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Original article

EARLY CHANGES IN LEFT-VENTRICULAR EJECTION FRACTION AND LONGITUDINAL DEFORMATION IN PATIENTS WITH BREAST CANCER AT ANTHRACYCLINE CONTAINING REGIMENS

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Abstract

Background: Anthracyclines (ATs) are the most frequent used anti-cancer drugs in breast cancer (BC) patients. Certain demographic parameters and risk factors are closely linked to anthracycline-induced cardiotoxicity manifestation as the most feared adverse effect. Echocardiography is pivotal in evaluation of left-ventricular (LV) cardiac dysfunction as a serious complication.

Aims: The study aimed to assess the differences in selected echocardiographic parameters related to LV systolic function including longitudinal strain (LS%) according to cardiovascular (CV) risk factors and demographic characteristics and their relations in BC patients treated with ATs.

Methods: Thirty patients with newly diagnosed BC scheduled to receive ATs were examined. The following demographic parameters and risk factors were evaluated: age, body mass index, obesity, hypertension, diabetes, physical activity and total AT dose. The echocardiographic evaluation consisted of parameters for LV systolic function estimation, including LV ejection fraction (LVEF%) and LS%. Statistical analysis was done with the SPSS, v.25.0.

Results: LVEF%, GLS%, and LS% in two/four chamber view (A4c/A2c) statistically significantly decreased at the control evaluation (p=0.036, p=0,002, p=0,031, p=0,019). Correlation between the differences in LVEF% between two visits showed a significant relation with the absence of physical activity (p=0,029), while a significant correlation of the LS% decrease was also found in A4c view with diabetes (p=0.024).

Conclusion: ATs initiate frequent echocardiography changes in BC patients. Close monitoring and regular surveillance ensure early diagnosis of serious cardiotoxic complications. Cancer therapy-related cardiac dysfunction (CTRCD) is a broad spectrum of possible presentations, and serial LVEF% and LS% measurement are ideal tools to identify the disease in early, asymptomatic stage and guide further therapeutic strategies.

Keywords: anthracyclines, breast cancer, echocardiography, ejection fraction, longitudinal strain

Introduction

Breast cancer (BC) is the most common malignant disease in the female population. Around 13% of women, or one in eight women, will develop invasive BC in their lifetime[1].

Meanwhile, BC accounts for about 30% of all newly diagnosed malignancies in women each year[2]. Unfortunately, about one in 39 women has the chance to die from this disease.

Anthracyclines (ATs) are among the most effective and widely used anti-cancer chemotherapeutics (HT). ATs consist of first-line treatment protocols and regimens in almost all forms of BC; either as a non-adjuvant or adjuvant setting; in localized, early stages or advanced forms; HER2-neu negative and triple negative BC, as well as adjunctive to targeted therapy in HER2-neu positive patients[4]. Anthracyclines-induced cardiotoxicity (ATIC) is the most serious complication, and heart failure (HF), cardiac injury and cardiomyopathy are the most common presentations comprising cancer therapy-relat

ed cardiac dysfunction (CTRCD).

Despite studies of delayed presentation and chronic toxicity, it has been largely accepted that ATIC is most likely a progressive phenomenon, presenting like non-convincing and unrecognized cardiomyopathy and that strategies for early detection are cornerstone for adverse cardiac events reduction[7]. The ability to predict ATIC is of great importance for a rapid therapeutic strategy and an overall good outcome. The world literature reviews numerous risk factors, significant for possible facilitating the occurrence of AT cardiotoxicity, which results in obtaining mandatory primary and secondary prevention strategies for close monitoring of targeted high and very high risk patients[9]. In addition to the well known risk factors like prior history of cardiovascular disease (CVD) and previous cardiotoxic treatment, demographic characteristics and lifestyle habits present inconsistent findings of mutual association. As older age is widely reported as the main demographic characteristic that advances the risk of developing cardiotoxicity[10], smoking for example in many publications does not confirm dependence with associated ATIC[11].

