

Assessment of Cardiovascular Functions in Survivors of Breast Cancer Patients Treated with Chemo-Radiation

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ABSTRACT

Introduction: Keeping in view the increasing incidence and better survival with treatment modalities of breast cancer and the associated toxicities, this study was intended to study the long term impact of these treatment modalities on cardiovascular status in survivors of carcinoma breast patients in Kashmir valley of Indian subcontinent.

Material and methods: A prospective study in which breast cancer patients treated by combined modality treatment protocol with curative intent were taken for study. Patients with any co-morbid medical conditions like chronic lung disease, hypertension, asthma or drug intake for the same or any were not included in the study. Patients included in the study group had histopathological documentation of Carcinoma Breast, female sex, age greater than 18 years and geographical location of Kashmir Valley. Patients were subjected to echocardiography (M-Mode/2D/Colour Doppler) using Toshiba Power vision System. Standard imaging protocol was used. Left valvular function, valvular regurgitation, pulmonary hypertension and pericardial effusion /constriction was assessed.

Results: The personnel habits and characteristics between the two groups were comparable. Serial echocardiography findings in study group were more or less similar over a period of two years. Only one new patient developed pericardial effusion. Incidence of diastolic dysfunction progressively increased from 9/50 cases to 12/50 cases. One new patient had developed mitral valve involvement and one new patient tricuspid involvement ($p > 0.05$).

Conclusion: Apart from the clear benefits of adjuvant chemo radiation, we should be aware of the potentially increased risk of cardiovascular and pulmonary sequelae following specific radiotherapy regimens in long-term breast cancer survivors. It is important to realize that our role as oncologists is not only to treat the tumour but also to improve the quality of life of our patients by preventing and treating the long term toxicities induced by chemo radiation.

Majority of the patients were having echocardiography documented asymptomatic cardiac abnormalities. At a mean follow up interval of 5.8 years in the beginning of study 12/50 (24%) were having cardiac sequelae. Over a time period of 2 years three new patients developed asymptomatic cardiac problems. The follow up time was less, need more follow up time and larger studies.

Keywords: breast cancer, long term toxicity, anthracycline, chemo radiation, cardiac sequelae.

toxicities of various treatment protocols used takes a paramount importance. A breast cancer patient may receive anthracyclines, trastuzumab, and radiation therapy before commencing hormonal therapy. Radiotherapy damage to coronary endocytes triggers inflammation and eventually leads to atherosclerosis.¹ The risk of cardiac disease seems to increase for decades after radiation therapy.⁸ Radiation in combination with chemotherapy is associated with a greater risk of heart failure, than with radiotherapy only. Smoking and radiation seemed to have a synergistic effect on increasing the risk of myocardial infarction.³ Acute cardiotoxic side effects of anthracyclines include pericarditis and myocarditis (which are rare and may occur during or after the first dose), left ventricular dysfunction, and arrhythmias⁴; delayed effects include CHF, which may manifest many years later.⁵ Doxorubicin toxicity is exponentially dose-dependent and increases dramatically when cumulative doses exceed 500 mg/m². Among patients ages 65 years or older, a higher CHF risk was associated with anthracycline chemotherapy than with CMF chemotherapy or no chemotherapy.⁶ Among hormonal Agents, tamoxifen is associated with higher rates of venous thromboembolic disease and stroke than the placebo control.⁷ Aromatase Inhibitor therapy is associated with a more un-favourable cardiovascular risk profile than tamoxifen (TAM).⁸ Trastuzumab⁹, a humanized monoclonal antibody is associated with improved disease-free survival, but it is cardiotoxic, especially when given concomitantly with paclitaxel after AC. Cardiac function is usually measured by using echocardiography (ECHO) and multiple-gated acquisition (MUGA), also known as radionuclide angiography¹⁰, to measure resting LVEF. Breast cancer patients treated with adjuvant chemo-endocrine therapy (CET) have a significantly and markedly lower cardio-respiratory fitness and cardiac functional reserve compared with age- and sex-matched controls.

Breast cancer is emerging as a major concern in female population of Kashmir valley with its incidence showing an

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INTRODUCTION

The successful treatment of breast cancer has improved survival to such an extent that it has bred myriad challenges associated with survivorship. The long-term

increasing trend. Keeping in view the increasing incidence and better survival with treatment modalities of breast cancer and the associated toxicities, this study was intended to study the long term impact of these treatment modalities on cardiovascular status in survivors of carcinoma breast patients in Kashmir valley of Indian subcontinent.

