Original Article

Efficacy of Echocardiographic Parameters in Predicting Chemoradiotherapy-Induced Cardiotoxicity in Patients With Breast Cancer

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ABSTRACT

Objective: Using echocardiographic parameters, we sought to predict cardiotoxicity in patients with breast cancer before treatment.

Methods: The study recruited 53 left-sided breast cancer patients with no previous history of heart failure or cancer treatment. The patients underwent 2D and 3D echocardiography before and 6 months after the end of treatment. The main criterion for cardiotoxicity was a reduction in posttreatment LVEF exceeding 10% compared with pretreatment. Systolic and diastolic parameters were compared between 2 groups: complicated and noncomplicated. Binary logistic regression was used to predict cardiotoxicity.

Results: The patients' mean age was 49 ± 11.2 years. No statistical differences existed between the groups in demographics and cardiac risk factors at study commencement. Posttreatment, 4 echocardiographic parameters (E/A ratio, sPAP, LVEF, and LVGLS) were significantly changed compared with pretreatment echocardiography. The regression analysis showed that E/A ratio was effective in predicting cardiotoxicity (sensitivity = 68%, specificity = 76%, AUC =77%; and P <0.001).

Conclusions: Echocardiography, aside from its usefulness in diagnosing cardiotoxicity, can be valuable in predicting complications, especially in patients with breast cancer at higher risk of cardiotoxicity due to chemotherapy and radiotherapy in the chest wall area.
(Iranian Heart Journal 2023; 24(3): 62-69)

KEYWORDS: Cardiotoxicity prediction, Echocardiography, LVEF, Chemotherapy, Radiotherapy

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Received: June 22, 2022 **Accepted:** August 1, 2022

Breast cancer is the most common cancer in females. It includes about 24.5% of new cancer cases and 15.5% of new deaths in women worldwide. [1] Adjuvant treatments like radiotherapy and systemic therapy (refer to endocrine therapy, chemotherapy, and biological therapy) are additional treatments given after surgery to reduce the chance of local or distant recurrence. [2] On the other hand, cardiovascular diseases are the leading causes of death globally [3-5] and constitute a group of disorders of the heart and blood vessels, such as congenital heart diseases, [6] coronary heart disease, cerebrovascular disease, and peripheral arterial disease. [7,8] Recent developments in medical imaging and therapy have enhanced treatment and diagnosis. [9,10] Although current cancer therapies enable long-term survival, many therapies have short- and long-term cardiotoxic effects. [11] Cardiotoxic reactions can be irreversible (Type I reaction), which is dose-related, or they can produce the temporary loss of cardiac contractility or result in cardiac stunning (Type II reaction), which is not dose-related. [11] The early detection of chemoradiotherapy-induced cardiotoxicity is of great interest as cancer therapy and drug combinations may be modified to reduce cardiotoxicity. [12] The evaluation of left ventricular ejection fraction (LVEF) is the detection method for cardiotoxicity. According to the guidelines of the European Society of Cardiology, a reduction of more than 10% in LVEF from the original value is defined as cardiotoxicity. Diagnostic tools for detecting cardiotoxicity are different imaging modalities, such as echocardiography, nuclear cardiac imaging, cardiac computed tomography, and cardiac magnetic resonance imaging. Among these modalities, echocardiography is a widely available, noninvasive, and nonradioactive technique and, thus, the method of choice for detecting myocardial dysfunction before, during, and after cancer therapy. [13] Three-dimensional echocardiography is the best method for the sequential evaluation of LVEF and LV volume measurements. [14] Determining patients with an increased risk of cardiotoxicity is useful for deciding the treatment strategy and completely avoiding or minimally using cardiotoxic chemotherapeutic substances. [15]

In the present study, we aimed to evaluate the efficacy of echocardiographic parameters in predicting chemoradiotherapy-induced cardiotoxicity.

METHODS

The current investigation enrolled 53 patients with left-sided breast cancer (Grade II or III) at the Cardio-Oncology Department of Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. The exclusion criteria were the metastatic phase, a history of heart failure, a history of cancer, or the use of chemotherapeutic agents. Demographic information, medical history, and medications taken by the patients were recorded before the start of the study. All the patients received 6 cycles of chemotherapy and adjuvant radiotherapy. The prescribed dose was between 50 and 60 Gy, with 2 Gy per fraction regime in the 3D conformal radiation therapy technique. In the case of conservative breast surgery, an additional booster dose was delivered to the treatment site.

