ORIGINAL ARTICLE

Assessment of Left Atrial Functions in Patients With Breast Cancer Receiving Trastuzumab and/or Chemotherapy

Abd Elmohsen M. Abdu [a], Wael H. Al Sheshtawy [b], Al-Hussein M. Zahran [a], Abdel Rahman D. Mohamed [a]

[a] Department of Cardiology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt
[b] Department of Clinical Oncology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Worldwide, more women will get breast cancer (BC) than any other type of cancer. The introduction of trastuzumab (TZ) to BC therapy has greatly improved the prognosis of women with HER2-positive cancer, whether it is adjuvant or metastatic.***

Aim: ***To evaluate left atrial functions in patients with breast cancer receiving trastuzumab and or chemotherapy, and to test the hypothesis that baseline left atrial functions can predict left ventricular dysfunction due to trastuzumab and or chemotherapy.***

Methods: ***Fifty patients with a confirmed histological diagnosis of early-stage or locally advanced (stages I-IIIC) breast cancer who were treated with TZ and those who received an anthracycline-based regimen were included in this prospective trial. The patients' HER2 overexpression was carefully monitored.***

Results: ***The chemotherapy group showed substantial decreases in Simpson's biplane EF, left atrial (LA) reservoir strain, LA conduit strain, and LA contractile strain at baseline and three months later (P<0.05). Significant increases in E/A, E/e', and LAVI were seen after 3 months compared to baseline (P<0.05). After 3 months, LV mass index hadn't changed appreciably. Simpson's biplane EF, LA reservoir strain, LA conduit strain, and LA contractile strain significantly decreased in the TZ group at baseline and three months later (P<0.05). E/A ratio increased considerably at baseline and three months later (P<0.05). After 3 months, LV mass index, E/e' ratio, and LAVI were similar to baseline.***

Conclusions: ***Our findings demonstrated that La functions (LA reservoir, conduit, and contractile strains) were significantly reduced after 3 months of treatment compared to baseline values in the overall study population, regardless of the treatment type and this can help identifying patients at risk of developing heart failure even when left ventricular function appears normal.***

Keywords: Breast Cancer; Chemotherapy; Left Atrial; Trastuzumab

1. Introduction

On a global scale, breast cancer (BC) affects more females than any other malignancy.[1] About 20% to 25% of breast cancer patients have an elevated risk of mortality due to more aggressive tumor proliferation and overexpression of human epidermal growth factor receptor-2 (HER2).[2]

Women with HER2-positive (HER2+) breast cancer now have much better prognoses thanks to the use of trastuzumab (TZ), a human monoclonal antibody that targets the extracellular part of the HER2 membrane protein. However, due to its potential cardiotoxicity, TZ must be administered with extreme caution, and the LV function of the patient must be closely monitored.[3]

A novel non-invasive ultrasound imaging method called speckle-tracking echocardiography (STE) may measure and assess global and regional myocardial function without relying on insonation angle or heart translational motions.[4]

Accepted 15 April 2025.
Available online 30 June 2025

* Corresponding author at: Cardiology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: doctordiabz24@gmail.com (A. D. Mohamed).

https://doi.org/10.21608/aimj.2025.446619

Speckle tracking, in the context of standard 2-dimensional sonograms, is the foundation of STE. Speckles are spots produced by the interaction of the ultrasonic beam with cardiac fibers.

Until this advanced echocardiographic method was developed, the only way to accurately analyze the various deformation components that make up myocardial dynamics was with tagged MRI.[5]

Tagging magnetic resonance imaging (MRI) has the potential to be the gold standard in this field, but its prohibitive price tag, restricted availability, relative acquisition complexity, and lengthy picture processing make it impractical for widespread application.[6]

By monitoring the position of speckles during the cardiac cycle, speckle tracking echocardiography allows for the semiautomatic development of myocardial deformation in three spatial dimensions: radial, circumferential, and axial. The frequency, direction, and speed of LV rotation can also be determined by STE.[7]

Due to its semiautomatic nature, speckle-tracking echocardiography ensures high levels of repeatability both within and between observers.[8]

Despite the fact that this novel method was initially developed for use just in analyzing LV function, it has now been shown in a number of studies to be applicable to other chambers of the heart, including the left atrium (LA).[9]

This study set out to examine the role of left atrial functions in individuals with breast cancer taking trastuzumab and/or chemotherapy, and to see if these functions could foretell the development of left ventricular dysfunction as a side effect of these treatments.

