologically equivalent to conventionally fractionated radiotherapy.

Objective: This study was conducted to evaluate cardiac toxicities between hypo and conventionally fractionated radiotherapy.

Methods: This quasi-experimental study was done at the National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from January 2019 to December 2019, 60 patients were purposively assigned into two groups and each group included 30 patients. Arm A: received Conventional fractionated radiotherapy (50Gy/25 fractions over 5 weeks, at 2Gy/fraction). Arm B: received Hypo- fractionated radiotherapy (40.05 Gy in 15 fractions over 3 weeks at 2.67 Gy/fraction). Echocardiography (ECHO), Electrocardiography (ECG) was performed to find the cardiac toxicities.

Results: The mean age of the patients in arm A was 50.03 ± 6.82 years and that of arm B was 48.08 ± 5.08 years. No significant statistical difference was found between the two groups regarding socio-demographic variables and clinical presentations. Most of the patients in both arms showed grade 0 cardiac toxicity (arm A: 70% and arm B: 80%) & few showed grade 1 cardiac toxicity (arm A: 20% and arm B: 13.3%) and three patients (10.0%) in arm A and two patients (6.66%) in arm B had shown grade 2 cardiac toxicities six months after treatment. However, this difference was statistically not significant (p >0.05). Before treatment, the ejection fraction (EF) of arm A and arm B were 63.3 ± 5.621 and 64.7± 4.991. Six months after treatment the EF of both arms decreased (arm A 60.2 ± 4.051 & arm B 60.9 ± 5.121) but the difference was statistically not significant (p >0.05).

Conclusion: Hypo-fractionated radiotherapy in the adjuvant setting for the treatment of left breast cancer has no additional cardiac toxicity in comparison to conventionally fractionated radiotherapy while maintaining same efficacy.

Keywords: Hypo-fractionated Radiotherapy, Conventional Fractionated Radiotherapy, Cardiac Toxicity, Breast Carcinoma, Post Mastectomy.

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Introduction:

Breast cancer is the leading cancer among women worldwide and in Bangladesh the incidence is the highest of all malignancies among female patients. The incidence of breast cancer is about 19% & five-years prevalence is about 35.19% among Bangladeshi women[1]. In radiation oncology practice, breast cancer typically comprises approximately 25% of total patient caseload[2]. The patients undergoing mastectomy, adjuvant radiation therapy should be considered to the chest wall, as indicated, where the risk of local recurrence is high.

In recent years, the cardiac risk of radiation is a deep concern and has been discussed in various studies. The most common radiation induced heart injury is pericarditis. A dose of 50Gy in conventional fractions produces about 11% incidence of pericarditis[3]. Generally, pericarditis is observed as acute and late toxicity, as well as congestive cardiac failure, ischemic coronary artery diseases, arrhythmia, cardiomyopathy, valvular diseases, conduction abnormalities, myocardial infarction, any of which can manifest years or decades after original treatment[3]. Radiation therapy is an important component in the multidisciplinary treatment of breast cancer. Due to contour of the left chest wall, some portion of the heart has to be included in the tangential portals that receives significant amount of radiation dose[4]. Furthermore, administration of anthracycline based chemotherapy, HER-2 receptor blocker-Trustuzumab & some co-morbid conditions may provoke radiation induced cardiac complications for chest wall irradiation[5].

The conventional fractionated radiotherapy though proven effective, might be inconvenient to patients of undergoing daily treatment for 5 weeks along with increased healthcare expenditures. In case of huge workload, hypo-fractionation approach reduces the number of fractions, total treatment duration, multiple hospital attendance and economic burden on patients. It might be an alternative solution for a fractionated regimen for a subset of patients with the same radiobiological equivalent without compromising efficacy[6]. Moreover, radiobiological data suggest that breast cancer cells may be more sensitive to larger radiation fraction doses compared to conventional fraction doses due to low á/â values (d" 5Gy). The á/â ratio for heart is also low, usually <2Gy. Heart should be protected irrespective of the dose fractionation regimen used[7,8].