Imaging

Transthoracic echocardiography in M-mode and the Doppler technique was performed on each patient before and 6 months after the completion of treatment. Imaging was done by echocardiographic specialists using the Philips EPIQ 7 Ultrasound System according to the standard protocol and the recommendations of the American Society of Echocardiography. Cross-sectional images were obtained in the LV parasternal long- and short-axis views and the apical 4- and 2-chamber long-axis views. The analysis of the 3D images was performed

using offline TOMTEC-ARENA TTA2 and QLab, version 13.0.

The following echocardiographic parameters were acquired in both (pre and post) imaging phases: LV end-diastolic volume, interventricular septum, right ventricular end-diastolic volume, early diastole peak velocity, peak velocity flow in late diastole, right ventricular systolic excursion velocity, tricuspid annular plane systolic excursion, left atrial area, systolic pulmonary pressure (sPAP), LV volume, LVEF with the 3D HeartModel software, LV end-systolic volume, LV end-diastolic volume, peak velocity of systolic pulmonary vein, septal mitral annulus velocity, left ventricular global longitudinal strain (LVGLS), and LV posterior wall thickness.

A reduction of more than 10% in posttreatment LVEF compared with pretreatment LVEF was considered cardiotoxicity.

Statistical Analysis

Statistical analysis was performed using SPSS, version 22. Continuous variables are presented as mean ± SD. Between-group comparisons were analyzed using the unpaired *t* test. The paired *t* test was utilized to compare the mean of the variables observed in the 2 imaging phases. The Kolmogorov-Smirnov test was applied to analyze normality. A univariate binary logistic regression model was employed to evaluate the efficacy of the variables in predicting cardiotoxicity. The receiver operating characteristic (ROC) curve was obtained, and the area under the curve (AUC) was calculated to investigate the predictive value of the regression model. Differences were considered significant at a *P* value of less than 0.05.

RESULTS

Patient Characteristics

Fifty-three patients with left-sided breast cancer at a mean age of 49 ± 11.2 years were assessed in 2 groups of complicated and noncomplicated. The mean body mass index and the mean body surface area were 2.3 ± 4.3 and 1.8 ± 0.18, respectively. Based on changes in LVEF in posttreatment echocardiography, 31 patients (60%) had cardiotoxicity. The study population's demographic characteristics are presented in Table 1, which shows no significant differences between the 2 groups concerning cardiac risk factors (P >0.05).

Comparisons of Echocardiographic Parameters

Table 2 shows comparisons of echocardiographic parameters between the complicated and noncomplicated groups before and after treatment. E/A ratio, sPAP, LVEF, and LVGLS were significantly decreased in the complicated group posttreatment. This reduction was observed in the noncomplicated group as well, but it failed to constitute statistical significance.

Figure 1 depicts the posttreatment longitudinal strain bull's eye plot and the 3D LV volume quantification with the 3D HeartModel software in a patient with left-sided breast cancer. The reduction in the strain was obvious in the basal inferior, basal inferolateral, basal anteroseptal, mid-ventricular inferoseptal, mid-ventricular inferior, and mid-ventricular inferoseptal segments. The measurements also indicated a decrease in the patient's LVEF.

Cardiotoxicity Prediction

As shown in the previous section, 4 echocardiographic parameters (E/A ratio, sPAP, LVEF. and LVGLS) can be used as potential prediction indicators. Table 3 demonstrates the univariate logistic regression of these parameters. Only E/A ratio was associated with subsequent cardiotoxicity (P =0.01), whereas LVEF, LVGLS, and sPAP were not statistically significant potential predictors of cardiotoxicity.

Figure 1 illustrates the ROC curve of the prediction of cardiotoxicity by E/A ratio. The sensitivity and specificity of the prediction were 68% and 76%, respectively, with the model having an AUC of 77% (P <0.001).

