Cardiac toxicity in breast cancer patients

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Abstract

Aim:

To asses cardiac toxicity post radiotherapy in left cancer breast patients with different fractionations.

Methods:

This is a prospective randomized study conducted at Kasr El-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK). Cardiological assessment using RTOG toxicity criteria was done for left sided breast cancer patients after at least five years of conformal radiation therapy. There were two arms of radiation, conventional (50Gy/25sttt/5 Ws) and hypofractionation (42.5 Gy /16 fractions /3 1/5 weeks).

Results

Thirty patients were included in each arm. After a median follow up of 62 months (range 60 to 72), cardiac dysfunction developed more in the conventional arm but was insignificant (P value =0.36). Grade I & II toxicity was 83.3 vs 70% and grade III was 3.3% in the hypofractionated arm only. The rate of local-regional tumor relapse at 5 years was similar (3.3%).

Conclusion:

Hypofractionated radiotherapy decreased cardiac toxicity though not statistically significant, however it is more cost effective and time consuming.

Keywords:

breast cancer, cardiac toxicity, hypofractionation, Egypt

Introduction

There was relative increase of 30% of cardiac death among women treated with radiotherapy before the 1980s. At that time the radiotherapy technique was 2D treatment planning with large volume of the heart included [1]. This has improved significantly after this era [2, 3].

Recently over the last decades, there has been an increase in the number of cancer centres offering radiation therapy in Egypt. However, this has not accommodated the increasing number of patients requiring treatment and has resulted to an increased waiting times for patients with breast cancer to start radiotherapy.

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Hypofractionation regimens are particularly useful in solving such problems. However, a high dose per fraction is known to cause some unacceptable late effects which may not be clinically apparent for 10–20 years [4]. Using 50 Gy in 25 fractions of 2 Gy/fraction is considered to be the standard and the most commonly used regimen. Many authors however have described many different fractionations [5, 6].

In Egypt, patients often live far away from cancer treatment centers and are often accompanied by family members during treatment. Daily radiotherapy treatment over several weeks can be very inconvenient for the patient and family members. This creates a burden on the family during the long periods of treatment.

The use of shorter fractionation schedules was reported in Britain and Canada [5, 6]. The UK

START Trial published in 2008 comparing 50 Gy/25 fractions to 40 Gy/15 fractions has shown that 40 Gy in 15 fractions seems to offer rates of local–regional tumour relapse and late adverse effects at least as favorable as the standard schedule of 50 Gy in 25 fractions [7].

The benefit of adjuvant radiotherapy (RT) in decreasing relapse in breast cancer patients is counterbalanced by an increased risk for death from cardiac events [8]. Also, several systemic agents might also increase the toxicity of RT including endocrine therapy, chemotherapy (CT), or molecular targeted therapies. Most trials split cardiac toxicity when focusing on heart disease into systemic therapies or RT. Consequently, these studies do not provide exhaustive information on long-term cardiac toxicity from all parts of adjuvant treatment. New insights are necessary to improve the understanding of cardiac toxicity. There is growing evidence that cardiac toxicity is an issue of both systemic agents and radiotherapy [9]

The aim of this pilot study was to assess cardiac toxicity in left breast cancer patients at least 5 years after receiving 3D conformal radiotherapy either conventional or hypofractionated. Analysis of this Egyptian population was done in correlation with patient related risk factors, chemotherapy received, and type of radiotherapy fractionation in relation to cardiac toxicity.

Methods

This is a prospective study conducted at Kasr El-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK). All left sided breast cancer patients receiving 3D conformal radiotherapy from January 2005 till December 2007 were included. These patients received either conventional or hypofractionated radiotherapy (50Gy/25sttt/5 or 42.5 Gy /16 fractions /3 1/5 weeks). Proper history taking and clinical examination were done for all patients. Cardiological assessment was done by ECG and echocardiography before, 6 months and 5 years after radiotherapy. Radiation therapy oncology group (RTOG) toxicity criteria [10] was done for left sided breast cancer patients after at least five years of conformal radiation therapy.

Radiotherapy

All patients underwent post-operative RT planning using the three-dimensional treatment planning system. Computed Tomography (CT) images were obtained every 5-10 mm and transferred to the treatment planning system (ECLIPS). Delineation of all target volumes and risk organs to the planning system on all CT cuts was done. All plans were done by the same medical radiation physicist. The breast or chest wall was treated isocentrically using 2 tangential beams with selective multi-leaf blocking to protect risk structures “heart and lungs”. IMLNs, if indicated were included in the tangential beams.