Aim

The aim of this study was to determine possible changes in selected echocardiographic parameters reflecting left ventricular (LV) systolic function, including global longitudinal deformation (GLS%) according to certain demographic characteristics and cardiovascular (CV) risk factors, as well as their relation in patients with BC receiving AT therapy.

Materials and methods

This was a clinical prospective study conducted in the period 2022-2023 in the echocardiographic laboratory of the City General Hospital 8 September in Skopje. Thirty patients with newly diagnosed BC receiving AT-consisting therapeutical protocol in the University Clinic for Radiotherapy and Oncology were evaluated with conventional 2D transthoracic echocardiography (TTE). The pre-set inclusion and exclusion criteria selected patients aged 18 and over, LV ejection fraction (LVEF%) ≥40%, non-preexisting significant valvular disease, atrial fibrillation, unstable cardiac conditions and significant wall motion abnormalities. All patients involved, should have had good image quality, life expectancy more than 1 year, and mandatory confirmed informed consent for voluntary participation in the study. Patients scheduled for baseline risk stratification for AT cardiotoxicity according to the referent European Society of Cardiology (ESC) recommendations[6], followed baseline 2D TTE with standard assessments of LV systolic function and evaluation of longitudinal strain (LS%). The evaluation was performed according to the professional association recommendations[30], and following pre-existing standard protocol for control follow-ups relying on patient's individual overall cardiotoxic risk[6]. The recommended protocol included two visits for patients with mild and moderate risk (baseline and after the 4th cycle), and additional visit for high-risk patients after the 2nd cycle.

The evaluated demographic parameters and risk factors were: age, body mass index (BMI), obesity, hypertension (HTA), diabetes (DM), physical activity and total AT dose. The echocardiographic evaluation included parameters to assess LV systolic function, such as LVEF%, as well as LS% determination.

Echocardiographic measurements were performed on commercially available equipment (GE-Vivid 7, USA) using a multifrequency transducer, and GLS% assessment followed the same standard protocol using a special computer analysis software.

Statistical analyses were processed using the statistical program SPSS, version 25.0 (IBM SPSS, Inc, Chicago, Illinois). Comparison between groups was performed with the nonparametric Wilcoxon Sign Rank test for related pairs (same variable at first *versus* second visit). Correlation between parameters was examined by Pearson and/or Spearman correlation. Multiple stepwise linear regression analysis was performed to determine independent predictors. For all data, significance was set for a value of $p<0.05$.

Results

A total of 30 patients were evaluated in this study, all with newly diagnosed BC, with an average age of 52.5±10.9 and a range of 34-76 years (Table 1). Twenty-nine patients (96.7%) had previous surgical treatment, and in terms of disease stage, two were in stage I (6.7%), 13 in stage II (43.3%) and 15 in stage III (50%) (Table 2). The mean BMI was 27.32±5.07, out of which 8 patients (26.7%) were obese (Table 1). Sixteen patients (53.3%) had HTA, 3 patients (10%) had DM, and 24 (80%) did not practice physical activity at all. Only one patient had heart failure with preserved LVEF% (3.3%) and she was in NYHA group II (Table 1).

All patients received 4 cycles of AT HT protocol. The mean range of the total AT dose was 403.13±35.47 or in the range of 320-480 mg, and the mean value indexed for the body surface area was 220.53 ± 12.64 (191.6 – 247.0) (Table 2). Fourteen patients were at low and medium risk (46.7%) and two were at high risk (6.7%) for ATIC development according to baseline risk stratification.