2. Patients and methods

The fifty patients who participated in this prospective study were all given either TZ or an anthracycline-based regimen, and they all had breast cancer that was either in its early stages or locally progressed (stages I-IIIC), according to histological diagnosis. Stringent monitoring was conducted on the patients' HER2 overexpression.

The research began in January 2023 following clearance from the Al-Azhar University Hospitals Ethical Committee in Cairo, Egypt. The patient signed informed consent.

We excluded patients who met the following criteria: a left ventricular ejection fraction (LVEF) below 50% at baseline, cardiomyopathy, significant renal insufficiency, a history of heart failure, a pacemaker, a defibrillator, a valve prosthesis, a mild or moderate valve illness, or a previous heart or renal transplant.

Every patient underwent a thorough evaluation that included taking their medical history, conducting a physical exam, and measuring their height, weight, BMI, and BSA in addition to conducting laboratory investigations. Medications such as TZ and chemotherapy were documented.

Echocardiography

The frame rate can range from 60 to 100 hertz. The data from three consecutive cardiac cycles are averaged to provide the reported value of each 2DE parameter. All measurements of the left ventricle, septum, and relative wall thickness were taken in accordance with the current standards. The ejection fraction (EF) of the left ventricle was calculated using the biplane method. The LV mass (LVM) was calculated using the updated ASE method in conjunction with the BSA index.

The recent recommendations define left ventricular hypertrophy as an LV mass index greater than 95 g/m2 for women and more than 115 g/m2 for males. The flow and deceleration time of the transmitral LV were evaluated with pulsed-wave Doppler in the apical four-chamber view.

During early diastole (e'), LV myocardial velocities were obtained using tissue Doppler imaging in the apical four-chamber view. A sample volume was placed at the septal and lateral regions of the mitral annulus. In order to determine the E/e' ratio, the septal and lateral mitral annuli's peak early diastolic relaxation velocities (e') were averaged. The evaluation of left ventricular diastolic performance was done using the mitral E/A and E/e' ratios. Using volumetric and strain studies, we were able to calculate the LA phasic function.

Three different phases of the cardiac cycle were used to obtain LA volumes: Prior to the mitral valve opening, the maximal LA volume was determined. At the start of atrial systole, which is the peak of the P wave in the electrocardiogram, the pre-A (pre atrial contraction) LA volume was measured. Finally, the minimal LA volume was measured at the closure of the mitral valve.

We used the biplane approach in both four- and two-chamber perspectives to determine the volumes of all the LAs, and we indexed all the values for BSA. We computed the total emptying volume (a parameter in the LA reservoir function) as the difference between the maximum and minimum LA volumes. We computed the passive emptying volume (a parameter in the LA conduit function) as the difference between the maximum and pre-A LA volumes. We computed the active emptying volume (a parameter in the LA booster function) as the difference between the pre-A and minimum LA volumes.

The software automatically generated an

average longitudinal strain curve after manually tracing the LA endocardium. With the software's six strain curves for each of the two views (four-chamber and two-chamber), a total of twelve LA segments were investigated in each patient. In any case, the program gives a single curve that stands in for the mean longitudinal strain of six sections in two-chamber and four-chamber perspectives; this is done to make longitudinal strain calculations easier.

This graph displays the total longitudinal strain in the LA, which is a parameter of the LA reservoir function. The cumulative longitudinal strain and associated strain rates for the LA were calculated by averaging the findings from the four-chamber and two-chamber apical views. At the systolic phase of the left ventricle, the LA systolic strain rate reveals the function of the reservoir; at the early and late diastolic phases of the left ventricle, the strain rates reveal the functionalities of the conduit and the booster pump, respectively.

