Evaluation of cardiotoxicity induced by different regimens of cancer therapy in women with breast cancer

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Abstract

In recent years, a significant success has been achieved in the treatment of breast cancer with the development of new effective therapeutic regimens in addition to traditional therapies. Along with the mentioned positive trends an increasingly urgent problem, cancer-therapy related side effects have emerged. The most important is the cardiac dysfunction or cardiotoxicity which essentially worsens the prognosis and ranks the first among the fatal complications caused by cancer therapy. All of the above has become a determinant of the actualization of the issue of early diagnosis and management of cardiotoxicity. According to the guidelines, the left ventricular ejection fraction is considered the main measurement for predicting and detecting cardiotoxicity, however, the decrease in LVEF mainly occurs in the late stages, when a large myocardium area is damaged. Our review analysis suggests that the global longitudinal strain is a more sensitive and accurate marker for detecting early, subclinical, subtle left ventricular dysfunction and heart failure than standard echocardiographic parameters (left ventricular ejection fraction). The drop in global longitudinal strain is informative in asymptomatic patients even with preserved ejection fraction, predicts reduction of ejection fraction and subsequent cardiotoxicity, with diagnostic and predictive ability superior to EF and other strain parameters. Speckle tracking echocardiography is an advanced imaging technique designed for better feasibility than standard echo to detect subclinical cardiotoxicity in breast cancer patients. The three-dimensional echocardiography is potentially superior to the two-dimensional echocardiography in early detection of cardiac dysfunction. Biomarkers may be useful for predicting cardiotoxicity. Administration and monitoring of cardioprotective therapy via global longitudinal strain should potentially improve cardiac function in patients at risk of cancer-related cardiotoxicity. Early detection of cardiotoxicity can help modify cancer therapy prevent irreversible heart damage.

Keywords: breast cancer, cardiotoxicity, GLS, ejection fraction, speckle tracking, 3D /2D TTE/ STE , biomarkers

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Introduction

Breast cancer is the most frequently diagnosed cancer [1;2], is the most common type of cancer in women in Georgia (32%)[3] and all over the world [1;2;4]. According to the data of the Georgian Cancer Registry, the breast cancer incidence rate per 100,000 women was 82.8% in 2018[3], and according to WHO data, 7.8 million women were diagnosed with breast cancer between 2015 and 2020[1]. The incidence increases proportionally along with age, more than 60% of new cases occurring in the 50-70 age group (postmenopausal women)[1;3]. Recently, significant improvements in therapeutic regimens and early cancer detection programs have increased the number of cancer survivors[5], but the breast cancer still represents the leading problem among the causes of morbidity, mortality and disability of the population [1;4;5] among cancers the leading cause of death in women[2;6] of all ages. The growing number of patients is caused by an increase in cancer development and cardiovascular risk along with age[7], as well as short and long-term side effects of cancer therapy[1;8], the most important among them is cardiotoxicity, which significantly worsens the prognosis[9]. Currently, it is well-known that different treatment regimens can cause various cardiovascular disorders[10;11;12;13], however, cardiotoxicity is mainly considered as symptomatic or subclinical left ventricular (LV) dysfunction and heart failure[8;9;10;14;15;16]. Anthracyclines most often cause cardiotoxicity and approximately 60% of patients die of heart failure within 2 years of admission[8;9;10;17;18].

Breast cancer patients receive different therapeutic modalities, with different potential for interaction and therefore, cardio toxic effects[9;15]. Cardio toxicity has been classified as follows: "early" (adverse effects on oncological therapy) or "late" (late consequence of early myocyte damage due to progressive cardiac remodeling)[9] and by pathophysiological origin: irreversible (type I) e.g. Anthracyclines are characterized by irreversible, permanent myocardial damage due to apoptosis and necrosis, especially after the first dose in terms of the cumulative administered dose (dose-dependent)[8;10;19;20;21;22] and reversible (type II) cardiotoxicity, characterized by the dose-independent reversible myocardial damage e.g. Trastuzumab[21;23;24;25]. Clinical

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studies have confirmed cardiovascular damage with new mechanisms [8;9;14;17;18;26;27;28]. Modern techniques provide the improved heart protection during radiotherapy, but is clearly known for its heart disease of predominantly the apical regions especially during radiation therapy of the left breast[12;29;30;31], Anthracyclines and radiation therapy exhibit dose-dependent cardiotoxicity [21;31].