Table 1. Baseline characteristics of patients

Age (years)	52.5±10.9
Min.-max.	34-76
BMI (kg/m^2)	27.32±5.07
Min.-max.	19.20-38.60
obesity* (%)	8/26.7
hypertension (n/%)	16/53.3
Diabetes (n/%)	3/10
Physical activity (n/%)	
none	24/80
occasional	4/13.3
regular	2/6.7
Heart failure (n/%)	1/3.3
NYHA (n/%) class I	29/96.7
class II	1/3.33

BMI body mass index, NYHA New York Heart Association, *Obesity= BMI ≥30 kg/m2

Table 2. Staging, AT dose and risk stratification

Prev. operative treatment (n/%)	29/96.7
Staging (n/%) I	2/6.7
IIa	3/10.0
IIb	10/33.3
IIIa	5/16.7
IIIb	1/3.3
IIIc	9/30.0
Total AT dose (mg)	403.13±35.47
Min.-max.	320-480
Total indexed AT dose (mg/m^2)	220.53±12.64
Min.-max.	191.6-247.0
AT risk stratification (n/%)	
mild	14/46.7
moderate	14/46.7
high	2/6.7

AT – anthracyclines

The echocardiographic parameters evaluating LV systolic function showed preserved LV systolic performances both at the baseline examination and at the control visit (Table 3). LVEF% was within the reference range at both examinations, yet at the second visit, its statistically significant decrease occurred (p=0.036) (Table 3, Figure 1).

Table 3. Comparison of echocardiographic parameters representing left ventricular systolic function between the first and second examination in 30 subjects

Parameter	I examination (n=30)	II examination (n=30)	p
LVEF%	66.33±5.22	64.23±503	**0.036**
LV APLAX (%)	-18.10±10.72	-19.36±2.64	0.330
LV A4c (%)	-20.84±3.13	-19.96±2.60	**0.019**
LV A2c (%)	-20.28±2.81	-19.42±2.88	**0.031**
LV GLS (%)	-20.52±2.33	-19.58±2.38	**0.002**
Segments with LV LS < 13% (n/%)	16/53.3	16/53.3	-
Number of segments with LV S<13%	2.57±1.55	1.78±1.89	0.888

LV left ventricle, LVEF left ventricular ejection fraction, APLAX apical long-axis view; A4c apical 4 chamber view; A2c apical 2chamber view; GLS global longitudinal strain; LS longitudinal strain; *p<0.05 for comparison between groups

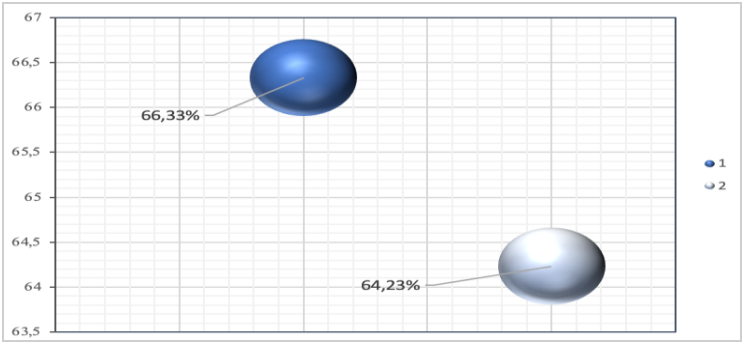

Fig. 1. Graphical presentation of LVEF decline from the first to the second visit

Longitudinal deformation (LS%) of the three different echocardiographic views, yet taken as a global one, presented within the reference ranges. At the control visit, except in the longitudinal parasternal view (aPLAX) which indicated a statistically insignificant improvement, in the other two views (A4c, A2c), as well as GLS%, there was a significant reduction of LS% (p=0.019, p=0.031, p=0.002**,** respectively) (Table 3, Figure 2). The number of segments with LV LS of < 13% indicated no change at the control examination, and the number of segments with LV LS of < 13% indicated a statistically insignificant decrease at the same visit (Table 3).