Following baseline LA functions (0), all patients underwent speckle tracking of LA function, which included reservoir strain, conduit strain, and contraction strain. Examination three months subsequent to chemotherapy initiation.

Several parameters were documented, including Simpson's biplane EF (%), LV mass index (g/m2), E/A ratio, E/e' ratio, LAVI (mL/m2), LA reservoir strain (%), LA conduit strain (%), and LA contractile strain (%).

Statistical analysis:

Data was analyzed using SPSS v26, which was developed by IBM Inc. and is based in Chicago, IL, USA. Numbers and percentages were used to represent qualitative variables. The two groups were compared using an unpaired Student's t-test for quantitative data, which were provided as means and standard deviations (SD). It was deemed statistically significant if the two-tailed P value was less than 0.05

3. Results

This study was carried out on 50 breast cancer patients younger than 56 years old admitted to Al-Azhar University Hospitals, Egypt.

The age ranged between 37-56 years with a mean value (±SD) of 46.14(±4.96) years. All patients were females. Regarding medical history, 16(32%) patients had DM and 19(38%) patients had HTN. Type of drug was Chemotherapy in 33(66%) patients and Trastuzumab in 17(34%) patients, table 1.

Table 1. Information on the patients' demographics

		N=50
AGE (YEARS)		46.1±4.96
SEX (FEMALE)		50(100.0%)
MEDICAL HISTORY	DM	16(32.0%)
	HTN	19(38.0%)
TYPE OF DRUG	Chemotherapy	33(66.0%)
	TRASTUZUMAB	17(34.0%)

The data is displayed as frequency or mean ± SD. Diabetes mellitus, or DM TZ: Trastuzumab, HTN: Hypertension.

At baseline, Simpson's biplane ranged between 55-69 % with a mean value (± SD) of 61(±3.51) %. LV mass index ranged between 54-68 g/m2 with a mean value (±SD) of 59.07(±4.19) g/m2. E/A ratio ranged between 0.7-1.4 with a mean value (±SD) of 1.09 (±0.18). E/e' ratio ranged between 0.9-8.9 with a mean value (±SD) of 7.5(±1.1). LAVI ranged from 23.3 to 29.8 mL/m2 with a mean value (±SD) of 26.44(±2.31) mL/m2.

LA reservoir strain ranged between 32-39 % with a mean value (±SD) of 36.28(±1.96) %. LA conduit strain ranged between 18-27 % with a mean value (±SD) of 21.84(±1.91) %. LA contractile strain ranged between 10-18 % with a mean value (±SD) of 14.44(±2.14) %, table 2.

Table 2. Echocardiogram data from the research participants at baseline and three months later are compared

	BASELINE (N=50)	AFTER 3 MONTHS (N=50)	P
SIMPSON'S BIPLANE EF (%)	61±3.51	58±3.17	<0.001*
LV MASS INDEX (G/M^2)	59.1±4.19	59.1±4.38	0.931
E/A RATIO	1.09±0.18	1.24±0.16	<0.001*
E/E' RATIO	7.5±1.1	8±0.56	0.01*
LAVI (ML/M^2)	26.4±2.31	27.7±2.01	0.005*
LA RESERVOIR STRAIN (%)	36.3±1.96	30.9±2.77	<0.001*
LA CONDUIT STRAIN (%)	21.8±1.91	19.1±2.49	<0.001*
LA CONTRACTILE STRAIN (%)	14.4±2.14	11.9±2.79	<0.001*

Data is presented as mean ± SD. * Significant P value < 0.05. EF: Ejection fraction,

LV: left ventricle, LA: Left atrium, LA: Left atrial.

In patients received chemotherapy, Simpson's biplane EF, LA reservoir strain, LA conduit strain and LA contractile strain were significantly lower after 3 months compared to baseline (P-value<0.001). E/A ratio, E/e' ratio and LAVI were significantly higher after 3 months compared to baseline (P-value<0.05). LV mass index was insignificantly different between after 3 months and baseline., table 3.