Table 1: Pretreatment comparisons of demographics and clinical characteristics between the 2 study groups

Characteristic	Complicated (N = 31) mean ± SD	Noncomplicated (N = 22) mean ± SD	*P* value
Age, y	49.4 ± 12.5	48.4 ± 8.4	0.7
Body mass index	27.9 ± 4.7	28.5 ± 3.7	0.6
BSA	1.7 ± 0.2	1.8 ± 0.14	0.4
Heart rate (bpm)	79.7 ± 10.2	81.5 ± 9.2	0.5
Systolic blood pressure (mm Hg)	120.6 ± 12.5	119.5 ± 11.6	0.7
Diastolic blood pressure (mm Hg)	78.1 ± 12.4	78.2 ± 7.2	0.9
Family history of cancer	17	11	0.7
Surgery	21	10	0.1
Smoking status	1	1	0.8
Diabetes	3	2	0.9
History of hypertension	6	4	0.9
History of dyslipidemia	7	2	0.19
Chronic anemia	3	4	0.36
Thyroid dysfunction	3	1	0.48
ASA	1	1	0.8
Aldactone	4	2	0.66
Atorvastatin	5	2	0.54
Aldactone	14	11	0.7
Lisinopril	9	4	0.36
Losartan	2	0	0.22
Valsartan	1	0	0.39

Table 2: Comparisons of functional echocardiographic parameters between the complicated and noncomplicated groups before and after treatment

Parameter	Complicated			Noncomplicated		
	Pretreatment	Posttreatment	*P* value	Pretreatment	Posttreatment	*P* value
LVEDD, mm	44.3 ± 4.5	45.0 ± 2.6	0.4	45.7 ±5.3	46.4 ± 3.1	0.2
IVS, mm	7.7 ± 1.1	8.1 ± 0.9	0.1	7.8 ± 1.3	7.9 ± 0.9	0.06
RVEDD, mm	28.3 ± 3.1	28.1 ± 2.7	0.7	29.4 ± 3.0	29.6 ± 3.7	0.8
E/A ratio	1.15	1.00	0.015 *	1.09	0.99	0.13
RVS velocity, cm/s	11.8 ± 1.9	11.6 ± 1.4	0.6	12.2 ± 2.5	11.4 ± 2.2	0.06
TAPSE, mm	21.7 ± 2.5	21.6 ± 2.8	0.8	21.9 ± 3.2	20.7 ± 3.1	0.1
LA area, cm^2	16.2 ± 2.7	15.9 ± 2.0	0.5	15.4 ± 2.1	16.1 ± 1.6	0.3
sPAP, mm Hg	23.0 ± 5.1	27.8± 6.2	0.001 *	24.1± 3.8	25.2 ± 6.1	0.4
LV volume by 3D, cm^3	90.1 ± 16.7	91.4 ± 7.2	0.6	86.6 ± 10.0	86.7 ± 8.4	0.7
LVEF with the HeartModel software	58.9 ± 6.8	49.2 ± 4.4	0.001 *	58.5 ± 3.2	53.7 ± 4.8	0.5
LVESV	44.1 ± 20.5	45.8 ± 7.9	0.6	41.4 ± 17.6	44.2 ± 12.3	0.9
LVEDV, cm^3	89.0 ± 15.8	91.2 ± 14.6	0.5	85.4 ± 16.4	95.9 ± 26.4	0.6
S-Septal, cm/s	6.7 ± 1.1	7.0 ± 1.2	0.1	7.2 ± 1.2	7.6 ± 1.2	0.5
E-Septal, cm/s	8.6 ± 2.2	8.4 ± 2.0	0.6	8.0 ± 2.4	8.4 ± 2.0	0.7
E-Lateral, cm/s	11.8 ± 2.9	11.0 ± 2.4	0.1	11.8± 2.9	11.2 ± 1.7	0.2
LVGLS	-19.3 ± 2.9	-17.0 ± 1.5	0.001 *	-19.3 ± 3.4	-17.3 ± 1.3	0.3
LVESD, mm	28.2 ± 5.3	28.2 ± 7.1	0.5	30.5 ± 5.3	30.9 ± 5.8	0.4
LVPWD, mm	7.7 ± 1.2	8.1 ± 1.2	0.1	7.5 ± 0.9	7.4 ± 1.1	0.1