One of the main factors contributing to the increased risk of cardiotoxicity caused by the cancer therapy is existing cardiovascular disease and risk factors [8;32]. A high-risk determinant is both the number of risk factors and their severity.

Nowadays the conventional criteria for the diagnosis of cancer therapy-related cardiac dysfunction (CTRCD) depend on symptoms of heart failure and/or changes in left ventricular ejection fraction (LVEF)[33]. However, the symptoms are limited due to the overlap of heart failure and cancer symptoms. Transthoracic Echocardiography (TTE) is the cornerstone of imaging in patients with malignant tumors at all stages—before, during, and after therapy [8;16;17;18;24;26;31;32;34]. It provides: before decision-making on specific cancer treatment regimens determination of potential cardiotoxic early and late effects with risk assessment (which allows the correct selection-modification of treatment), identification and prediction of subclinical and symptomatic cardiovascular dysfunction, long-term follow-up and evaluation of the effectiveness of cardioprotective intervention[16;18;26;32]. Currently, the left ventricular ejection fraction (LVEF) estimation by two-dimensional (2D) echocardiography is the most validated and commonly used parameter in detecting, monitoring and predicting cardiotoxicity due to its wide availability, low cost, and safety [8;9;26;31], but several research suggests that it is not sensitive enough to detect early and subtle changes in cardiac function[9;15;25;35]. The marked reduction of the left ventricular ejection fraction (LVEF) is often a late phenomenon, which appears only in extensive damage of myocardial tissue and is a sign of overt heart failure [9;15], due to the late diagnosis and delayed cardioprotective intervention, the systolic function cannot be restored in up to 58% of patients[9]. One promising method is the assessment of global longitudinal strain (GLS) by the speckle tracking echocardiography (STE), which has emerged as a powerful and sensitive marker of an early, subclinical, subtle left ventricular dysfunction in women with breast cancer. Studies have shown that the drop in GLS preceded a reduction in ejection fraction (EF) and subsequent development of cardiotoxicity, has diagnostic and predictive superiority compared with 2D EF and other stress parameters. (GLS) can be used as a direct marker of heart failure and is informative in asymptomatic patients (in detecting subclinical cardiotoxicity with preserved EF)[9;15;16;25;35;36;37]. GLS is already included in recent consensus documents on cardiotoxicity[8;33]. Additionally, the prognostic value of regional differences in a longitudinal strain has been demonstrated in several studies [43;44;45]. In addition to the above, the early and permanent cardiotoxicity was detected, which is characterized by only partial reversibility [42]. Research has revealed the superiority of three-dimensional (3D) STE to two-dimensional (2D) echo[10;15;37;38;39;40;41]. A number of studies suggest that GLS can enhance personalized risk-benefit decision-making, facilitate the use of cardioprotective strategies to prevent progression to the advanced stage of heart failure (HF) and thus, potentially improve cardiac function in patients at risk of cardiotoxicity [25;33;44]. Noteworthy is the SUCCOUR study, the first international multicenter prospective randomized controlled trial that had 23 international sites, enrolled 331 patients with at least 1 cardiovascular risk factor with cardiotoxic chemotherapy, men aged 54+/- 13, 94% were female, 88% had breast cancer, both GLS and EF were evaluated in these patients. The SUCCOUR study has investigated GLS-guided cardio protective therapy the avert drop in LVEF and enhance the possibility of the cardiovascular outcome. It has shown that that patients with CTRCD in the LV EF-managed arm had more reduced LV EF at long-term follow-up than in the GLS-managed arm; The results support the use of GLS during CTRCD tracking and also demonstrated that the three-dimensional echocardiography has greater reproducibility and accuracy in assessment of LVEF, although all methods of LVEF assessment are hemodynamically dependent and less sensitive than myocardial strain measurements [25;33; 34].