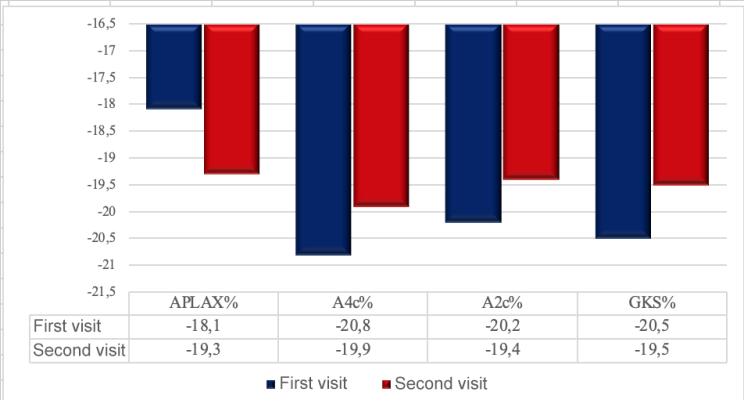

Fig. 2. Graphical presentation of the change in LV deformation from the first to the second visit

An analysis of the correlation of certain demographic parameters, risk factors and/or associated diseases and parameters related to AT dose with the echocardiographic markers of LV systolic function, as well as LS%, was performed and the results are listed in tables 4 and 5.

We found a significant association of LVEF% decline with older age at both visits, and higher BMI, presence of HTA and lack of physical activity at the second visit. The correlation of lower LVEF% with obesity was found with borderline significance at the second visit. Decline of LS% in aPLAX view according to our study had a significant association only with obesity and higher BMI at the first visit. LS% decline in A4c view was significantly associated with older age and total AT dose at the second visit, and presence of DM at the first visit. With a borderline significance we found lower LSA4C associated with higher BMI, obesity and lack of physical activity at the first visit (Table 4).

According to GLS% decline, we found a significant association with older age at second visit and total AT dose at the first visit. With a borderline significance, GLS% decline was associated with obesity at the first visit and presence of HTA at both visits (Table 5). A significant association of LS% decline in A2c view was found with older age, presence of HTA and lack of physical activity at both visits, and presence of DM, obesity and total AT dose at the first visit. We also found a borderline significant correlation of LS% A2c decline with obesity at the second visit.

In many studies, presence of segments with LV LS<13% was found significant to predict overall potential HF worsening[5]. In our study, we found a significant association of presence of segments with LV LS<13% with higher BMI, obesity, HTA, lack of physical activity and total AT dose at the first visit, and presence of DM at both visits (Table 5).

Table 4. Presentation of significant and borderline significant correlations of LV functional parameters at the first and second visit

	LVEF1 (%)	LVEF2 (%)	LV APLAX1 (%)	LV APLAX2 (%)	LV A4c1 (%)	LV A4c2 (%)
age	r=-0.409. p=0.025	r=-0.510. p=0.004	-	-	-	r=-0.438. p=0.015
BMI	-	r=-0.398. p=0.029	r=-0.374. p=0.042	-	r=-0.344. p=0.062	-
HTA	-	r=-0.496. p=0.005	-	-	-	-
DM	-	-	-	-	r=-0.379. p=0.039	-
obesity	-	r=-0.344. p=0.055	r=-0.423. p=0.020	-	r=-0.318. p=0.087	-
Physical act.	-	r=0.366. p=0.047	-	-	r=-0.340. p=0.066	-
Tot.AT dose (mg/m2)	-	-	-	-	-	r=0.396. p=0.030

AT anthracyclines, APLAX apical long-axis view, A4c apical 4ch view; BMI body mass index; HTA hypertension, DM diabetes mellitus, LV left ventricle, LVEF left ventricular ejection fraction

Table 5. Presentation of significant and borderline significant correlations of LV functional parameters at the first and second visit

	LV A2c1 (%)	LV A2c2 (%)	GLS1 (%)	GLS2 (%)	Segments with LV LS<13% 1(n/%)	Segments with LV LS<13% 2(n/%)
age	r=-0.476. p=0.008	r=-0.432. p=0.017	-	r=-0.429 p=0.018	r=0.328. p=0.076	-
BMI	r=-0.438. p=0.015	-	-	-	r=0.510. p=0.004	-
HTA	r=-0.506. p=0.004	r=-0.371. p=0.044	r=-0.336. p=0.070	r=-0.310. p=0.095	r=0.607. p=0.0001	-
DM	r=-0.379. p=0.039	-	-	-	r=0.356. p=0.053	r=0.356. p=0.053
obesity	r=-0.440. p=0.015	r=-0.309. p=0.096	r=-0.322. p=0.082	-	r=0.494. p=0.006	-
Physical act.	r=0.455. p=0.012	r=-0.419. p=0.021	-	-	r=-0.465 p=0.010	-
Tot. AT dose (mg/m2)	r=0.388. p=0.034	-	r=0.432. p=0.017	-	r=-0.471. p=0.009	-