Ten years START (A and B) trial, together with long-term results of Ontario trial strengthen the evidence of using hypo-fractionated schedules for breast cancer radiotherapy[7,8]. In perspective of Bangladesh, incidence of breast cancer is highest among female population & most of the patients attend in advanced stages. Patients who are treated with adjuvant radiotherapy particularly to the left chest wall following mastectomy, with our available radiation facilities, cardiac complications should be addressed and reported properly by close collaboration with oncologists and cardiologists. Majority of previous trials have provided data on cardiac toxicity for conventionally fractionated radiotherapy, but data pertaining to adverse cardiac effects following post mastectomy hypo-fractionated radiotherapy is still limited[4].

The objective of the study was to assess and compare cardiac toxicities between hypo-fractionated and conventional fractionated radiotherapy in the adjuvant treatment of left-sided post-mastectomy patients and also to observe demographic characteristics of the responders.

Materials and Methods:

This study was conducted as a Quasi-experimental study at Radiation Oncology Department in National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka from January 2019 to December 2019 and approved by the Ethical review committee of NICRH. Informed consent was taken from each patient before enrolling in the study.

A total of 60 patients were allocated, equally distributed in two arms A and B. In arm A, 30 patients receive conventionally fractionated radiotherapy whereas in arm B, further 30 patients were recruited to receive hypo-fractionated radiotherapy. Purposive sampling technique was used due to limited time

period. All patients completed chemotherapy before start of radiotherapy. Pretreatment evaluation included specific pathology review, clinical examination, and relevant laboratory investigations, and radiological imaging. Cardiac evaluation was performed by electrocardiography (E.C.G), echocardiography (ECHO), cardiac enzymes (where applicable).

Inclusion criteria: a) Histopathologically proven invasive duct cell carcinoma underwent left sided mastectomy b) Adult women (preferably 20 to 65yrs) c) T_2, T_3, T_4 primary lesion &N_1, N_2, N_3 nodal status d) Patients were required to have ECOG performance status up to scale 2 e) Patient without distant metastasis.

Exclusion criteria: a) Patients who had undergone breast-conserving surgery b) pregnant or lactating women c) prior radiotherapy to chest wall d) pre-existing heart diseases or chronic heart diseases e) patients with chest malformations or other malignant diseases.

Radiotherapy treatment planning:

All patients received post mastectomy adjuvant external beam radiotherapy to left chest wall with 2D technique by using 6MV Linear Accelerator. Patients were simulated with a conventional simulator and placed with proper immobilization devices to provide stability and reproducibility for subsequent treatment. An isocentric technique of medial & lateral tangential fields was constructed for chest wall & direct anterior field for supraclavicular irradiation. To reduce beam divergence at the posterior border of the field, half beam blocking was done using independent collimators to block the posterior half of the beam with the aim to reduce dose to heart and lungs. Central Lung Distance (CLD) was considered less than 2 cm & Maximum Heart Distance (MHD) within 1 cm. Proper skin care were ensured throughout the treatment period.

Patient assessment: During radiotherapy, every patient was assessed weekly for safety evaluation and compliance. Clinical responses were evaluated by performance status, systemic examination including cardiovascular system & other necessary investigations like complete blood count, biochemical tests, ECG, Echocardiography, cardiac enzymes (where applicable) were done. To assess cardiac toxicity, the National Cancer Institute's Common Terminology Criteria for Adverse Events, v.3.0 (CTCAE.v.3.0) was considered. Percentage decline in ejection fraction (EF) was used to grade cardiac adverse events. Grade (Gr) 0: asymptomatic, resting EF>60%, Gr 1: asymptomatic, resting EF <60-50%, Gr 2: asymptomatic, resting EF<50-40!, Gr 3: symptomatic, CHF, EF <40-20% and Gr 4: refractory CHF or poorly controlled; EF < 20%[6].