LV, Left ventricle; RV, Right ventricle; EDD, End-diastolic volume; ESV, End-systolic volume; TAPSE, Tricuspid annular plane systolic excursion; IVS, Interventricular septum; EF, Ejection fraction; LA, Left atrium; sPAP, Systolic pulmonary artery pressure

Values are mean ± SD.
*: significant

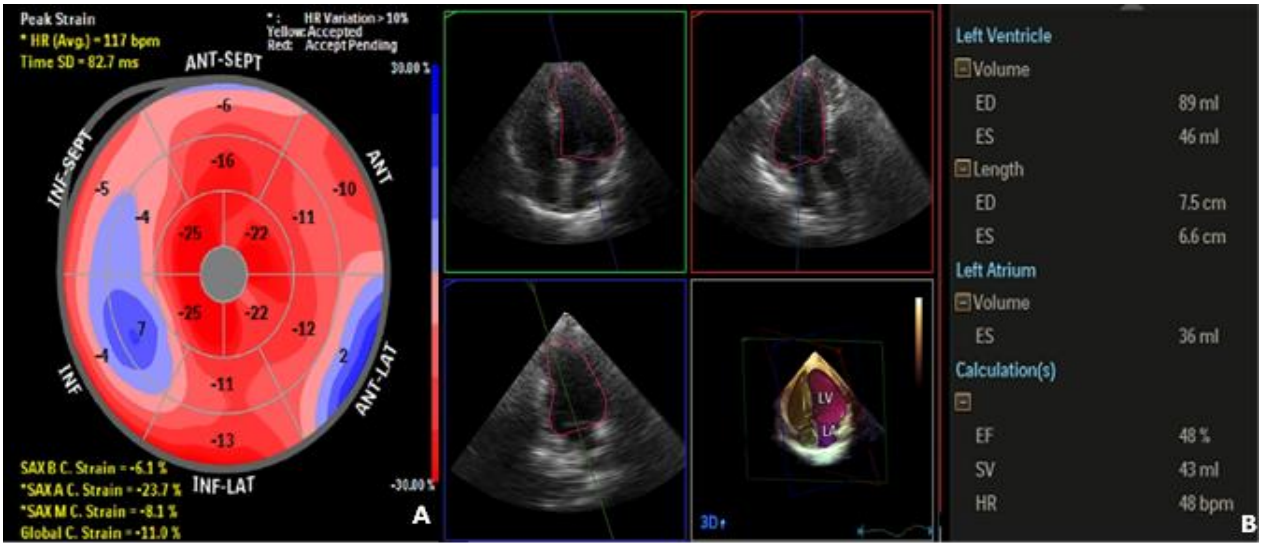

Figure 1: A) The figure depicts the longitudinal strain bull's eye plot in a patient with left-sided breast cancer. A decreased longitudinal strain can be seen in the basal inferior, basal inferolateral, basal anteroseptal, mid-ventricular inferoseptal, mid-ventricular inferior, and mid-ventricular inferoseptal segments. **B**) Automated methods for the analysis of left ventricular function with the 3D HeartModel software in the same patient show a reduced ejection fraction after treatment.

Table 3: Univariable analysis of the potential predictors of cardiotoxicity

Parameter	Odds Ratio	95% CI	*P* value
E/A ratio	1.07	1.0 – 1.1	0.01 *
sPAP	1.08	0.8 – 1.3	0.48
LVEF	0.97	0.8 – 1.1	0.74
LVGLS	0.95	0.7 – 1.2	0.67

*: significant
E/A ratio, Ratio of early to atrial inflow velocities; sPAP, Systolic pulmonary artery pressure; LV, Left ventricle; EF, Ejection fraction; LGS, Longitudinal global strain