Table 3. Comparison between baseline and after 3 months regarding echocardiographic findings of the studied patients received chemotherapy

	BASELINE (N=33)	AFTER 3 MONTHS (N=33)	P
SIMPSON'S BIPLANE EF (%)	60.27±2.98	57.58±3.03	<0.001*
LV MASS INDEX (G/M^2)	58.73±3.89	58.91±3.92	0.851
E/A RATIO	1.08±0.19	1.25±0.18	<0.001*
E/E' RATIO	7.65±0.56	7.94±0.57	0.041*
LAVI (ML/M^2)	26.69±2.26	28.07±1.95	0.01*
LA RESERVOIR STRAIN (%)	36.18±2.1	31.45±2.25	<0.001*
LA CONDUIT STRAIN (%)	22.03±2.1	19.88±2.26	<0.001*
LA CONTRACTILE STRAIN (%)	14.15±2.24	11.58±3.08	<0.001*

The data is displayed as mean ± SD. * P value < 0.05 is considered significant. LV stands for left ventricle, and EF for ejection fraction. LA: Atrial left.

In patients received trastuzumab, Simpson's biplane EF, LA reservoir strain, LA conduit strain and LA contractile strain were significantly lower after 3 months compared to baseline (P value<0.05). E/A ratio was significantly higher after 3 months compared to baseline (P value=0.004). LV mass index, E/e' ratio and LAVI were insignificantly different between after 3 months and baseline, table 4.

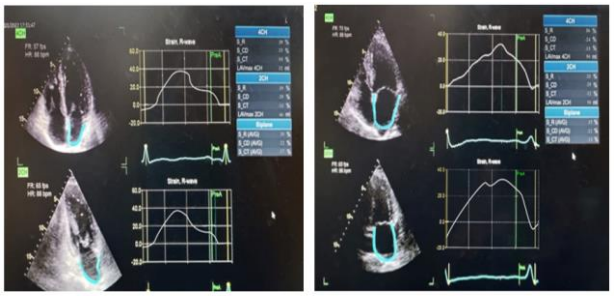
Table 4. Comparison between baseline and after 3 months regarding echocardiographic findings of the studied patients received trastuzumab

	BASELINE (N=17)	AFTER 3 MONTHS (N=17)	P
SIMPSON'S BIPLANE EF (%)	62.41±4.08	58.71±3.41	0.007*
LV MASS INDEX (G/M^2)	59.72±4.77	59.59±5.27	0.938
E/A RATIO	1.1±0.15	1.24±0.1	0.004*
E/E' RATIO	7.21±1.71	7.99±0.54	0.084
LAVI (ML/M^2)	25.97±2.41	26.95±1.98	0.206
LA RESERVOIR STRAIN (%)	36.47±1.7	29.76±3.38	<0.001*
LA CONDUIT STRAIN (%)	21.47±1.46	17.53±2.21	<0.001*
LA CONTRACTILE STRAIN (%)	15±1.87	12.41±2.09	<0.001*

The data is displayed as mean ± SD. * P value < 0.05 is considered significant. LV stands for left ventricle, and EF for ejection fraction. TZ: Trastuzumab, LA: Left atrial.

Case presentation

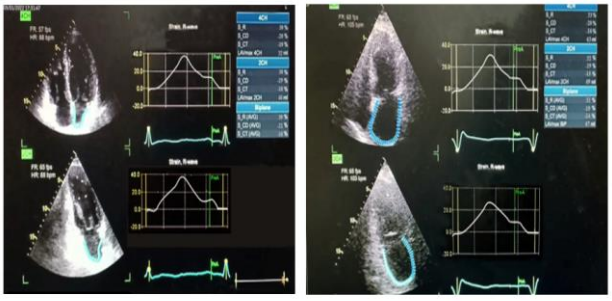
Case 1: A forty-eight-year-old female, non-diabetic and non-hypertensive patient. Examination showed: BP:110/70, RBS:101 and BMI:19.3 Kg/m^2.