Patients were carefully re-evaluated 6 weeks after completion of radiotherapy and cardiac assessment was done every three months interval. Data at baseline at the end of radiation treatment and six months after follow up were analyzed in the study. Symptoms occurring between the start of radiotherapy and 90 days after this time point were classified as "Acute" and symptoms occurring six months after the end of treatment were defined as "Late" toxicity[6].

Continuous variables were expressed as mean ± SD and were compared by Student t-test. Categorical data were expressed as numbers and percentages and were compared via the Chi-square test and Fisher's exact tests. A two-tailed test was applied and a *p-value* of <0.05 was considered as significant.

Results:

This quasi-experimental study was carried out to assess and compare the cardio-toxicities between hypo-fractionated and conventional fractionated radiation therapy to post mastectomy left breast cancer patients. Total study population was 60 among which 30 were in conventional fractionation radiation (arm A) and 30 were in hypo-fractionation radiation (arm B).

Both treatment groups were comparable in terms of age, parity, education, economic status & ECOG performance status. Prevalence of smoking was low in both arms. No statistically significant difference was found between two groups.

Table-I

Patient characteristics:

Variables		Arm A	Arm B	t-value	df	*p*-value	Test
Mean age(± SD) Years		50.03(± 6.82)	48.08(± 5.08)	-1.117	53.662	0.269	Unpaired t-Test
Variables			Arm An (%)	Arm Bn (%)		*p*-value	Test
Smoking	Smoker		2 (6.7)	3 (10.0)			
	Non-smoker		28 (93.3)	27 (90.0)		1.00	Fisher"s
Parity	Nulliparous		2 (6.7)	2 (6.7)		Exact	
	Primipara		11 (36.7)	7 (23.3)		Test	
	Multi-para		16 (53.3)	20 (66.7)		0.769	
	Grand multi-para		1 (3.3)	1 (3.3)			
Education	Illiterate		10 (33.3)	10 (33.3)			
	Below primary		17 (56.7)	13 (43.3)			
	SSC		3 (10.0)	5 (16.7)			
	HSC		0 (0.0)	2 (6.7)		0.371	
Economic	Poor		27 (90)	25 (83.3)		-	
Status	Middle Class		2 (6.7)	5 (16.7)			
	Rich		1 (3.33)	0 (0.0)		0.841	
ECOG	Grade 0		18 (60.0)	20 (66.7)		Fisher's	
performance	Grade 1		11 (36.7)	9 (30.0)		Exact	
status	Grade 2		1 (3.3)	1 (3.3)	0.305	Test	

Both treatment groups were compared for clinical parameters (Staging, nodal status, resection margin status, lympho-vascular space invasion, perineural invasion). No statistically significant difference was found between two groups.

Table-II

Tumor Characteristics

Variables		Arm A n (%)	Arm B n (%)	*P* -value	Test
Clinical staging	Stage II	10 (25.0)	12 (40.0)	>0.287	Chi Square
	Stage III	20 (75.0)	18 (60.0)		Test
Nodal Status	Positive	26 (86.7)	25 (83.3)	1.00	Fisher"s Test
	Negative	4 (13.3)	5 (16.7)		Exact
Margin status	Negative	9 (30.0)	11 (36.7)		
	Positive	12 (40.0)	13 (43.3)	0.437	
	Close	6 (20.0)	6 (20.0)		
	Multifocality	3 (10.0)	0 (0.0)		
Lympho-	Not identified	11 (36.7)	7 (23.3)		
vascular	Present	14 (46.6)	19 (63.4)	0.459	
space	Absent	5 (16.7)	4 (13.3)		
invasion					
Perineural	Not identified	24 (80.0)	24 (80.0)		
invasion	Present	6 (20.0)	5 (16.7)	1.00	
	Absent	0 (0.0)	1 (3.3)		

Distribution of patients by adverse cardiac events, cardiac toxicity grading, echocardiographic changes (Fraction shortening and LV Posterior wall thickness) were assessed for comparison between two arms.