MATERIAL AND METHODS

A prospective study in which breast cancer patients treated by combined modality treatment protocol (i.e, operated followed by chemoradiation \pm hormonal therapy) with curative intent were taken for study from 2009 to 2011 in the Department of Radiation Oncology, Sher-i-Kashmir Institute of medical Sciences (SKIMS) Srinagar, Kashmir, which is a Deemed University and a Tertiary care Referral Institute.

Patients having following characteristics were excluded:

- Co-morbid medical conditions like chronic lung disease, hypertension, asthma or drug intake for the same.
- Previous history of any chest wall irradiation or chemotherapy other than for carcinoma breast.
- Active smoker, ex-smoker.
- Geographical location other than Kashmir valley like high altitude (Ladakh) or, low altitude (Jammu).

Patients included in the study group had:

- Histopathological documentation of Carcinoma Breast.
- Female sex.
- Age greater than 18 years.
- Geographical location; Kashmir Valley.

Initially sixty patients were included in the study group, however ten patients were dropped from final analysis due to irregular follow up. The remaining fifty patients were reviewed at six monthly intervals during their follow-up. In the control group, fifty subjects were included and evaluated. These included age and sex matched healthy volunteers from general population (usually relatives of the patients). Written informed consent was taken from all the participants enrolled in the study. In study group of patients, all were operated (lumpectomy or mastectomy) and had received post operatively chemoradiation. Chemotherapy given to the patients included three types of regimens; FEC (5-Fluorouracil, Epirubicin, Cyclophosphamide), CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) and FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide). All patients had received radiation dose of 45 Grey to primary chest wall, ipsilateral axilla and supraclavicular area \pm 40 Grey to internal mammary area in 20 fractions.

Patients were subjected to echocardiography (M-Mode/2D/Colour Doppler) using Toshiba Power vision System. Standard imaging protocol was used. Left valvular function, valvular regurgitation, pulmonary hypertension and pericardial effusion /constriction was assessed. Pulmonary artery hypertension was assessed using tricuspid regurgitation jet on Doppler. Pericardial thickness was measured and associated abnormalities like constrictive pericarditis and pericardial effusion were looked for.

Ejection fraction was estimated for assessment of left

ventricular (LV) function. Cutoff value of 55% or less was considered indicative of LV systolic dysfunction. Left ventricular diastolic dysfunction was assessed using Mitral inflow Doppler study. Mitral E-velocity, A-velocity, E/A ratio and deceleration time (DT) were estimated. Diastolic dysfunction was categorised in four grades:

- Grade I diastolic dysfunction (mild); Impaired relaxation with normal filling.
- Grade II diastolic dysfunction (moderate); Pseudonormalized mitral inflow pattern.
- Grade III diastolic dysfunction (severe reversible); Reversible restriction.
- Grade IV diastolic dysfunction (severe irreversible); Irreversible restriction.

Within the study group, changes in the cardiac parameters with respect to patient characteristics (age, laterality of disease, tumor size, menopausal status, hormonal status, time period since diagnosis) and treatment characteristics (cumulative anthracycline dose received, inclusion of internal mammary portal in radiation therapy,) were also studied.

STATISTICAL ANALYSIS

The data collected was recorded on a CRF (clinical record form) given as an annexure A. Data was described as percentages and averages. Intergroup comparison of the metric variables was done by student's t-test where non metric variables were compared by Chi-square, Mann-Whitney U test and Fisher's test. P-value of <0.05 was considered significant.

RESULTS

The Age \pm SD in the study group was 47.3 ± 5.8 years and in the control group was 48.2 ± 5.6 years. As far as the menstrual parameters between the two groups are concerned no significant difference was observed with regard to their age at onset of menarche, frequency and duration of menstrual cycles. Menopausal status between the two groups was also comparable. All cases in both groups were multiparous ($p>0.05$). Majority (70%) of the patients had tumour location on left side. Most of the patients had T2 stage (70%) and positive nodal status (90%). With regard to receptor status 18/50 (36%) were positive for estrogen receptor, 8/50 (16%) were negative for same and its status was unknown in 24/50 (48%). Progesterone receptor status was positive for 30%, negative 22% and unknown for 48%. HER-2 NEU receptor status was available in 15 patients out of whom only one patient was positive and rest 14 were negative.