(A) (B)

Figure 1. (A) Baseline and (B) Follow-up chemotherapy biplane 2D STE technique for LA quantification.

Case 2: A forty-nine-year-old, diabetic and non-hypertensive patient. Examination showed BP:120/80, RBS:115 and BMI:24.4 Kg/m^2.



(A) (B)

Figure 2. (A) Baseline and (B) Follow-up trastuzumab biplane 2D STE technique for LA quantification

4. Discussion

Numerous reports have documented the detrimental effects of chemotherapy, radiation, targeted therapy, and immunotherapy on the cardiovascular system, which is a major concern in the context of advanced cancer treatment.[10]

Direct or indirect DNA damage induction is associated with the anticancer mechanism of ANTs. The amount of harm grows with cumulative dosages of ANTs, and cardiotoxicity is a side effect that is dose-limiting.[11]

The onset period is a useful criterion for classifying cardiotoxicity as either acute or chronic. In rare cases, anti-nuclear antibody treatment can cause acute cardiotoxicity, which has clinical features with acute toxic myocarditis, including myocardial damage, interstitial edema, and inflammatory cell infiltration.[12]

On the other hand, dilated cardiomyopathy is a more common manifestation of chronic ANT-induced cardiotoxicity in both animal models and human hearts. Heart weight growth and chamber enlargement are hallmarks of the disease. Human tissue with myogenic fiber loss within cells and vacuolar degeneration, accompanied by sarcoplasmic reticulum (SR) enlargement and consolidation, is the most typical pattern.[13]

Among female cancers, BC is by far the most common in Poland and the rest of the globe .[14]

After three months of treatment, our 2D echocardiography results showed substantial changes in multiple important parameters. Both the chemotherapy and TZ groups showed a decline in left ventricular ejection fraction (LVEF). The left atrial volume index (LAVI), the mitral E/A ratio, and the E-to-e' ratio all changed, suggesting that LV diastolic function and remodeling had changed.

These results are consistent with those of other research in the subject, with a few exceptions. Yaylali et al.,[15] reported significant increases in LAVImax and LAVIp after chemotherapy, while Bergamini et al.,[16] identified a correlation between baseline LA AVI and TZ-related cardiotoxicity, as well as a correlation between LA dilatation and cardiac dysfunction. Lots of research has focused on how it affects diastolic function.

Upshaw et al.,[17] noted that deterioration of diastolic function often precedes systolic dysfunction in cancer therapeutics.

However, Negishi et al.,[18] discovered no statistically significant changes in the e' value between the groups of patients with and without cardiac dysfunction caused by cancer treatments (CTRCD).

The left atrial (LA) conduit, reservoir, and contractile strains were significantly reduced after three months of treatment, according to our study. These findings are largely consistent with the growing body of evidence on LA function impairment in BC patients undergoing chemotherapy and/or TZ treatment. Regarding conduit strain, our results align with those of Shi et al.,[19] who observed reduced LAScd immediately after anthracycline therapy in non-Hodgkin lymphoma patients.

Laufer-Perl et al.,[20] observed a significant reduction in LASr in 50% of their patients, while Lassen et al.,[21] reported significant declines in LAεres in both CTRCD and non-CTRCD groups. The reduction in contractile strain we observed is partially corroborated by Timóteo et al.,[22], who discovered that, out of all the BC treatment outcomes, only LASct decreased in the first year.

However, Shi et al.,[19] noted an initial increase in LASct immediately after anthracycline therapy, possibly as a compensatory mechanism.

Lassen et al.,[21] reported a significant decline in LA booster pump strain in the non-CTRCD group. It's worth noting that some studies have found differences in LA strain parameters between patients who developed CTRCD and those who did not.

Park et al.,[23] LA strain analysis may have predictive relevance if the decrease in PALS observed at the end of chemotherapy is a good predictor of future CTRCD following TZ therapy.

