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Cardiac toxic effect of radiation therapy in patients receiving adjuvant trastuzumab treatment, as examined by LVEF of echocardiography: an experimental research

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Background: Radiation in breast cancer patients may result in cardiovascular disease affecting the pericardium, myocardium, and cardiac valves.

Objective: This study aimed to evaluate the cardiotoxic consequences of radiotherapy in breast cancer patients who underwent adjuvant trastuzumab treatment by echocardiographic left ventricular ejection fraction (LVEF) measurement.

Methods: In this retrospective study patients treated with postoperative breast irradiation with adjuvant trastuzumab were examined in terms of LVEF. Eithy five patients with age of 31–76 referred to the radiotherapy department of 5 Azar Hospital of Gorgan, Iran between years 2013 and 2020 were analyzed. Patients were divided into two left sided and right sided breast groups. Patients are routinely assessed every 3 months by echocardiocraphgy. LVEF values was measured at intervals of 3, 6, and 12 months after treatment onset.

Result: On the left side, the average of LVEF immediately decreased after treatment, compared to before treatment (Δ LVEF = 0.021), which shows the impact of trastuzumab. The LVEF average 3 months after treatment onset showed a significant decrease (Δ LVEF = 0.043) indicating a synergistic effect of trastuzumab and radiotherapy. LVEF average 6 months and 1 year after treatment onset showed a decrease but not significant (Δ LVEF = 0.009 and 0.013, respectively).In the right breast LVEF average immediately 3 months after treatment showed a significant decrease (Δ LVEF = 0.011 and 0.057, respectively). Nevertheless, LVEF average does not show a significant decrease after 6 months and 1 year after treatment in the right side group (Δ LVEF = 0.0002 and 0.018, respectively).

Conclusion: Our results showed LVEF changes within one year following treatment in left sided breast cancer was more than right side , but the difference was not significant ,which may be due to the short period of our study based on the protocol of our department. More changes in the left side must be due to placing of the heart in the path of radiation. The study showed that LVEF may be an indicative measure for assessing radiation and adjuvant treatment effects on cardiac function.

Keywords: breast cancer, cardiotoxicity, ecocardiography, HER + , LVEF, radiotherapy, trastuzumab

Introduction

Long-term investigations showed radiation therapy may have cardiotoxic effects. Athough radiation treatment regimens for breast cancer have been changed and the radiation dose to the heart totally are reduced many studies verified such a level of radiation dose may also lead to cardiac failures in which the radiation hazards to the heart and time of occurrence of the effect are unknown.

Radiotherapy can reduce the probability of recurrence and death due to breast cancer at early stages. Although long time studies show that radiotherapy can induce cardiotixicity[1]. Nowadays, radiation doses received by the heart due to technique improvements has been reduced. Yet some studies showed that

HIGHLIGHTS

- Our results showed left ventricular ejection fraction changes within 1 year following treatment in left sided breast cancer was more than right side, but the difference was not significant.
- More changes in left side must be due to placing of the heart in the path of radiation.
- The study showed that left ventricular ejection fraction may be an indicative measure for assessing radiation and adjuvant treatment effects on cardiac function.

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such a level of radiation may have cardiotoxic effects, but the time and level of effects resulted from radiation is not clear and depends to many parameters[2].

Trastuzumab (Herceptin) is a humanized monoclonal antibody, which attaches to the extracellular domain of human epidermal growth factor receptor 2 (HER2) and hence inhibits cell growth[3]. The main mechanism of action resulting to clinical advantage of trastuzumab is not clearly known but its anticancer effect in vitro has already been shown since 20 years. HER-positive (HER2 overexpression of the receptor) patients consists 15–25% of breast cancer cases. By adjuvant treatment of HER2-positive patients with trastuzumab survival would be improved, which is confirmed by the four major international studies[4,5]. Trastuzumab is well tolerated by most of patients. In a minority of patients treatment may be temporarily ceased due to cardiotoxic effects of it[4–6]. It has been shown that the risk of developing cardiac failure in patients receiving anthracyclines is more[1].

Anthracyclines may have cardiotoxic consequences in most patients with primary breast cancers. By the way, it is clear that the radiotherapy and trastuzumab both can work as a cardiotoxic effector. They act as an oxidative stressor that induce irreversible damage to myocites (necrosis and apoptosis). The extent of cardiac failure depends on the cumulative dose of drug[7].