If supraclavicular lymph nodes were irradiated, half beam blocked supraclavicular field was used with suitable gantry angle rotation away from the cord with posterior-superior blocking in the tangential portals to decrease overlap in the junction area.

Digitally reconstructed radiographs (DRRs) were generated for the two tangential portals, supraclavicular portal and for 2 simulation portals using gantry angles of 0 and 90 degrees for easy anatomical judgment.

Plans were evaluated and approved by both physician and physicist. This was based on the following: Homogeneity of dose distribution inside the target volume(s) which was considered acceptable if the part of the PTV receiving a dose between 95 and 107% of the prescribed dose of 5040 cGy in 28 fractions of 1.8 Gy was at least 80% (ICRU report 50); the volume of the lung that received at least 20Gy (V 20 Gy) was not allowed to exceed 31% as grade II pnemonitis can be kept at maximum of 8%; the volume of the heart that received at least 40Gy (V 40Gy) was not allowed to exceed 30%.

Simulation was done to localize treatment portal isocenters on patient surface using their definition in relation to the C.T reference point from the treatment planning system data by means of distances in X ,Y and Z directions.

During the first session, Electronic portal images (EPIs) were taken using I-view Electronic portal image device (EPID) of ELEKTA (I-view)

and matched to DRRs. Differences of more than 5mm were not accepted. A weekly check was done to report toxicity (according to RTOG criteria) and managing them. Matching of new portal images were done at least every 1-2 weeks. Differences of 0-4.9 mm were accepted and 5mm or more were not accepted and in this situation patients were re-simulated. For each patient, dose-volume histograms (DVHs) for target, lung and left ventricle for left-sided cancers were calculated.

Both arms were compared considering Planning Data Evaluating the Dose Homogeneity inside PTVs (Dmax.: the maximum dose received by 5% of the PTV, Dmin.: the minimum dose received by 5% of the PTV) and its coverage (V45Gy:- the percentage of the PTV volume which received at least 45 Gy, V40Gy:- the percentage of the PTV volume which received at least 40 Gy). Planning Data Evaluating the Toxic Dose to Risk Organs was also done (V20Gy: The percentage volume of the left lung which received at least 20Gy, V30Gy: The percentage volume of the left lung which received at least 30Gy).

Clinically, the toxicity was assessed according to RTOG criteria (Table 1) using echocardiography, ECG and clinical cardiological examination. Analysis of the patient's related risk factors, type of chemotherapy, radiotherapy and hormonal therapy received was done and correlated to cardiac toxicity as well as local control in both types of fractionation.

Body mass index (BMI) was calculated by the following equation:

BMI = mass (kg) / (Height (m))2

Chemotherapy

All patients received chemotherapy prior to radiotherapy. Chemotherapy regimens included FAC, (5-fluorouracil, doxorubicin - cyclophosphamide, 5-fluorouracil), FEC (5-fluorouracil - epirubicin - cyclophosphamide) and Taxane based with or following anthracycline (6 TAC or 4 AC+4P).

The FAC regimen was the most commonly given regimen (66.6%). This was followed by the FEC given in 23.3% of the conventional and 30% of the hypofractionated arm. Taxane based regimen was the least used in this era and accounted for 13.3%.

Hormonal therapy

Hormonal therapy was given for 5 years after radiotherapy in hormone positive patients in the conventional and hypofractionated arm (76.6% vs 79.9%). All premenopausal patients in both arms received tamoxifen. With regards to post-menopausal women, they received tamoxifen for 2.5-3 years followed by aromatase inhibitor (letrozole) to complete 5 years. Hormone receptor negative patients were kept under follow up only and constituted 15%.

Target therapy

It is well known that trastuzumab adds to cardiac toxicity caused by anthracyclines, taxanes and radiotherapy. Her2 neu was assessed in only few patients at that time and target therapy was not a routine practice in the department.

Statistical analysis

Data was statistically described in terms of mean +/- standard deviation (+/- SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square (X2) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 13 for Microsoft Windows.

Results

Sixty patients were included in the study. The median follow up of patients was 62 months (range 60 to 72). The age range for the conventional arm was 40-65 years with a mean of 52 while it was 34-60 years with a mean of 45.1 in the hypofractionated group.