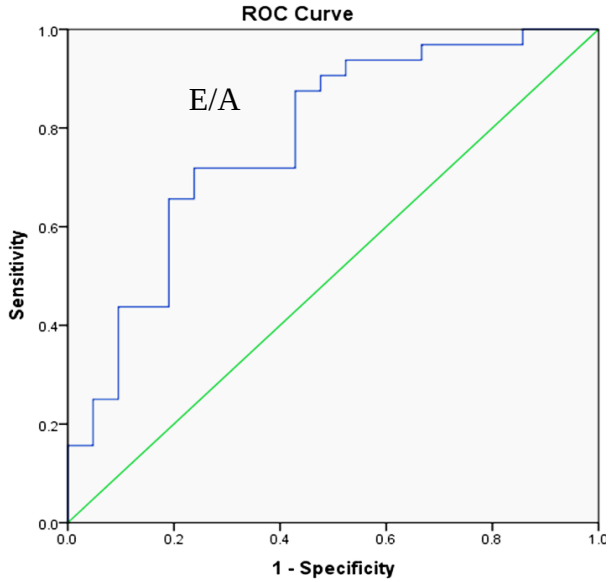

Figure 2: The image illustrates the ROC curve analysis of E/A ratio, showing a significant increase in the predictive performance of cardiotoxicity.

DISCUSSION and CONCLUSIONS

Recent developments in chemotherapeutic agents and radiotherapy techniques have led to increased survival rates. Nonetheless, chemoradiotherapy-induced normal tissue toxicity is still a grave concern. Cardiotoxicity is one of the most significant side effects of chemotherapy drugs in patients with cancer, especially breast cancer, where the heart absorbs a relatively high radiation dose. [16] Therefore, the early detection and prediction of cardiotoxicity due to the use of medications and the selection of alternative methods for treatment with fewer side effects will be valuable. Monitoring LVEF, an index of cardiotoxicity, via 2D echocardiography is the most widely used method for evaluating cardiotoxicity. In the present study, according to prior investigations, our basis for considering cardiotoxicity in patients was a reduction of greater than 10% in LVEF in posttreatment echocardiography compared with pretreatment echocardiography. Our results showed that LVEF and LVGLS decreased after chemoradiotherapy in all patients, although this reduction was significant in 32 out of 53 patients. Nevertheless, our findings indicated that LVEF was a relatively insensitive tool for predicting chemoradiotherapy-induced cardiotoxicity at an early stage. Many studies have examined the effects of chemotherapy and radiation on the reduction of LVEF and LVGLS and have obtained similar results. [17-20]
Reproducibility of the serial assessment of LV volume and LVEF is a challenge in echocardiography screening during cancer treatment. We used the 3D HeartModel software to obtain robust and reproducible LV measurements. After treatment, we witnessed average reductions of 12% and 10% in GLS in the complicated and noncomplicated groups, respectively. Still, several studies have concluded that a fall in GLS of between 10% and 15% can predict subsequent cardiotoxicity. [21-23] We observed no statistically significant relationship between this parameter and the prediction of cardiotoxicity. Our results also demonstrated that E/A ratio (the ratio of early to atrial inflow velocities) could be used to predict cardiotoxicity. Thus, in comparison with systolic parameters, the assessment of diastolic function by echocardiography may predict cardiotoxicity in patients.
The developments in cancer treatment techniques and screening programs have led to increased attention to patient survival, along with the success of the treatment result. The recent availability of novel and more sensitive diagnostic tools has improved our ability to detect subclinical cardiotoxicity. Echocardiography plays a major role in this emerging area, with recent advances in echocardiographic technology generating a large body of evidence supporting the presence of subclinical chemotherapy-induced cardiotoxicity. New software and hardware features have also augmented measurement accuracy and the repeatability of results. Periodic measurements of systolic and diastolic cardiac parameters indicate an association between some parameters and cardiotoxicity. These features also help to predict complications, which can prove valuable not only in decision-making vis-à-vis treatment but also in the reduction of patients' physical complications and costs imposed on the health system. Despite the valuable results that have been found in this field, achieving definitive results requires sizable study populations. Moreover, the use of new image processing methods, such as radiomics, and data analysis methods, such as machine learning, can improve the results of studies.

Study Limitations

The number of patients in this prospective study was relatively small, and our access to

the patients' chemotherapy regimens was limited. Furthermore, follow-up procedures were delayed for some patients given the higher risk at which our study population was during the COVID-19 pandemic.