AT anthracyclines, A2c apical 2ch view, BMI body mass index; GLS global longitudinal strain, HTA hypertension, DM diabetes mellitus, LS longitudinal strain, LV left ventricle

After we noticed a significant decrease of LVEF% at the second visit (Table 3), a correlation analysis of the differences of LVEF% between the two visits (2.10±4.85) with all demographic characteristics, risk factors and total cumulative AT dose followed, and a significant association of the LVEF% reduction was found obtained only with the absence of physical activity (r=-0.399, p=0.029) (Figure 3).

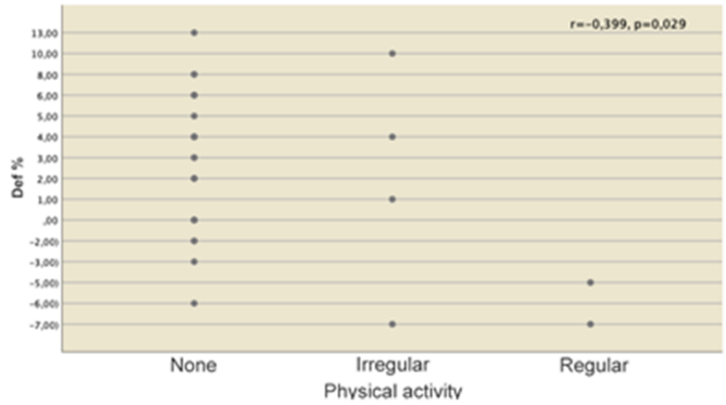

Fig. 3. Graphical presentation of the correlation of the difference in the LVEF% at the first and second visit with the intensity of physical activity

On the other hand, due to a significant decrease of LSA4c (0.87±2.82), A2c (0.86±1.99), as well as GLS% (0.94±1.48) (Table 3), we also analyzed the correlation of the differences between the two visits for all three parameters with all the above-mentioned variables and a significant correlation of the LS% decrease was found in A4c view with the presence of diabetes mellitus
(r=-0.410, p=0.024), and the decrease of LSA2c was borderline significant (r=-0.351, p=0.057) associated with a higher indexed total AT dose (mg/m2) (Figure 4).

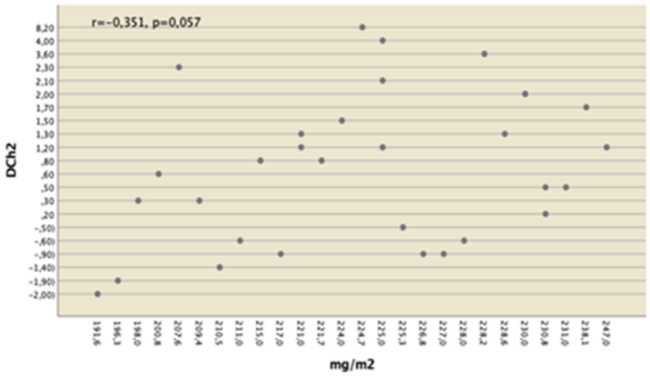

Fig. 4. Graphical presentation of the correlation of the difference in the LV deformation in 2ch view at the first and second visit with the total cytostatic dose in mg/m2

Discussion

ATs are the basic standard of anti-cancer therapy in patients with BC. In a meta-analysis of 123 randomized studies in 100,000 women, comparing multiple HT regimens in early-stage BC patients, a collaborative group of researchers found a 36% reduced mortality with application of standard, more effective AT regimens *vs.* without HT[12]. A recent meta-analysis with the same number of subjects has indicated that patients who include AT protocols in their treatment of early stage, operable BC have up to 14% lower risk of disease

recurrence compared to monotaxane regimens without AT[13]. At the same time, ATIC is a feared side effect, and main reason for cancer therapy limitation, which affects the patient's overall survival. According to a meta analysis from 2013, ATIC clinical presentation was registered in 6% of patients in a follow-up period of 9 years, and subclinical toxic manifestations were described in 18% of the treated patients with ATs[14].

