

## Study of Cardiac Toxicity after Post Mastectomy Hypofractionated Radiotherapy to Chest Wall in Patients with Carcinoma Breast

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### Abstract

**Background:** Cardiac complications following chest wall irradiation are inevitable. The effects of conventional radiotherapy (RT) delivering 50 Gy in 25 fractions have been clearly demonstrated in a large number of trials. but also causes inconvenience to elderly patients of undergoing daily treatment for 5 to 7 weeks, increases workload on radiation machine and add-ons to health care expenditures. in this trial we tried to quantify the cardiac adverse events after post-mastectomy hypofractionated RT.

**Material and methods:** Total 40 patients following post mastectomy with breast cancer in which radiation was indicated were included in this study. All patients had echocardiography (ECHO) done before start of RT, and then at three monthly intervals till last follow up. The Common Terminology Criteria (CTC) for Adverse Events v 5.0 was employed to evaluate early and late effects of RT.

**Result:** Majority of patients were between 45 to 65 years of age (70%). A total 7 patients only developed grade 3 adverse effect (17.5%) at the follow up of 1 year.

**Conclusion:** Use of hypofractionated RT for chest wall irradiation post-mastectomy is safe with no clinically significant acute or late cardiac adverse event noted at a follow up of 1 years.

**Keywords:** Hypofractionated radiotherapy (RT); breast cancer; postmastectomy; cardiac toxicity

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### I. Introduction

Postmastectomy radiation to chest wall is usually given in 5 weeks with fraction size of 2Gy delivered in 25# .many trials have proved this effectiveness of conventional fractionation, but also causes inconvenience to elderly patients of undergoing daily treatment for 5 to 7 weeks, increases workload on radiation machine and add-ons to health care expenditures(1,2).Based on many trials results, use of hypofractionated radiation has gained significant popularity as adjuvant treatment following breast conserving surgery(3,4).But the data on how hypofractionated radiation used post-mastectomy affects the normal tissue is still limited (5).

Chest wall radiation after mastectomy exposes normal tissue to dose which can lead to acute as well as long term complications. Linear Quadratic Model is often used to formulate the equivalent regimens based on the a/b values of early and late reacting tissues. This ratio is nothing but the dose D at which the components of cell killing that are proportional to dose i.e.,  $bD^2$ . Breast tissue are sensitive to fraction size with a/b values 5 Gy or less(6). So change in dose per fraction can produce relatively large changes in effects of radiation on this tissue. The opposed tangential portals exposes heart to significant amount of radiation doses especially when left sided chest wall is treated, raising the normal tissue complication probability.

Heart is intermediate between kidney and central nervous system. The a/b ratio for heart is low <2Gy. The threshold dose may be as low as 20Gy if more than 50% of heart is irradiated. Radiation induced cardiomyopathy results from dense and diffuse fibrosis, a slowly evolving lesion leading to impaired function. The main aim of this prospective study is to evaluate and quantify the burden of hypofractionation on cardiac tissue using 2DECHO.

## II. Material And Methods

Total 40 patients following post mastectomy with breast cancer in which radiation was indicated were included in this study after informed consent. Eligibility criteria included post mastectomy female patients, histologically proven disease, >20 years age. Patients having chronic heart disease, pregnant lactating, previous history of chest wall radiation, chest malformation were excluded from this study. All patients completed their adjuvant chemotherapy before starting radiation.

All patients underwent hypofractionated radiation to chest wall to a dose of 39Gy/13#(3Gy per fraction). External beam radiation was administered by LA machine with opposed tangential portals with or without single anterior supraclavicular field as per indication. Patients were placed on breast board with hand above head. Radiation fields were drawn on the skin and contours were taken. Two dimensional planning was done in all patients.

ECHO was done in all patients before the starting of radiation, then at 3 months and 6 months to assess the baseline status and early and late adverse effect. The Common Terminology Criteria for adverse events 5.0 was employed to evaluate early and late effects of radiation on left ventricular ejection fraction (LVEF). Descriptive statistics were used to present the data. The assessment was done between difference in ejection fraction at different times with age, hypertension, diabetes, body mass index, chemotherapy and hormonal therapy and laterality of disease. Pearson chi-square test was used to assess correlation of numerical variables.