Limitations of standard two-dimensional (2D) echocardiography are technical aspects and volume changes[15;35], two-dimensional speckle tracing (STE) is superior to the above tool in early diagnosing cardiotoxicity, but it depends on image quality, needs constant inspection, load dependence and main limitation is tracking of 'out-of-plane' speckle motion[46]. New advanced imaging technique, such as 3D speckle tracking echocardiography (STE), has emerged as an alternative to overcome the problems, is promising, more sensitive modality in the early diagnosis and prediction of especially subclinical left ventricular dysfunction [9;15;16;35;42], eliminating geometric assumptions, allow tracking of 'out-of-plane' speckle motion, enables the analysis of the entire left ventricle from a single volumetric data set with the simultaneous estimation of all strain parameters (time saving compared with 2D STE and be relevant to the clinical practice), has greater reproducibility of successive assessments and better correlation with cardiac magnetic resonance [9;15;35]. 3D STE demonstrates that deterioration of the myocardial mechanics includes all components of deformation and reveals changes that cannot be identified by simple 2D quantitative measurements[15;35]. The global longitudinal strain (GLS) was proposed as the optimal STE parameter for predicting cardiotoxicity[8;15;35;44]. When the three-dimensional 3D echocardiography is not available 2D GLS and also E/e' ratio are recommended to detect early LV dysfunction [15;21].

For the risk assessment and early detection of cardiotoxicity determination of high sensitive troponins (hs TnI or TnT) and natriuretic peptides (B-type natriuretic peptide (BNP) or terminal pro-BNP (NT-proBNP)[8;16;18;21;22;26;31;32;34;37;39;47;48] are recommended. However, some researches do not confirm the prognostic value of cardiospecific biomarker[48;49].The possibility of NT-proBNP is more effective in the late stage, when EF is reduced and cardioprotective therapy is less effective[47] many factors affect the levels of biomarkers [5;18;50].

Baseline GLS can predict the left ventricular dysfunction[34;40]. In breast cancer patients a decline in GLS was identified already in 3 months from the start of the therapy before a decrease in LVEF, with the development of symptoms of EF at subsequent follow-up [15;26]. Segmental changes in LV deformation have also been reported in studies [43;44;45]. At low, medium or high-risk patients, it is important to have a certain frequency of echocardiographic control [16;17]. Baseline echocardiography (LVEF and GLS) is recommended in all patients to assess LV function or any structural heart disease prior to a potentially cardiotoxic therapy, it assists in cardiovascular risk stratification in most cancer therapies [8;9;16;17;18;24;26;31;32;34]. Early assessment of cardiac function with echocardiography and biomarkers (troponin, NT-proBNP), especially at high-risk patients, should be repeated at regular intervals during treatment (after every 2-4 cycles for anthracyclines) [8;16;18;26;31;32;34] and for long-term follow-up at 3- 6- and 12 months after the end of the treatment, especially among those with early cardiotoxicity[8;16;18;20;26;31;32]. A prompt initiation of heart failure treatment (ACEI/ARB, beta-blockers) is recommended in case of drop in LVEF <50%, reduction in strain

>15%, and/or increase in biomarker[8;18;25]. The GLS-guided cardioprotective therapy potentially reduces the decline in LVEF and should remain the preferred technique for detecting cardiotoxicity [25;34].