Both treatment groups were comparable in terms of performance status, tumour stage and adjuvant chemotherapy and hormone treatment. There was an imbalance in age and grade as shown in (Table 2). The mean follow-up was 62 months in the hypofractionation RT group and 63 months in the conventional fractionation group.

Analysis of the patient's related risk factors, type of chemotherapy, radiotherapy and hormonal therapy received was done and correlated to cardiac toxicity (Table 3).

Cardiac toxicity was more common in patient above 45 years with high body mass index, receiving anthracycline chemotherapy and conventional fractionation radiotherapy.

Grade III cardiac toxicity occurred in only one patient. She was above 45 years with high BMI, receiving taxane following anthracycline based regimen. She was treated with 3D hypofractionated radiotherapy.

Cardiac dysfunction measured by RTOG toxicity criteria in patients treated in the 3 D hypofractionated arm was less than those treated with 3 D conventional fractionation, however the difference was statistically insignificant. (73.36% vs 83.3%, p= 0.36). Local control and epsilateral relapse was not significant between the 2 arms (p=1, 1/30, 3.3% in each arm).

The variation of echocardiographic parameters before treatment, six months and 5 years after radiotherapy is shown in table 4. The ejection fraction 5 years after radiotherapy was decreased by less than 60% and this was statistically significant in relation to age above 45, high body mass index, aromatase inhibitors and conventional radiotherapy. Adding taxanes to anthracycline showed no significant difference. (Table 5)

Discussion

New insights are necessary to improve the understanding of cardiac toxicity. The issue of whether systemic agents, radiotherapy, hormonal treatment or predisposing factors lead to cardiac toxicity or not seems to be now settled. It is obvious that it is a combination of these.

In our study, all of the patients have received cardiotoxic chemotherapy including anthracycline alone or combined with taxanes. Furthermore 85% were kept on hormonal treatment for 5 years. All of the patients have received 3 D conformal radiotherapy and this markedly decreased the heart dose and was associated with less cardiotoxicity than the old techniques. As regards to hypofractionated radiotherapy, the patients in this arm did not show any significant difference in cardiac toxicity or locoregional relapse after a median follow up of 62 months.

There was relative increase of 30% of cardiac death among women treated with radiotherapy before the 1980s. In this era, the breast, chest wall, axillary area and internal mammary lymph nodes were irradiated. The excess risk of cardiovascular events is difficult to define due to lack of reliable dosimetric data. The radiotherapy technique at that time was 2 D treatment planning with large volume of the heart included [1].

Analysis from the SEER suggested that improvements in radiotherapy planning could have reduced cardiac toxicity. Among patients treated during 1973–82 and receiving radiotherapy, the cardiac mortality ratio (left versus right tumor) was 1.58 (1.29–1.95) after 15 years or more. For patients diagnosed during 1993–2001, the cardiac mortality ratio was 0.96 (0.82–1.12), less than 10 years afterwards [2]. This was also confirmed by Patt [3] et al. found no increased in cardiac morbidity up to 15 years after "modern" adjuvant RT for left-sided BC.

In the 1990's the standardization of breast radiotherapy (START) trial and the Canadian trial have encouraged the clinician to offer patients shorter duration, and higher dose irradiation for early breast cancer. Hypofractionated radiotherapy demonstrated excellent local control and was not associated with long term morbidity [5, 7].

The START trial is a multicenter United Kingdom–based phase 3 randomized controlled study of radiotherapy after surgery. The aim of the trial was to test the benefits of fraction sizes less than 2.0 Gy in terms of loco-regional tumor

control, late normal tissue responses, quality of life, and cost-effectiveness in patients with early breast cancer. It was divided into 2 studies (START trial A and B). The START trial A looked at 2236 women who have completely excised invasive breast cancer. They were randomly assigned to receive either 50 Gy of radiation delivered in 25 fractions over 5 weeks or 41.6 Gy or 39 Gy delivered in 13 fractions on alternate days over 5 weeks. Patients were followed for a median of 5.1 years. In trial B, 2215 women received either 50 Gy in 25 fractions over 5 weeks or 40 Gy delivered in 15 fractions over 3 weeks. Patients were followed for a median of 6 years. The incidence of ischemic heart disease was minimal in the START trial (2%, 2.1% in trial A and B respectively) [7].