The main surgical procedure undergone by patients was mastectomy in 43/50 (86%) while as breast conservation surgery was done in seven patients. All patients received external beam radiotherapy to primary tumour site/chest wall, ipsilateral supraclavicular area and axilla, but 32/50 (64%) patients had also received radiation to internal mammary as well. 47/50 patients had received anthracycline based chemotherapy. The most common agent being epirubicin in 37/50 (74%) followed by adriamycin 10/50(20%). Total cumulative mean dose of epirubicin and adriamycin was 645

mg and 320 mg respectively. Out of 50 patients in study group 12 (24%) had cardiac involvement at baseline (0-month) compared to one patient in control group ($p < 0.05$) (Table-1). Pericardial involvement in the form of pericardial effusion was present in one patient in study group, diastolic dysfunction present in 9/50 (18%) in study group compared to only one patient in control group ($p < 0.05$). Six patients in study group had valvular involvement while as no patient in control group had valvular involvement. Isolated grade I diastolic dysfunction was found in 4 patients in study group, while four patients were having mild mitral regurgitation in addition to grade I diastolic dysfunction and one patient was having mild aortic regurgitation associated with diastolic dysfunction. Isolated mild mitral regurgitation was present in one patient only. Left ventricular systolic dysfunction was present in one patient

only. All of the above echocardiography findings were not associated with any clinical symptoms.

Serial echocardiography findings in study group were more or less similar over a period of two years (Tables-2,3). Only one new patient developed pericardial effusion. Incidence of diastolic dysfunction progressively increased from 9/50 cases to 12/50 cases. One new patient had developed mitral valve involvement and one new patient tricuspid involvement ($p > 0.05$). Two new patient developed systolic dysfunction. One patient became symptomatic for systolic dysfunction at the closure of study that was previously having asymptomatic left ventricular dysfunction.

No patient in control group had developed any fresh cardiac lesion, while as three patients developed fresh cardiac lesions on echocardiography. Two new patients had developed systolic dysfunction. One patient had become symptomatic for

Echo Finding	Study Group		Control Group		p -value	
	n=	%	n=	%		
Pericardial Effusion	01	02	0	0	0.317 (NS)	
Diastolic Dysfunction	09	18	1	2	0.008 (Sig)	
Mitral Valve Regurgitation	05	10	0	0	0.022 (Sig)	
Aortic Valve Regurgitation	01	02	0	0	0.317 (NS)	
LVSD (EF≤55%)	01	02	0	0	0.317 (NS)	
Over all Cardiac Status	Sequelae	12	24	1	2	0.001 (Sig)
	Normal Echo	38	76	49	98	
Total	50	100	50	100		

Abbreviations: LVSD = Left ventricular systolic dysfunction; EF = Ejection Fraction.

Note: Few cases in the study group had more than one echo abnormality

Table-1: Distribution of cases in two groups according to their echocardiographic findings at baseline (0 month).

Echo Finding	Baseline		6 month		12 month		18 month		24 month		p-value	
	n	%	n	%	n	%	n	%	n	%		
Pericardial Effusion	01	02	01	02	01	02	01	02	02	04	0.607 (NS)	
Diastolic Dysfunction	09	18	10	20	11	22	11	22	12	24	0.417 (NS)	
Mitral Valve Regurgitation	05	10	06	12	05	10	06	12	06	12	0.368 (NS)	
Tricuspid Valve Regurgitation	00	00	00	00	01	02	01	02	01	02	0.368 (NS)	
Aortic Valve Regurgitation	01	02	01	02	02	04	02	04	03	06	0.223 (NS)	
LVSD (≤55%)	01	02	01	02	01	02	2	4	3	6	0.421 (NS)	
Over all cardiac Status	Sequelae	12	24	12	24	13	26	14	28	15	30	0.411 (NS)
	Normal Echo	38	76	38	76	37	74	36	72	35	70	

LVSD = Left ventricular systolic dysfunction; EF = Ejection Fraction.

Note: Few cases in the study group had more than one echo abnormality.