Veinot[1] during a retrospective surgical study on patients underwent radiotherapy between 1973 and 1992 showed arterial, valvular, and coronary damages, in addition to pericarditis and myocardial fibrosis. Romond *et al.*[6] based on 78 randomized studies showed rising survival of patients by radiation therapy is accompanied with significant increase of cardiac problems, especially in traditional regimens.

Three large cohort studies showed a correlation between radiation dose to the heart and cardiac mortality in women underwent radiotherapy for breast cancer. The first study published by Darby *et al.*[8] in 2013 showed a 7.4% increase of coronary events per gray of radiation dose to heart. The study showed risk of cardiovascular events begin in the first 5 years following radiotherapy and will rise up to 30 years after radiotherapy. In a study conducted by Van den Bogaard *et al.*, 910 women who underwent conservative treatment were examined in 2017[3]. The primary endpoint was an acute coronary event. The authors measured the average dose to different parts of the heart. The average received dose was 2.37 Gy and the mean following time was 7.6 years. Three percent of patients experience acute coronary event and the added risk per each Gy to heart volume in the first 9 years following radiotherapy was measured as 16.5%. It was shown that a 5 Gy radiation dose to the left ventricle is the most prognostic factor for cardiac events. Ever[7] showed reversibility of reduction of the left ventricular ejection fraction (LVEF) after discontinuing of trastuzumab. They found only ultrastructural changes in heart biopsies. There is a little data showing a long lasting decrease of LVEF after trastuzumab. Annual monitoring is emphasized by cardiologist for patients received trastuzumab[9].

This study aimed to examine the cardiotoxic consequences of radiotherapy in breast cancer patients who underwent adjuvant trastuzumab treatment by echocardiographic LVEF measurement. As only one percent of breast cancer cases are men so we only included women in our study.

Methods

This study was a retrospective with discreptional analysis approach. Eighty-five women referred to the radiotherapy department of 5 Azar Hospital of Gorgan, for breast cancer treatment, were included in our study. The age range were within 31–76 years and patient were admitted between 2013 and 2021. It is normally being checked in our treatment protocol that patients do not have any history of cardiac morbidity. Patients were divided into two groups of left sided and right sided breast cancer. Echocardiography is performed routinely every 3 months following the start of treatment. Since heart volume is in the path of treating beam for left sided breast cancer by different extent so radiation is considered as an important factor to reduce LVEF. Both of left and right sided breasts groups received the same dose of trastuzumab, so decreasing LVEF due to this drug in both groups should be equal. LVEF values were analyzed by a non-parametric Mann–Whitney *U* test at a significance level of 0.05 for two groups.

All patients were treated by 6 MV X-rays from the Artiste linear accelerator of Siemense Company. The applied dose to the gross tumor volume were 54 Gy with a fraction of 2 Gy.

All of patients referring to our department are treated through 4 cycles of adriamycin and cyclophosphamide (AC) chemotherapy (each cycle two weeks) and then depending to being HER + or HER- undergo a chemotherapy regimen of plexitaxol with or without trastuzumab (Herceptin) for 12 weeks. Finally, in the case of HER + Herceptin will continue until to the end of 1 year after the start of treatment. Radiotherapy begins concomitantly with Herceptin.

In this study, just patients receiving Herceptin were examined. For any patient a data sheet was set including age, ethnicity, side of treated breast, chemotherapy regimen, HER + /-, trastuzumab and finally LVEF value for every echocardiography test. LVEF before starting treatment was taken as the baseline LVEF. The time of study for each patient is one year during which five echocardiography tests were taken (one before AC regimen, one at the end of the AC regimen, one at the end of peclitaxol ± Herceptin regimen and two during Herceptin treatment. It must be noticed that last the two echocardiography tests were performed after radiotherapy.

Inclusion and exclusion criteria

Normally 15–25 percent of patients are HER + and if echography LVEFs is greater than or equal to 45%, after four first chemotherapy cycles, they will receive trastuzumab as adjuvant treatment. As antracyclines may lead to LVEF reduction, after four cycles of chemotherapy by adriamycin and cyclophosphamide echocardiography is performed. If LVEF was less than 45% patient was excluded from the study. The examined patients were chosen from 340 patients coming to our department.