Table-III

Distribution of Patients by Adverse Cardiac Events

Variables		Arm A n (%)	Arm B n (%)	*P*-value	Test
Adverse cardiac events	Ischaemic heart diseases	1 (3.33)	1 (3.33)	1.00	Fisher's Exact Test
	Hypertension	2 (6.66)	1 (3.33)	0.351	
	Hypotension	0 (0.0)	1 (3.33)	-	
	Pericarditis	1 (3.33)	1 (3.33)	1.00	
	No adverse cardiac events	26 (86.67)	26 (86.67)	-	
Cardiac toxicity (6 months after follow up)	Grade 0	21 (70.0)	24 (80.0)	0.656	
	Grade 1	6 (20.0)	4 (13.3)		
	Grade 2	3 (10.0)	2 (6.66)		

Variables			Arm A (Mean±SD)	Arm B (Mean±SD)	*P*-value	Test
Echo-cardiographic changes (Mean ± SD)	Ejection Fraction*	Before Treatment	63.3±5.621	64.7±4.99	0.36	Unpaired "t"test
		After 6 months	60.2±4.051	60.9±5.121	0.61	
	Fraction shortening**	Before Treatment	38±3.421	39±2.984	0.89	
		After 6 months	34±3.011	35±3.210	0.87	
	LV Posterior wall thickness	Before treatment	9±1.51	9±1.66	0.62	
		After 6 months	10±1.77	10±1.79	0.61	

* Ejection Fraction (EF): Ejection fraction is a percentage of blood pumped into the body during each heartbeat. It's the fraction of end-diastolic volume (EVD) that is ejected with each beat; that is stroke volume (SV) divided by EVD. An EF of 60%-75% is considered normal. The lower the ejection fraction, the more severe the heart failure may be (Khan et al., 2014).

**Fraction shortening (FS) is calculated by the formula mentioned: $FS = \frac{LVEDD - LVESD}{LVEDD} \times 100\%$, where LVEDD stands for LV end diastolic dimension in mm while LVESD stands for LV end- systolic dimension in mm. FS>18% is considered normal.

Discussion:

This study was done at the National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka from January 2019 to December 2019 for comparison of cardiotoxicities between hypo-fractionated and conventional fractionated radiotherapy in the adjuvant treatment of post mastectomy left breast carcinoma. Patients who met the inclusion criteria were analyzed

and cardiac toxicities were observed in this study. The present study has been conducted to evaluate the cardiac risk of radiation, specially for post mastectomy patients whereas most of the previous studies were for post breast conservative surgery. Majority of the patients in both arms were 41 to 50 years of age. The mean age of the arm A patients was 50.03 (± 6.82) years and that of the arm B was 48.08 (± 5.08) years. No significant difference was observed between these two groups (p >0.05) which was similar to the study conducted by Alagizy & Elshanaway[5]. Equal numbers of patients in both arms (33.3%) were illiterate but majorities had below primary level education (17 in arm A and 13 in arm B). About half of the patients in both arms were from poor class (90% in arm A and 83.3% in arm B). Majority of patients were multi-parous 53.3% in arm A and 66.7% in arm B. Prevalence of smoking in both arms were negligible (p value = 1.00).

Positive node was found in most of the cases in both arms (arm A 86.7% and arm B 83.3%). The positive margin was found in considerable numbers of patients in both arms (arm A 40.0% vs. arm B 43.3%). Lympho-vascular space invasion was found (63.4%) in arm A and (46.6%) in arm B while perineural invasion was found in (16.7%) and (20%) of patients respectively. Regarding performance status, most of the patients in both arms were ECOG performance grade 0. Majority of the patients were in stage III (Arm A -75%, Arm B -60%) and few patients were in stage II (Arm A -25%, Arm B- 40%). There was no statistically significant difference in clinical parameters between the two groups. These findings are similar to the study done by Alagizy and Elshenawy[5].

Thoracic radiotherapy may determine pathological involvement of the pericardium, myocardium, cardiac valves, conduction system, coronary arteries, subclavian and carotid arteries resulting pericarditis, pericardial effusion, fibrous thickening of pericardium, valvular fibrosis, and atherosclerosis[4]. Furthermore, some independent risk factors of cardiovascular diseases like age, hypertension, diabetes mellitus, hypercholesterolemia, family history of early myocardial infarction and smoking might influence radiation induced cardiotoxicities[3].