Table-2: Comparison of serial echocardiography findings at six monthly intervals in study group cases (n = 50).

Echo Finding	Study Group		Control Group		P-value	
	n=	%	n=	%		
Pericardial Effusion	02	04	0	0	0.31	
Diastolic Dysfunction	12	24	1	2	0.002 (sig)	
Mitral Valve Regurgitation	06	12	0	0	0.012 (sig)	
Aortic Valve Regurgitation	03	06	0	0	0.15	
Tricuspid Valve	01	02	0	0	0.31	
LVSD (≤55%)	03	06	0	0	0.15	
Over all cardiac Status	Sequelae	15	30	1	2	0.000 (sig)
	Normal Echo	35	70	49	98	
Total	50	100	50	100		

Note: Few cases in the study group had more than one echo abnormality.

Table-3: Distribution of cases in two groups according to echocardiography findings at their last follow up (24 month).

systolic dysfunction that was previously asymptomatic. The two new echocardiography findings of aortic regurgitation and one new finding of mild mitral regurgitation was found on patients on whom only diastolic dysfunction of grade I was present. The tricuspid regurgitation was the only finding detected for the first time in a patient at the closure time of study. The new three findings of diastolic dysfunction was noted in patients previously having other abnormalities.

DISCUSSION

Adjuvant therapies have been shown to have a significant impact on reducing the risk for breast cancer recurrence and overall mortality. Chemoradiation therapy remains an important and frequently used treatment option in the adjuvant setting, and the associated short-term adverse events are very well described. However, there is not sufficient information regarding the long-term sequelae of most chemotherapeutic agents and radiation treatment in this setting. These adverse events are frequently overshadowed by the well demonstrated clinical efficacy and/or reassuring short-term safety profiles of the different chemo radiation therapy regimens commonly used today. Anthracycline-based regimens with epirubicin or doxorubicin have been widely used in the adjuvant treatment of breast cancer since 1980s. It is very well described that these agents carry a significant risk for cardiac toxicity, which is exponentially dose dependent¹¹, similarly late sequelae of radiotherapy are well known. The purpose of this study was to analyze and assess the cardiovascular implications in survivors of carcinoma breast patients treated with postoperative chemo radiation and ±hormone therapy. This was a prospective case control study in which fifty breast cancer patients and fifty healthy volunteers from general population were included. Patients who refused to consent and had other co morbidities were not included the study. Cardiac status was assessed by performing serial echocardiography at six monthly intervals over a period of two years.

The study group and control group cases were comparable according to their personal habits and characteristics. Most of them were middle aged at presentation. The age at presentation among the studied breast cancer patients was 47.3±5.8 years, this age of presentation was in accordance with the study of Sunita Sexana et al¹², Raina V. et al¹³, Fakhro A.E. et al¹⁴, Priya Hazrah et al.¹⁵ In our study most of the patients (70%) belonged to rural area where as 30% belonged to urban area. This was probably due to the reason that more than 75% of population of Kashmir reside in the rural areas. With regard to the parity among the breast cancer patients, all the patients in our study were multiparous and married, although nulliparity is a risk factor for breast cancer. This was comparable to figures shown by Sexana et al.¹²

The tumour location for most 35/50 (70%) of patients was on the left breast. Left breast tend to be more involved in breast cancer compared to the right breast and the most common location being upper outer quadrant.¹⁶ A palpable lump was present in 100% patients while discharge from the nipple was the commonest symptom 14 (28%) patients, followed

by pain in breast in 6 patients, comparable with figures of A. Mehmood et al.¹⁷ Majority 36/50 (72%) of the patients had tumour size between 2cm and 5 cm. Lymph node positive status was present in 45/50 (95%) of cases. These findings of advanced disease presentation in the form of node positivity were in accordance with the study conducted by Arshad Mehmood et al.¹⁷

With regard to hormone receptor status, estrogen receptor (ER) analysis was available in twenty six patients out of which eighteen were positive and eight negative, while as its analysis was not available in twenty four patients. Progesterone receptor status was available in twenty four patients, out of which thirteen were positive and eleven were negative, while as its analysis was not done in 26 patients. HER-2 NEU receptor status was available in 15 patients out of whom only one was positive and rest were negative.