Conclusions

It is an increasingly supported assumption that GLS is helpful in early detection of subtle changes in LV systolic function, GLS has a greater prognostic and diagnostic value than LVEF and also the ability of advanced echo-techniques (2D and especially 3D speckle tracking) to detect subclinical cardiotoxicity is an obvious advantage. It is especially important to develop GLS-guided screening-diagnostic methods and algorithms in women with breast cancer, that will allow us to detect subtle structural-functional heart disorders at an early stage, reduce the likelihood of cancer-related cardiovascular complications, provide prevention, implement long-term effective monitoring and cardioprotective strategies in order to improve the final outcomes .GLS can enhance personalized decision-making regarding risks and benefits.

References

1. Breast Cancer. Available online: (accessed on 14 February 2022). https://www.who.int/news-room/fact-sheets/detail/breast-cancer
2. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries;Sung HFerlay JSiegel R et al.CA: A Cancer Journal for Clinicians (2021) 71(3) 209-249;DOI: 10.3322/caac.21660
3. Epidemiological characteristics of and risk factors for breast cancer in the world;Momenimovahed ZSalehiniya H;Breast Cancer: Targets and Therapy;DOI: 10.2147/BCTT.S176070
4. Cardiac Biomarkers in Patients with Cancer: Considerations, Clinical Implications, and Future Avenues;Bracun V,Aboumsallem J,van der Meer P et al.Current Oncology Reports 2020;DOI: 10.1007/s11912-020-00930-x
5. Breast Cancer;Version 3.2022 — May 7, 2022;NCCN.org;NCCN Guidelines for Patients® available at www.nccn.org/patients
6. Global cancer incidence in older adults, 2012 and 2035: A population-based study;Pilleron SSarfati DJanssen-Heijnen M et al.International Journal of Cancer (2019) 144(1) 49-58;DOI: 10.1002/ijc.31664
7. 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);Zamorano JLancellotti PRodriguez Muñoz D et al.European Journal of Heart Failure (2017) 19(1) 9-42;DOI: 10.1002/ejhf.654
8. Early Detection of Cardiotoxicity in patients receiving cancer Chemotherapy Using three-dimensional and Speckle Tracking Echocardiography;Ebaid H,Sarhan R,Mansour A;International Journal of the Cardiovascular Academy (2020) 6(4) 169;DOI: 10.4103/ijca.ijca_43_20
9. To study the usefulness and comparison of myocardial strain imaging by 2D and 3D echocardiography for early detection of cardiotoxicity in patients undergoing cardiotoxic chemotherapy;Alam S,Chandra S,Saran M et al.;Indian Heart Journal (2019) 71(6) 468-475;DOI: 10.1016/j.ihj.2019.11.253
10. Therapy-induced cardiotoxicity in breast cancer patients: a well-known yet unresolved problem;Florescu D et al.Discoveries (2019) 7(1) e89; DOI: 10.15190/d.2019.2
11. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 1;Chang HMoudgil RScarabelli T et al.Journal of the American College of Cardiology;DOI: 10.1016/j.jacc.2017.09.1096
12. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 2;Chang HOkwuosa TScarabelli T et al.Journal of the American College of Cardiology;DOI: 10.1016/j.jacc.2017.09.1095
13. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician;Perez ITaveras Alam SHernandez G et al.Clinical Medicine Insights: Cardiology;DOI: 10.1177/1179546819866445
14. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: A balance with feasibility;Santoro C,Arpino G,Esposito R et al.European Heart Journal Cardiovascular Imaging (2017) 18(8) 930-936;DOI: 10.1093/ehjci/jex033
15. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC);Čelutkienė J,Pudil R,López-Fernández T et al.;European Journal of Heart Failure (2020) 22(9) 1504-1524;DOI: 10.1002/ejhf.1957
16. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: The CARDIOTOX registry;López-Sendón J,Álvarez-Ortega C,Zamora Auñon P et al.;European Heart Journal (2020) 41(18) 1720-1729;DOI: 10.1093/eurheartj/ehaa006
17. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology;Pudil R,Mueller C,Čelutkienė J et al.;European Journal of Heart Failure (2020) 22(11) 1966-1983;DOI: 10.1002/ejhf.2017
18. Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity;Tadokoro TIkeda MIde T et al.JCI Insight (2020) 5(9);DOI: 10.1172/jci.insight.132747
19. Understanding Anthracycline Cardiotoxicity From Mitochondrial Aspect;Huang JWu RChen L et al.Frontiers in Pharmacology;DOI: 10.3389/fphar.2022.811406
20. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer;Nicolazzi MCarnicelli AFuorlo M et al.European Review for Medical and Pharmacological Sciences (2018) 22(7) 2175-2185;DOI: 10.26355/eurrev-201804-14752
21. Cardiotoxicity of Anthracyclines;Cardinale D,Iacopo F,Cipolla C;Frontiers in Cardiovascular Medicine;DOI: 10.3389/fcvm.2020.00026
22. Trastuzumab-containing regimens for metastatic breast cancer;Balduzzi SMantarro SGuarneri V et al.Cochrane Database of Systematic Reviews;DOI: 10.1002/14651858.CD006242.pub2
23. Molecular Mechanisms of Cardiomyocyte Death in Drug-Induced Cardiotoxicity;Ma WWei SZhang B et al.Frontiers in Cell and Developmental Biology;DOI: 10.3389/fcell.2020.00434
24. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy; Thavendiranathan P, Negishi T, Somerset E et al.; Journal of the American College of Cardiology (2021) 77(4) 392-401;DOI: 10.1016/j.jacc.2020.11.020
25. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations;Curigliano GLenihan DFradley M et al.Annals of Oncology (2020) 31(2) 171-190;DOI: 10.1016/j.annonc.2019.10.023
26. Mechanisms, monitoring, and management of tyrosine kinase inhibitors–associated cardiovascular toxicities;Chaar M,Kamta J,Ait-Oudhia S;OncoTargets and Therapy 2018;DOI: 10.2147/OTT.S170138
27. Heart Failure with Targeted Cancer Therapies: Mechanisms and Cardioprotection;Hahn VZhang KSun L et al.See more;Circulation Research (2021) 128(10) 1576-1593;DOI: 10.1161/CIRCRESAHA.121.318223
28. Breast radiotherapy-related cardiotoxicity. When, how, why. risk prevention and control strategies; Díaz-Gavela A,Figueiras-Graillet L,Luis Á et al.Cancers;DOI: 10.3390/cancers13071712
29. Cardiac mortality after radiotherapy, chemotherapy and endocrine therapy for breast cancer: Cohort study of 2 million women from 57 cancer registries in 22 countries; Henson KMcGale PDarby S et al.International Journal of Cancer (2020) 147(5) 1437-1449;DOI: 10.1002/ijc.32908
30. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline summary;Armenian SLacchetti CLenihan D;Journal of Oncology Practice;DOI: 10.1200/JOP.2016.018770
31. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society;Lyon ADent SStanway S et al.European Journal of Heart Failure (2020) 22(11) 1945-1960;DOI: 10.1002/ejhf.1920
32. Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes: The SUCCOUR Trial; Negishi T, Thavendiranathan P,Negishi K et al.;JACC: Cardiovascular Imaging (2018) 11(8) 1098-1105;DOI: 10.1016/j.jcmg.2018.03.019
33. Single Versus Standard Multiview Assessment of Global Longitudinal Strain for the Diagnosis of Cardiotoxicity During Cancer Therapy;Thavendiranathan P,Negishi T,Coté M et al.JACC: Cardiovascular Imaging (2018) 11(8) 1109-1118;DOI: 10.1016/j.jcmg.2018.03.003
34. Three-dimensional speckle-tracking echocardiography for the global and regional assessments of left ventricle myocardial deformation in breast cancer patients treated with anthracyclines; Coutinho Cruz M,Moura Branco L,Portugal G et al.;Clinical Research in Cardiology (2020) 109(6) 673-684;DOI: 10.1007/s00392-019-01556-1
35. A review of current trends in three-dimensional analysis of left ventricular myocardial strain;Nabeshima YSeo YTakeuchi M;Cardiovascular Ultrasound;DOI: 10.1186/s12947-020-00204-3