Concerning chemotherapy (CT), Fumoleau [11] et al. recently compared incidence and risk factors of left ventricular dysfunction in BC patients receiving or not epirubicin-based adjuvant chemotherapy. The 7-year risk of left ventricular dysfunction was 1.36% (95% CI 0.85–1.87) in patients receiving anthracycline, versus 0.21% (95%CI: 0.00–0.52) in patients who had not received epirubicin ($p = 0.004$) and two significant risk factors were identified: age=P65 years and body mass index (BMI) >27 kg/ m^2. Most cardiac effects were transient and well controlled, but follow-up was probably insufficient and these data did not take into account other cardiotoxic agents [12].

Other CT agents were recently involved in the development of cardiac failure. Taxans have been associated with myocarditis, ventricular tachycardia, atrioventricular blocks, and myocardial infraction. More particularly, paclitaxel may potentially aggravate doxorubicin-induced cardiotoxicity [13]. 5-Fluoro-Uracile (5-FU) may also carry some cardiac hazard. The incidence of angina related to perfusion of 5-FU ranges from 1.2% to 18% [14]. Cyclophosphamide may cause both completely reversible and irreversible life-threatening heart failure by its biologically active metabolites and consecutive cardiomyocyte damage [15].

With regards to trastuzumab, the risk of cardiac toxicity was significantly increased when given concurrently with AC (anthracycline plus cyclophosphamide) (27%), compared to patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3–7%). In most patients, cardiac dysfunction improved following initiation of standard medical treatment. Based on these results, it was concluded that anthracyclines and trastuzumab should not be given concurrently [16].

The treatment with either aromatase inhibitors (AI) or tamoxifen does not seem to significantly increase the risk for cardiovascular disease in BC survivors. Tamoxifen is associated with higher rates of venous thromboembolic disease[17], but consequent cardiac toxicity has not been demonstrated. Meta-analyses showed no increase in myocardial infraction or cardiac deaths in patients receiving tamoxifen [18]. The 100-month analysis of the ATAC trial showed no significant difference in the incidence of cardiovascular – related deaths in patients receiving either AI or tamoxifen, but significant differences in toxicity profile were found [19]. Patients receiving anastrozole had fewer cerebrovascular (2% versus 3%, respectively; $p < 0.03$) and thromboembolic (3% versus 5%; $p < 0.0004$) events than those receiving tamoxifen. In contrast, hypertension occurrence was increased in patients receiving anastrozole (13% versus 11%, $p < 0.04$). This concern about AI cardiac safety was also highlighted by the analysis of the large Breast International Group (BIG) 1–98 randomized trial, which demonstrated that patients receiving letrozole developed about twice as many severe cardiac events as those receiving tamoxifen (3% versus 1.4%; $p < 0.001$) [20]. However, this excess of cardiac events is outweighed by the superior control of recurrence afforded by AI compared with tamoxifen. Overall cardiac toxicity with endocrine therapy remains rather low, but probably at the same level with most forms of recent radiotherapy.

In our study, the locoregional relapse was 3.3% (1/30) in each arm of radiotherapy. There was no significant difference in disease free

survival or overall survival between both groups. Longer follow up period is needed.

In post-conservative breast surgery radiotherapy, the Canadian study by Whelan et al. compared 50 Gy in 25 fractions to 42.5 Gy in 16 fractions over 22 days. The study did not demonstrate any significant difference in cosmesis or local recurrence between both groups. According to this trial in June 2003, the National Surgical Adjuvant Breast and Bowel Project in Canada have permitted the Canadian formulation as an acceptable alternative to the more traditional 50 Gy in 25 fractions [21].

The 10-year results of hypofractionated radiotherapy for breast cancer was demonstrated by Whelan et al showed a risk of 10 years local reccurence of 6.7% among the 612 women assigned to standard irradiation as compared to 6.2% among the 622 women assigned to the hypofractionated regimen. At 10 years, 71.3% of women in the control group as compared to 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome [22].

In an Egyptian study composed of 107 patients treated with 3 fractionationed schedules of radiotherapy post mastectomy, (50 Gy over 25 fractions, 45Gy over 17 fractions and 40Gy over 15 fractions) there was no statistical difference in local control(p= 0.88) with significant grade II-III erythema in the two hypofractionated arms (p= 0.001) [23].