Acknowledgments

We wish to thank Mrs Fatemeh Nabhani (Cardio-Oncology Department, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran) and Mrs Nasim Jafari (Echocardiography Department, Rajaie Cardiovascular Medical and Research Center, Tehran, Iran) for providing us with technical support.

REFERENCES

1. Riis M. Modern surgical treatment of breast cancer. Annals of Medicine and Surgery. 2020; 56:95-107.

2. Latif J, Mehta S. Adjuvant treatment for breast cancer. Surgery (Oxford). 2021.

3. Azarfarin R, Sheikhzadeh D, Mirinazhad M, Bilehjani E, Alizadehasl A. Do nondiabetic patients undergoing coronary artery bypass grafting surgery require intraoperative management of hyperglycemia? Acta Anaesthesiologica Taiwanica. 2011; 49(2):41-5.

4. Hakim H, Samadikhah J, Alizadehasl A, Azarfarin R. Chronobiological rhythms in onset of massive pulmonary embolism in Iranian population. Middle East J Anesthesiol. 2009; 20:369-75.

5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. Journal of the American College of Cardiology. 2020; 76(25):2982-3021.

6. Ziyaeifard M, Alizadehasl A, Aghdaii N, Rahimzadeh P, Masoumi G, Golzari SE, et al. The effect of combined conventional and modified ultrafiltration on mechanical ventilation and hemodynamic changes in congenital heart surgery. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2016; 21.

7. Cardiovascular diseases (CVDs) 11 June 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

8. Ansari-Ramandi MM, Maleki M, Alizadehasl A, Amin A, Taghavi S, Alemzadeh-Ansari MJ, et al. Safety and effect of high dose allopurinol in patients with severe left ventricular systolic dysfunction. Journal of cardiovascular and thoracic research. 2017; 9(2):102.

9. Ziyaeifard M, Alizadehasl A, Aghdaii N, Sadeghi A, Azarfarin R, Masoumi G, et al. Heparinized and saline solutions in the maintenance of arterial and central venous catheters after cardiac surgery. Anesthesiology and pain medicine. 2015; 5(4).

10. Soulat-Dufour L, Addetia K, Miyoshi T, Citro R, Daimon M, Fajardo PG, et al. Normal values of right atrial size and function according to age, sex, and ethnicity: results of the world alliance societies of echocardiography study. Journal of the American Society of Echocardiography. 2021; 34(3):286-300.

11. Henning RJ, Harbison RD. Cardio-oncology: cardiovascular complications of cancer therapy. Future cardiology. 2017; 13(4):379-96.

12. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. New England journal of medicine. 2011; 365(14):1273-83.

13. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). European heart journal. 2016; 37(36):2768-801.

14. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH.

Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. Journal of the American College of Cardiology. 2013; 61(1):77-84.

15. Kostakou PM, Kouris NT, Kostopoulos VS, Damaskos DS, Olympios CD. Cardio-oncology: a new and developing sector of research and therapy in the field of cardiology. Heart failure reviews. 2019; 24(1):91-100.

16. Alizadehasl A. Cardio-Oncology. Practical Cardiology. 1. 2 ed. Elsevier: Elsevier; 2021.

17. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. Journal of the National Cancer Institute. 2010; 102(1):14-25.

18. Jensen BV, editor Cardiotoxic consequences of anthracycline-containing therapy in patients with breast cancer. Seminars in oncology; 2006: Elsevier.

19. S Gillespie H, J McGann C, D Wilson B. Noninvasive diagnosis of chemotherapy related cardiotoxicity. Current cardiology reviews. 2011; 7(4):234-44.

20. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. Journal of the American College of Cardiology. 2009; 53(24):2231-47.

21. Baratta S, Damiano M, Marchese M, Trucco J, Rizzo M, Bernok F. Serum markers, conventional Doppler echocardiography and two-dimensional systolic strain in the diagnosis of chemotherapy-induced myocardial toxicity. Rev Argent Cardiol. 2013; 81(2):139-46.

22. Mornoş C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Canadian Journal of Physiology and Pharmacology. 2013; 91(8):601-7.

23. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circulation: Cardiovascular Imaging. 2012;5(5):596-603.