36. Early detection of cardiotoxicity by 3D speckle tracking imaging of area strain in breast cancer patients receiving chemotherapy.Chen JWang LWu F et al.Echocardiography (2019) 36(9) 1682-1688; DOI: 10.1111/echo.14467
37. Anthracyclines and regional myocardial damage in breast cancer patients. A multicentre study from the Working Group on Drug Cardiotoxicity and Cardioprotection, Italian Society of Cardiology (SIC) ; Zito CManganaro RCusma Piccione M et al; European Heart Journal Cardiovascular Imaging (2021) 22(4) 406-415;DOI: 10.1093/ehjci/jeaa339
38. The combined role of NT-proBNP and LV-GLS in the detection of early subtle chemotherapy-induced cardiotoxicity in breast cancer female patients;Sulaiman L,Hesham D,Abdel Hamid M et al.;Egyptian Heart Journal (2021) 73(1);DOI: 10.1186/s43044-021-00142-z
39. Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis;Oikonomou E,Kokkinidis D,Kampaktsis P et al.;JAMA Cardiology (2019) 4(10) 1007-1018;DOI: 10.1001/jamacardio.2019.2952
40. Assessment of Myocardial Work in Cancer Therapy-Related Cardiac Dysfunction and Analysis of CTRCD Prediction by Echocardiography;Guan J,Bao W,Xu Y et al.Frontiers in Pharmacology (2021) 12;DOI: 10.3389/fphar.2021.770580
41. Abnormalities in 3-Dimensional Left Ventricular Mechanics With Anthracycline Chemotherapy Are Associated With Systolic and Diastolic Dysfunction;Zhang K,Finkelman B,Gulati G et al.JACC: Cardiovascular Imaging (2018) 11(8) 1059-1068;DOI: 10.1016/j.jcmg.2018.01.015
42. Early detection of subclinical left ventricular dysfunction after breast cancer radiation therapy using speckle-tracking echocardiography: Association between cardiac exposure and longitudinal strain reduction (BACCARAT study);Walker VLairez OFondard O et al.Radiation Oncology (2019) 14(1);DOI: 10.1186/s13014-019-1408-8
43. Left ventricular segmental strain and the prediction of cancer therapy-related cardiac dysfunction;Demissei BFan YQian Y et al.European Heart Journal Cardiovascular Imaging (2021) 22(4) 418-426;DOI: 10.1093/ehjci/jeaa288
44. Relationship between regional left ventricular dysfunction and cancer-therapy-related cardiac dysfunction;aijo YKusunose KOkushi Y et al.Heart (2020) 106(22) 1752-1758;DOI: 10.1136/heartjnl-2019-316339
45. 2- and 3-Dimensional Myocardial Strain in Cardiac Health and Disease;Voigt JCvijic M;JACC: Cardiovascular Imaging;DOI: 10.1016/j.jcmg.2019.01.044
46. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis;Michel LMincu RMahabadi A et al.European Journal of Heart Failure (2020) 22(2) 350-361;DOI: 10.1002/ejhf.1631
47. Cardiotoxicity and cardiovascular biomarkers in patients with breast cancer: Data from the geparocto-gbg 84 trial;Rüger ASchneeweiss ASeiler S et al.Journal of the American Heart Association (2020) 9(23);DOI: 10.1161/JAHA.120.018143
48. Aromatase inhibitors use and risk for cardiovascular disease in breast cancer patients: A population-based cohort study;Sund M,Garcia-Argibay M,Garmo H et al.Breast (2021) 59 157-164;DOI: 10.1016/j.breast.2021.07.004
49. The Role of Biomarkers in Cardio-Oncology;Ananthan KLyon A;Journal of Cardiovascular Translational Research;DOI: 10.1007/s12265-020-10042-3 .