In a study done by Ciervide et al, two hypofrationated regimen of radiotherapy were given to 145 patients (42 Gy in 15 fractions and 40.5 Gy in 15 fractions) with an additional daily boost of 0.5 Gy to the surgical cavity. After a median follow-up of 5 years, the ipsilateral local recurrence rate was 4.1% [24].

With regards to cardiac toxicity, it is extremely difficult to compare results between trials that have addressed this issue from different aspects. Some studies focused on chemotherapy induced cardiac toxicity while others have mentioned only radiotherapy induced ones. Other studies have demonstrated the effect of patient underlying risk factors.

In this study, only one patient (3.3%) in the hypofractionated arm developed grade III cardiac toxicity manifested by echocardiography. The patient was 55 years, left sided breast cancer, hypertensive and received adjuvant 6 cycles anthracycline combined with taxane based chemotherapy and tamoxifen as hormonal therapy. In the START trial, 7 patients (0.9%) in the hypofractionation arm developed grade III cardiac toxicity. This difference is attributed to the small number of patients included in the present study and the short follow up period [7].

The imbalance noticed between the 2 arms regarding patient characteristic's age and grade, is not of great impact as St. Gallen consensus of 2007 which considered age of less than 35 years and more than grade I as independent prognostic factors for node negative disease only [25].

The number of the study population was small as well as the relative short time of follow up. The study was also limited in using laboratory indicators of cardiac toxicity as tyrosine kinase as well as more sophisticated imaging techniques like angiography. These were not available for routine use in our centre as we are in a developing country and have limited resources.

We conclude from this work that the clinician must be aware that cardiac toxicity in left breast cancer patients is a multi-factorial issue. Choosing and monitoring the type of chemotherapy according to the patient condition is very important in decreasing late cardiac toxicity. New radiotherapy technique using 3 D conformal radiotherapy has resulted in minimal dose to the heart leading to decrease late cardiac toxicity and death. Abbreviated course of radiotherapy is more convenient and less costly to Egyptian patients to minimize long periods of radiotherapy with acceptable local control and minimal cardiac toxicity.

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Tables

Table(1)-RTOG Toxicity Criteria

Toxicity	Grade 0	Grade I	Grade II	Grade III	Grade IV
Cardiac function	None	Asymptomatic / decline of resting EF by <20% of baseline value	Asymptomatic / decline of resting EF by >20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF

CHF: congestive heart failure, EF: Ejection fraction

RTOG Toxicity Criteria: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) (11).

Table 2: Clinico-Pathological Features for Both Groups

Arm	A 30 patients	B 30 patients	p-value
Age(years)-(mean+/- SD) -range	52+/-7.15 40-65	45.1+/-8.079 34-60	**0.001**
WHO Performance status: - 0 -1 -2	18(60%) 12(40%) 0(0%)	18(60%) 12(40%) 0(0%)	1.0
Menopausal status: Pre* Post	 13(43.3%) 17(56.7%)	 20(66.7%) 10(33.3%)	 0.119
Pathology:-IDC	30(100%)	30(100%)	1
Grade - II -III	30(100%) 0(0%)	24(80%) 6(20%)	**0.024**
Intraductal Componant. no ≤ 25 % > 25 %	 27(90%) 2(6.7%) 1(3.3%)	 25(83.3%) 4(13.3%) 1(3.3%)	 0. 832
Quadrant –UOQ - IQs & Retroareolar - LOQ	21(70%) 4(13.3%) 5(16.7%)	20(66.7%) 5(16.7%) 5(16.7%)	 0.934
T -1 -2 -3 -4	4(13.3%) 20(66.6%) 3(10%) 3(10%)	5(16.7%) 18(60%) 3(10%) 4(13.3%)	0.754
-No. of +ve nodes: -0 -1-3 -≥4	9(30%) 17(56.7%) 4(13.3%)	11(36.7%) 13(43.3%) 6(20%)	 0.647
ER -positive - negative - not assessed	22(73.3%) 7(23.3%) 1(3.3%)	23(76.6%) 6(20%) 1(3.3%)	 0.761
PR - positive - negative - not assessed	23(76.6%) 7(23.3%) 0(0%)	22(73.3%) 6(20%) 2(6.7%)	 0.597
HER2u -positive -negative - not assessed	4(13.3%) 8(26.7%) 18(60%)	3(10%) 9(30%) 18(60%)	 0.904
Medical problems -DM -HTN -BA	7(23.3%) 5(16.7%) 1(3.3%) 1(3.3%)	5(16.7%) 8(26.7%) 4(13.3%) 1(3.3%)	0.748 0.532 0.353 1
Surgery:- -BCS -MRM	15 (50%) 15 (50%)	15 (50%) 15 (50%)	1
Chemotherapy:-6FAC - 6FEC -Taxenes(4AC + 4P or 6TAC)	20(66.6%) 7(23.3%) 3(10%)	20(66.6%) 9(30%) 1(3.3%)	 0.612
follow up period (months): -Range -Mean	 60-72 63	 60-72 62	 0.904