Limitations: A tiny sample size was one of the study's limitations. The study only included female patients with breast cancer; however, the findings might not apply to male patients or individuals with different forms of cancer. A longer-term evaluation is necessary to comprehend the temporal trajectory of LA and LV function, as the follow-up period was just three months. It is difficult to conclude that the changes we saw were caused by the therapies alone because our trial did not contain a control group that did not receive TZ or chemotherapy.

Although changes in LV and LA function indices were significant, they are still within normal. This may be related to short follow-up duration.

4. Conclusion

Whatever the treatment type, our results showed that after 3 months of treatment, all LA functions (LA reservoir, conduit, and contractile strains) were significantly lower than baseline values in the overall study population. This could help identify patients at risk of developing heart failure, even when left ventricular function seems normal.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.
2. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-92.
3. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, 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). Eur Heart J. 2016;37:2768-801.
4. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. J Am Soc Echocardiogr. 2007;20:234-43.

5. Götte MJ, Germans T, Rüssel IK, et al. Myocardial strain and torsion quantified by cardiovascular magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. J Am Coll Cardiol. 2006;48:2002-11.
6. Buchalter MB, Weiss JL, Rogers WJ, et al. Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging. Circ J. 1990;81:1236-44.
7. Teske AJ, De Boeck BW, Melman PG, et al. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. Cardiovasc Ultrasound. 2007;5:2-7.
8. van Dalen BM, Soliman OI, Vletter WB, et al. Feasibility and reproducibility of left ventricular rotation parameters measured by speckle tracking echocardiography. Euro J Echocardiography. 2009;10:669-76.
9. Vianna-Pinton R, Moreno CA, Baxter CM, et al. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr. 2009;22:299-305.
10. Totzeck M, Schuler M, Stuschke M, et al. Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease. Int J Cardiol. 2019;280:163-175.
11. Jeena MT, Kim S, Jin S, et al. Recent Progress in Mitochondria-Targeted Drug and Drug-Free Agents for Cancer Therapy. Cancers (Basel). 2019;12(1):4.
12. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol. 2020;17(8):474-502.
13. Murabito A, Hirsch E, Ghigo A. Mechanisms of Anthracycline-Induced Cardiotoxicity: Is Mitochondrial Dysfunction the Answer?. Front Cardiovasc Med. 2020;7:35.
14. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73:17-48.
15. Yaylali YT, Saricopur A, Yurtdas M, et al. Atrial function in patients with breast cancer after treatment with anthracyclines. Arq Bras Cardiol. 2016;107:411-9.
16. Bergamini C, Dolci G, Rossi A, et al. Left atrial volume in patients with HER2-positive breast cancer: one step further to predict trastuzumab-related cardiotoxicity. Clin Cardiol. 2018;41:349-53.
17. Upshaw JN, Finkelman B, Hubbard RA, et al. Comprehensive assessment of changes in left ventricular diastolic function with contemporary breast cancer therapy. JACC Cardiovasc Imaging. 2020;13:198-210.
18. Negishi K, Negishi T, Hare JL, et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26 493-8.
19. Shi J, Guo Y, Cheng L, et al. Early change in left atrial function in patients treated with anthracyclines assessed by real-time three-dimensional echocardiography. Sci Rep. 2016;6:25-512.
20. Laufer-Perl M, Arias O, Dorfman SS, et al. Left atrial strain changes in patients with breast cancer during anthracycline therapy. Int J Cardiol. 2021;330:238-44.
21. Lassen MCH, Arya F, Biering-Sørensen T, et al. Left atrial strain is reduced following trastuzumab in breast cancer patients. Echocardiography. 2024;41:15-751.
22. Timóteo AT, Moura Branco L, Filipe F, Galrinho A, Rio P, Portugal G, et al. Cardiotoxicity in breast cancer treatment: what about left ventricular diastolic function and left atrial function? Echocardiography. 2019;36:1806-13.
23. Park H, Kim KH, Kim HY, Cho JY, Yoon HJ, Hong YJ, et al. Left atrial longitudinal strain as a predictor of Cancer therapeutics-related cardiac dysfunction in patients with breast Cancer. Cardiovasc Ultrasound. 2020;18:28.