In this study, cardiac toxicities were compared between the two arms after the completion of radiotherapy. Most of the patients in both arms showed grade 0 cardiac toxicity (arm A 70% & arm B 80 %). 20% of patients in arm A and 13.3% in arm B had shown grade 1 cardiac toxicities. 10.0% in arm A and 6.66% in patients in arm B had shown grade 2 cardiac toxicities. However, this difference was not statistically-significant (p >0.05). Ibrahim et al. reported that cardiac dysfunction was measured by RTOG toxicity criteria which was not statically significant[9] as similar to this study.

Echocardiographic changes between the two arms were also compared in the present study. Before treatment, the ejection fraction (EF) of arm A and arm B were 63.3 ± 5.621 and 64.7± 4.991. Three months after the treatment they were 62.2 ± 4.021 and 63.3 ± 5.021 and six months after treatment was 60.2 ± 4.051 & 60.9 ± 5.121 respectively but the difference was statistically not significant (p >0.05). Fraction shortening decreased six months after RT in both arms but the difference was not significant statistically and well above the normal limit. This inference was also true for posterior wall thickness. Posterior wall thickness (mm) slightly increased in both arms, but the difference was not statistically significant. These findings are in agreement with that of the Ibrahim et al. study[9].

Khan et al. in a study published in 1996, showed that risk factors like diabetes mellitus, hypertension and overweight, influence the overall risk of radiation induced heart disorders. Smoking also increases the relative risk[10]. Due to short follow up period and small sample size such relations could not be evaluated here. Moreover, besides cardiac toxicities, no other significant toxicities were found. So, other minor toxicities were not included in this study.

In the present study, after completion of radiotherapy only 1 patient (3.33%) in both arms developed ischemic heart disease, 2 patients (6.66%) in Arm A and 1 patient (3.33%) in Arm B developed hypertension, only 1 patient (3.33%) patient in Arm B developed hypotension, 1 patient (3.33%) in both arms developed pericarditis after 6 months of follow up. Rest of patients showed no cardiac adverse events. Studies from Darby et al. (2003) have found that it can take decades to develop cardiac damage after radiotherapy. Though the maximum follow-up period in this study was less than one year, longer follow up data is still needed to firmly establish the safety of hypo-fractionated radiotherapy following

mastectomy in left sided breast cancer patients in respect to cardiac toxicities. Till date, results from this study support the use of hypo-fractionated radiotherapy following post mastectomy left sided chest wall irradiation is safe with no clinically significant adverse cardiac events.

Limitations of the Study

Due to time constraint, cumulative long-term cardiac toxicities were not possible to evaluate which needs longer follow up period. Conformal treatment planning (Three-dimensional conformal radiotherapy, Intensity modulated radiotherapy) with Deep Inspiration Breath Hold (DIBH) technique was not done due to financial constraints and due to long queue.

Conclusion:

There is no additional cardiac toxicities of hypo fractionated radiotherapy in comparison to conventional fractionated radiotherapy following post mastectomy left sided chest wall irradiation while maintaining same efficacy. Results from this study supports the use of hypo-fractionated radiotherapy following post mastectomy left sided chest wall irradiation is safe with no clinically significant adverse cardiac events.

Recommendations

Further multi-center studies with large sample size and longer duration of follow up are required to reach a conclusive decision.

Author Contributions

Conceptualization, review and editing, MKR; Conduction of the study and writing of the original manuscript, SB; Data interpretation and statistical analysis, JI; Radiotherapy planning and data Collection, KT, TH; Methodology and data summarization BA, Cardiac toxicity analysis, TA, AM, NH, Dosimetry and Technical support for radiotherapy planning, SH; Overall supervision, MH. All authors have proofread the final version.

Conflict of Interests

There is no potential conflict of interests.

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Conflict of Interest

There is no conflict of interest regarding the research, authorship and publication of this article.

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