Changes in echocardiographic parameters for systolic function assessment during AT therapy are frequent. Serial LVEF% assessment is the most widely used technique for monitoring systolic changes during and after AT therapy and CTRCD diagnosis[15]. Yet, a significant LVEF% decline is already late echocardiographic change, and normal LVEF% does not exclude systolic dysfunction[8]. With the application of modern AT regimens, LVEF% reduction was observed in even smaller portion than previously found, thus emphasizing the need for more sensitive parameters for monitoring the systolic disfunction, such as myocardial deformation[16]. The most significant relative decrease was monitored in GLS% with as much as 13% relative reduction, distinguishing it as the most sensitive tool for monitoring early systolic disturbances in AT therapy[3]. In a single-center study of 140 patients with BC and evaluation of systolic function before AT therapy and early after 7 days, none of the patients had a decline in LVEF%, while 22% of patients had early subclinical systolic dysfunction as determined by GLS% reduction[17].

In our study, LVEF%, although within the reference ranges at the baseline and control assessment, indicated a statistically significant decrease at the second visit (p=0.036). Regarding changes in longitudinal deformation at the control visit, except for aPLAX which showed a statistically insignificant improvement, in A4c and A2c view and GLS% as average, there was a significant reduction of LS% also (p=0.019, p=0.031, p=0.002**,** consecutively).

The association of certain demographic characteristics and multiple comorbidities with an increased ATIC risk is already well known. The American Heart Association (AHA) published the first scientific report in which CVD and BC share common risk factors, frequent comorbidity, challenging therapy of both, and negative effects of cancer therapy on CV health[18]. Advanced age, over 65 years, is probably the most significant risk factor for side effects even at lower cumulative doses, and is the main reason for abstinence from ATs in the treatment of BC[19].

The increased BMI and obesity increase the overall CV risk, but at the same time this population has an increased risk of developing BC, especially the hormone positive forms[20]. A population with an increased BMI has an increased susceptibility to AT-induced CTRCD[21] and a negative impact of overall survival and period of stable remission[22]. According to another study, an increased amount of intraperitoneal fat tissue before the cancer treatment was associated with a decrease in LVEF% in patients treated with ATs, but not with BMI[23]. One of the few studies that separated increased body surface area (indexes above 2m²) with an increased risk of ATIC, mainly emphasized an association with increased weight in BC patients. The study was conducted in 12 centers in young patients, without previous CV anamnesis, and at the same time showed an increased risk of ATIC in patients with elevated blood pressure (BP) before cancer therapy as an independent predictor[24].

In a meta-analysis of 12 studies with 74,886 patients included, elevated BP in 8 studies was associated with a significantly higher risk of developing ATIC; in 4 studies it was significantly associated with a decrease in LVEF%, and a significant relationship was also observed between baseline elevated systolic and diastolic BP and ATIC[25]. A nine-year retrospective study of gene mutations predisposing to ATIC singled out DM associated with an increased risk of ATIC[26]. A meta-analysis of 18 studies comprising over 7,400 patients treated with ATs, summarized similar notifications: DM, elevated BP and obesity were

associated with an increased risk of ATIC, and it was significantly earlier detected by GLS% *vs*. LVEF% decline[27]. We found the physical activity frequently mentioned in recent cardio-oncology studies, manifesting a promising strategy for reducing the risk of potential cardiotoxicity, before, during and after completion of AT therapy. Physical activity increases CV reserve, improves cardiac perfusion and significantly prevents decline in LVEF% in patients treated with ATs[28,29].