Data analysis

The gathered data were entered to SPSS software version 23. Quantitative data were described by average and SD and qualitative data by frequency distribution table. Regarding LVEF mean and SDs before and 3, 6, and 12 months after treatment, the normality of LVEF changes within one year after treatment relative to before treatment was assessed by the Shapiro–Wilk test and no normal distribution was found. Therefore, the

Table 1

Age of patients in terms of side of breast.

Parameter	Breast side	Least	Most	Average ± SD	Significance
Age	Left	31	71	49.14 ± 10.78	0.69
	Right	32	76	50.04 ± 10.13	

nonparametric Mann–Whitney *U* test was used to analysis LVEF changes. χ^2-test was used to correlate qualitative data in two groups. The significance level was taken at 0.05.

Results

Eighty-five women were included in our study. The average age was 49.66 ± 10.36 within range of 31–76. 42% of patients were left sided breast cancer and the remainder were right sided. Table 1 compares the age of patients in terms of side of breast cancer.

Table 2 shows LVEFs average and SD 3 months, 6 months, and 1 year after treatment onset (the last two LVEFs is taken after radiotherapy) in terms of the side of breast cancer treated.

Immediately after treatment onset LVEF average falls significantly in the left breast group ($P = 0.029$). LVEF average shows a decrease 3 months after treatment onset ($P = 0.002$). LVEF average shows a reduction after 6 months and one year after treatment onset (which includes radiotherapy) but not significantly ($P > 0.05$).

In the right side breast cancer, the LVEF average immediately after treatment onset showed a significant decrease ($P = 0.033$).

Also, the LVEF average shows a significant decrease 3 months after treatment onset ($P = 0.029$) for right side breast cancer. However, LVEF average 6 months and 1 year after treatment onset (including radiotherapy) did not show a significant difference for right sided breast cancer.

According to the obtained results, LVEF changes immediately after treatment onset for the left side was more than right breast but this difference was not significant. Three months after treatment mean rank of LVEF for left side breast cancer was more than right breast cancer but not significantly.

Six months after treatment onset (which radiotherapy is also done), the mean rank of LVEF in the left side is more than right side which is not significant. One year after treatment onset (which radiotherapy is also done), the mean rank of LVEF for the left side is more than right side but it is not significant (Table 3).

Spearman's rank correlation coefficient test was performed to assess the correlation of LVEF changes with age. The test shows no significant correlation in both breast sides but in the left side there is a direct and in the right side an inverse correlation (Table 4).

Discussion

Radiotherapy is an important approach to treat breast cancer but may increase the probability of side effects like heart ischemic disease. A meta-analysis study done by Romond *et al.*[6] in 2005 showed that in spite of the increase of survival of breast cancer patients by adjuvant radiotherapy, a significant growth of cardiac illness is expected.

Darby showed a 4.7% linear increase of coronary events per each Gray of radiation[8]. Van den bogard reported a 5.16% increase of cardiac risk per each gray of radiation to heart volume within the first 9 years following radiation[3] which was in consistent with Darby results.

The aim of this study was to survey the cardiotoxic consequences of radiotherapy in breast cancer patients who underwent adjuvant trastuzumab treatment by echocardiographic LVEF measurement. We compared results obtained in left sided breast cancer with right side. Our results showed the mean rank of LVEF within one year following treatment in left sided breast cancer was more than right side but the difference was not significant. If the difference was significant our finding was in accordance with Darbey and Bogard's finding[2,8]. This may be due to the short period of our study, which of course was imposed by the protocol of our department. More changes in left side may be due to the place of the heart in the left side and being in the path of radiation for left sided breast cancer, which is normally 1.5 cm of depth. Moreover, as echocardiography tests are taken within one year following treatment this may attenuate differences. In the left breast, LVEF mean immediately after treatment onset shows a significant decrease relative to before treatment, which may be due to the antracycline effect. Three months after treatment onset (start of trastuzumab and radiotherapy), the LVEF mean showed a significant decrease, which shows the synergistic effect of antracyclines, herceptin, and radiotherapy. Other researchers verified that the incidence of RIHD is more in patients received high dose of radiotherapy or radiotherapy and antracyclines[10] which is in accordance to our findings. Anyway, radiotherapy and trastuzumab both work as a cardio toxic factor (10). Six months and

Table 2

LVEF values before and (3, 6, and 12 months) after treatment onset.