## III. Result

Total 40 patients were included in this study. The details of patients, tumor and treatment are shown in Table No. 1.

**Table 1.** Patients, tumor and treatment characteristics:

No.	characteristics	No. of patients
1.	Age(yrs) <45 ≥45	12 28
2.	Diabetes mellitus Yes no	08 32
3.	Hypertension Yes No	07 33
4.	Body mass index <25 ≥25	10 30
5.	Histology Ductal Lobular Others	39 01 00
6.	Nodal dissection Adequate (≥10) Inadequate(<10)	29 11
7.	Stage I II III	00 14 26
8.	Grade I II II	02 30 08
9.	Receptor status ER/PR+ ER and PR -	32 08
10.	HER 2 Status Positive Negative Not know	25 10 05
11.	Chemotherapy used CAF CEF AC-T	04 06 30
12.	Supraclavicular Field Yes No	28 12

Majority of patients were between 45 to 65 years of age(70%).Main histology was ductal carcinoma(97.5%) with only one patient with lobular histology.Also patients with comorbidities( DM-20%,HTN-17.5%) were evaluated.A total 29 patients had adequate lymph node dissection.Majority of patients were in stage III(65%) and with grade II disease.A total 30 patients were treated with taxane based chemotherapy and all chemotherapy was completed before starting radiation. The mean of LVEF values before and after radiation are shown in Table no.2.

**Table no.2** variation in mean values of LVEF

	Before RT	3 months	6 months
LVEF% (mean)	64.6	61.3	58.2

The CTC (v 5.0) cardiac adverse effects,acute and chronic grading is shown in table no.3. A total 7 patients only developed grade 3 adverse effect (17.5%).

**Table no.3:** Cardiac toxicity (CTC v 5.0)

Grade	No.of patients
0/1/2	Not applicable
3	7

#### IV. Discussion

Chest wall irradiation includes parallel opposed tangential fields which result in significant pathological damage leading to ischemia, fibrosis, pericarditis, valvular fibrosis etc(7). Various trials relieved the cases of fatal myocardial infarction associated with adjuvant radiation to breast(8). Hypo fractionation with fraction sizes >2 Gy introduced to lessen the workload of treatment and for convenience of patients.Though the two large trials Start A and B included post mastectomy patients no separate toxicity analysis was done by authors in this patient population.

In this study percentage decline in values of LVEF from baseline were investigated to quantify the hypo fractionated radiation induced early and late cardiac toxicity.By doing individual assessment only 7 patients showed grade 3 toxicity .Present study showed statistically significant difference in late cardiac toxicity when comparing left sided with right sided disease.(p=0.01)This is an agreement with the result of one trial who demonstrated an increased risk of cardiac death after treatment for left sided breast cancer(9).

Also radiation potentiates cardio toxic effect of certain chemotherapy drugs such as Adriamycin(10).In this study three chemotherapy regimens were used- CAF( cyclophosphamide, Adriamycin, 5-FU), CEF( cyclophosphamide, epirubicin, 5-FU) and AC f/b T (cyclophosphamide, Adriamycin and taxane) depending on disease status or treating physician preference and this also showed statistically significant difference (0.006).When considering h/o hypertension, it also showed the patients with hypertension had more grade 3 cardiac toxicity (0.001).Cardiac toxicity  $\geq 3$  was reported in 15% of the total patients with body mass index  $\geq 25$ ,with result approaching clinical significance (p= -1)(table no.4)

**Table no.4** association between demographic variable and grade 3 cardiac toxicity

Sr.no	variables	Without grade 3 toxicity	With grade 3 toxicity	P value
1	Age <45 $\geq 45$	09 23	03 05	0.6
2	Diabetes mellitus Yes no	07 25	01 07	0.55
3	Hypertension Yes no	02 30	05 03	0.001
4.	BMI <25 $\geq 25$	08 24	02 06	0.007
5	Laterality Left Right	17 15	08 00	0.01
6.	Chemotherapy used CAF CEF AC--T	01 04 27	03 02 03	0.006
7.	Hormonal therapy Tamoxifen Aromatase inhibitors	08 16	03 05	0.8

Opposed tangential portals used for chest wall RT exposes cardiac tissue leading to complication. Studies showed that it can take decades to develop cardiac damage after RT. Though the maximum follow up period in this study was only 1 year, more longer data is still needed.

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