All the patients were treated with surgery followed by chemo radiation. All patients had intraductal carcinoma on histology, figures comparable with the study conducted by Arshad et al.¹⁷ Mastectomy with lymph node dissection was the surgical procedure done in majority of patients 44/50 (88%), and in six (12%) patients breast conservation surgery was done. Breast conservation surgeries are done for early stage localized breast cancer while as modified radical mastectomy is the surgical procedure of choice for locally advanced disease.¹⁷ All patients received adjuvant chemotherapy and radiotherapy. 24/50 patients were treated with hormonal therapy in addition to radiotherapy and chemotherapy. The common chemotherapeutic drug regimen used to treat the breast cancer patients was FEC (5-fluorouracil, epirubicin and cyclophosphamide) in 76%, 5- fluorouracil, adriamycin and cyclophosphamide in 18%. Cyclophosphamide, methotrexate and 5- fluorouracil were used in 6% patients.

Over all 15/50 (30%) patients had cardiac involvement. Cumulative dose of anthracycline (epirubicin) in patients with cardiac involvement was higher (815mg) than in patients without cardiac involvement (685 mg). Similar results of dose dependent cardiac toxicity were observed by Nielson et al.¹⁸

In the beginning of our study out of 50 patients in study group 12 (24%) had an overall cardiac involvement compared to one patient in control group ($p > 0.05$). Pericardial involvement was present in one patient in study group, mild diastolic dysfunction (grade I) present in 9/50 (18%) in study group compared to only one patient in control group ($p > 0.05$). Six patients in study group had valvular involvement while as no patient in control group had valvular involvement. Only one patient (2%) was having asymptomatic left ventricular dysfunction in the form of ejection fraction less than fifty five percent. In our study only one patient developed symptomatic left ventricular dysfunction in the form of dyspnoea at mild routine activity at the completion of study who was having asymptomatic left ventricular dysfunction in the start of study. After a follow up of two years two new patients had developed asymptomatic left ventricular dysfunction that is in total of 3 (6%) patients. These results are comparable with

the study conducted by Fumoleau, et, al.¹⁹ The 7-year risk of LVD was 1.36% in their patients who received epirubicin based chemotherapy. Similar results from a study conducted by Jacques et al, (2004). All the patients were asymptomatic. The incidence of congestive heart failure (CHF) reaches 5% for doxorubicin and epirubicin, with cumulative doses of 400 and 920 mg/m², respectively.^{20,21}

Zambetti et al.²² (2001) observed 8% of systolic dysfunction in breast cancer patients treated with doxorubicin cumulative dose of (294mg/m²) and evaluated over a period of 11 years by echocardiogram. Bonnetterre et al²³ (2004) observed 2.3% CHF in highdose epirubicin 600 mg/m², with asymptomatic LVEF drop in 18 patients (n = 85); evaluated by echocardiography over a time period of 8 years. Ganz et al²⁴ (2008) observed LVEF of 61.4% versus 64.8% for Adriaycin and CMF respectively, over a period of 5–8 years. Asymptomatic left ventricular dysfunction (LDV) was observed in 18 patients after FEC100 and in one patient after FEC50. In these patients, treatment casualty was probable in eight patients. Two additional years after this assessment, all 18 patients were still asymptomatic. After more than 8 years of follow up, the cardiac toxicity observed after adjuvant treatment with FEC100 compromised two cases of well-controlled congestive heart failure (CHF) and 18 cases of asymptomatic left ventricular dysfunction (LVD).²⁵

CONCLUSION

Both earlier diagnoses of the breast cancer and novel chemo radiation therapy strategies have resulted in a considerable improvement in breast cancer survival. Apart from the clear benefits of adjuvant chemo radiation, we should be aware of the potentially increased risk of cardiovascular sequelae following specific radiotherapy regimens in long-term breast cancer survivors. It is important to realize that our role as oncologists is not only to treat the tumour but also to improve the quality of life of our patients by preventing and treating the long term toxicities induced by chemo radiation.

Majority of the patients were having echocardiography documented asymptomatic cardiac abnormalities. At a mean follow up interval of 5.8 years in the beginning of study 12/50 (24%) were having cardiac sequelae. Over a time period of 2 years three new patients developed asymptomatic cardiac problems. The follow up time was less, need more follow up time and larger studies.

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