Parameter	Breast side	Interval	Average ± SD	Δ LVEF	Significance
LVEF	left	before	0.58 ± 0.03	–	–
		After treatment	0.56 ± 0.06	0.021	0.029
		3 months	0.53 ± 0.11	0.043	0.002
		6 months	0.57 ± 0.04	0.009	0.09
		1 years after	0.57 ± 0.04	0.013	0.06
	Right	before	0.57 ± 0.04	–	–
		After treatment	0.56 ± 0.04	0.011	0.033
		3 months	0.52 ± 0.16	0.057	0.029
		6 months	0.57 ± 0.03	0.0002	0.98
		1 year	0.57 ± 0.03	0.0018	0.63

Table 3

Comparison of Δ LVEF before and after (3, 6, and 12 months) treatment in terms of breast side.

Parameter	Breast side	Avg ± SD	Mean rank	Significance
Δ LVEF before and after treatment	Left	0.02 ± 0.06	44.15	0.68
	Right	0.011 ± 0.04	42.15	
Δ LVEF before and 3 months after	Left	0.043 ± 0.098	46.11	0.28
	Right	0.057 ± 0.17	40.17	
Δ LVEF before and 6 months after	Left	0.009 ± 0.03	46.88	0.15
	Right	− 0.002 ± 0.04	40.15	
Δ LVEF before and 12 months after	Left	− 0.013 ± 0.04	46.21	0.24
	Right	− 0.0018 ± 0.04	40.64	

12 months after treatment onset LVEF mean show a reduction but not significant.

In the right breast immediately after treatment onset, the LVEF mean shows a significant decrease relative to before treatment. Moreover, LVEF mean 3 months after treatment onset shows a significant decrease but 6 and 12 months after treatment reduction was not significant.

There are many reports regarding the cardiotoxic effect of trastuzumab[6–9], therefore patients receiving this drug are routinely under check by echocardiography. But as in our study all of patients received trastuzumab, it is a background reducing factor for LVEF. So three months after treatment onset LVEF reduction may be a sign of the cardiotoxic effect of trastuzumab plus radiotherapy, which is in accordance to the results taken by authors working in this field[6–9].

The present study showed that more delicacy in treatment planning, regarding point of dose description and use of wedges and so on, plays an important role for saving heart. Findings show that new techniques like IORT can limit the risk of cardiac events following radiotherapy[9]. Among the cardiac events after radiotherapy are damage to the coronary arteries, myocardium fibrosis, and coronary heart disease. Using biomarkers like troponin and BNP can help to recognize high risk patients. Moreover, prescribing drugs like angiotensin antiplatelet can reduce the occurrence of cardiac disease following radiotherapy. The main strength of our study is introducing a routine technique to evaluating the cardiac consequence of radiotherapy and chemotherapy without any extra cost to Burdonon patients. The main limitation of our study is short period of it which may reduce the significance of differences and or more importantly minimize our window of observing a process. Furthermore, missing echocardiography records of some patients was a source of uncertainty of results.Using of the same echocardiography units is another source of error which may prolong the study.

Table 4

Correlation of Δ LVEF and age in terms of breast side.

	Left breast		Right breast	
Parameter	r	*P*	r	*P*
Δ LVEF before and after treatment	0.19	0.27	− 0.08	0.57
Δ LVEF before and 3 months after	0.27	0.11	− 0.18	0.21
Δ LVEF before and 6 months after	0.25	0.14	− 0.12	0.41
Δ LVEF before and 12 months after	0.09	0.60	− 0.15	0.29

Conclusion

Our study showed that the side effects of radiation therapy depends directly to applied radiation dose and number of fractions. Moreover, at lower ages and left sided breast cancers there is more chances of cardiac consequences following radiation therapy. Applying new radiotherapy modalities like IORT may reduce the chance of damage to the heart due to radiation. Damages to small and large vessel like the coronary arteries and then myocardium fibrosis are major consequences of radiation therapy side effects. Using biomarkers like troponin for identifying high risk patients may reduce the hazards of cardiovascular disease.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and its protocol was approved by the Ethics Committee of Golestan university of Medical Sciences. Signed informed consents were obtained from all individuals.

Consent for publication

Not applicable.

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Authors' contributions

R.K. and A.K.K.: study design and concept; M.S.G. and R.K.: literature search and drafting; M.S.G.: conducted the statistical analyses; R.K.: wrote the first draft of the manuscript; A.K.A. significantly contributed to the manuscript editing. All authors read and approved the final manuscript.

Conflicts of interest discloure

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

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