SD:- Standard Deviation , IDC:-Invasive Duct Carcinoma,T:- Tumor , N :-Nodal status,ER:-Estrogen Receptor , PR:-Progestron Receptor, HER2u:-C-erb 2receptor, DM:-Dibetus Melitus , HTN:-

Hypertension, BA :-Bronchial Asthma, FAC:- Flurouracil , Adriamycin , Cyclophosphamide, FEC :- Flurouracil , Eperubicin , Cyclophosphamide, AC+P :- Adriamycin , Cyclophosphamide+Paclitaxel TAC:-Taxotere , Adriamycin , Cyclophosphamide, MRM :-Modified Radical MastectomyBCS:- Breast Conservative Surgery, UOQ:- Upper Outer Quadrant , IQs:- Inner Quadrants, LOQ:-Lower Outer Quadrant, WHO: - World Health Organization, * peri –menopausal patients with less than 2 years cessation of menstruation were added to pre –menopausal.

Table 3 . Correlation between different risk factors and cardiac toxicity

Item		No	%	Cardiac toxicity			
				GI,II		GIII	
				No	%	No	%
Age	< 45	20/60	33.3%	14/20	70%	0/20	0%
	> 45	40/60	66.66%	32/40	80%	1/40	2.5 %
BMI	> 27 kg/m2	50/60	83.33%	40/50	80%	1/50	2%
	< 27 kg/m2	10/60	16.67%	5/10	50%	0/10	0%
Cardiac	Yes	0/60	0%	0/60	0%	0/60	0%
	No	60/60	100%	46/60	76.6%	1/60	1.67%
chemotherapy	FAC/FEC	56/60	93.3%	45/56	80.36%	0/56	0%
	Taxane	4/60	6.6%	1/4	25%	1/4	25%
Hormonal	Tamofen	33/60	55%	30/33	90.9%	0/33	0%
	AI	18/60	33.3%	16/18	88.89%	1/18	5.56%
	No	9/60	15%	0/9	0%	0/9	0%
Radiation	Conventional	30/60	50%	25/30	83.33%	0/30	0%
	Hypo fractionated	30/60	50%	21/30	70%	1/30	3.33%
Total		60/60	100%	46/60	76.6%	1/60	1.67%

BMI: Body mass index

Table 4. The variation of echocardiographic parameters before treatment, six months and 5 years after radiotherapy

Echocardiographic changes	Evaluation time		
Ejection fraction	Before	After 6months	After 5 years
Range	57-74	53-70	50-71
Mean	65 ± 5.631	66 ± 4.035	63 ± 5.346
Fraction shortening			
Range	33-45	28-42	23-41
Mean	39± 3.401	35 ± 3.741	32 ± 4.467
Posterior wall thickness(mm)			
Range	6-13	7-13	7-14
Mean	9 ± 1.450	10 ± 1.671	11 ± 1.561

Table 5. Ejection fraction (EF) 5 years after radiotherapy in relation to risk factors in 60 patients

Item		Total	EF <60%		P value
			No	%	
Age	> 45	40/60	30	75	0.001
	< 45	20/60	4	20	
BMI	> 27 kg/m2	50/60	38	76	0.001
	< 27 kg/m2	10/60	2	20	
chemotherapy	FAC/FEC	56/60	46	82.14	0.3
	Taxane	4/60	2	50	
Hormonal	Tamofen	33/60	4	12.12	0.0001
	AI	18/60	12	66.67	
Radiation	Conventional	30/60	10	33.33	0.05
	Hypo fractionated	30/60	4	13.3	

AI: Aromatase inhibitor, BMI: body mass index