In our study, the correlation of the differences of the first and second visits of LVEF% (2.10±4.85) indicated a significant association with the absence of physical activity (r=-0.399, p=0.029) (Figure 3), and reduction of LS% in A4c view with the presence of diabetes (r=-0.410, p=0.024). The decrease of LS% in A2c view was with a borderline significance associated with a higher indexed AT dose (r=-0.351, p=0.057).

In conclusion, the results obtained in our study are affirmative in findings that frequent changes in echocardiographic parameters assesing the LV systolic function in BC patients are present. Both LVEF% and LS% are sensitive tools for LV function follow-ups as they all showed significant decrease during AT therapy in our study. Lack of physical activity, cumulative, total AT dose and presence of diabetes mellitus are presented risk factors that showed a significant correlation asssociation with the decline of the parameters evaluating the LV systolic function from the begining to the end of the AT cardiotoxic therapy.

Conflict of interest statement. None declared.

References

1. World Health Organization. Breast cancer. 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/breast-cancer.
2. Breast Cancer Facts and Statistics. Breast cancer facts and statistics 2023. (accessed 2023, September 30). https://www.breastcancer.org/facts-statistics.
3. Santoro C, Arpino G, Esposito R, Lembo M, Paciolla I, Cardalesi C, *et al*. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. *Eur Heart J Cardiovasc Imaging* 2017; 18(8): 930-936. doi: 10.1 093/ehjci/jex033.
4. Mouabbi AJ. Breast cancer treatment protocols. Treatment of Noninvasive breast cancer. 2023. Available at: https://emedicine.medscape.com/article/2006464-overview.
5. Chimed S, Stassen J, Galloo X, Meucci M C, Knuuti J, Delgado V, *et al*. Prognostic relevance of left ventricular global longitudinal strain in patients with heart failure and reduced ejection fraction. *Am J Cardiol* 2023; *202*: 30-40, doi: 10.1016/j.amjcard.2023.06.058.
6. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, *et al*. 2022 ESC guidelines on cardio-oncology developed in collaboration with European Hematology Association, European Society for Therapeutic Radiology and Oncology and International Cardio-Oncology Society. *Eur Heart J* 2022; *43*(41): 4229-4361. doi: 10. 1093/eurheartj/ehac244.
7. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. *Front Cardiovasc Med* 2020; 7:26. doi: 10.3389/fcvm.2020.00026.
8. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, *et al*. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: A position statement on behalf of the Heart Failure association, European association of Cardiovasc. Imaging and cardio-oncology Council of ESC. *Eur J Heart Fail* 2020; 22(9): 1504-1524. doi: 10.1002/ejhf.1957.

9. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, *et al*. 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 ESC in collaboration with the International Cardio- Oncology society. *Eur J Heart Fail* 2020; 22(11): 1945–1960. doi: 10.1002/ejhf.1920.
10. Zamorano JL, Lancellotti P, Rodriguez Muñoz 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. *Eur Heart J* 2016; 37(36): 2768-2801. doi: 10.1093/eurheartj/ehw211.
11. Qiu S, Zhou T, Qiu B, Zhang Y, Zhou Y, Yu H, *et al*. Risk Factors for Anthracycline-Induced Cardiotoxicity. *Front Cardiovasc Med* 2021; 8: 736854. doi: 10.3389/fcvm. 2021.736854.
12. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *The Lancet* 2012; *379*(9814): 432-444. doi: 10.1016/S0140-6736(11)61625-5.
13. Braybrooke J, Bradley R, Gray R, Hills RK, Pan H, Peto R, *et al*. Anthracycline-containing and Taxane-containing chemotherapy for early-stage operable breast cancer: A patient-level meta-analysis of 100 000 women from 86 randomised trials. *The Lancet*. 2023; *401*(10384): 1277-1292. doi: 10.1016/S0140-6736(23)00285-4.
14. Lotrionte M, Biondi-Zoccai G, Abbate A, Lanzetta G, D'Ascenzo F, Malavasi V, *et al*. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol* 2013; *112*(12): 1980-1984. doi: 10.1016/j.amjcard.2013. 08.026.
15. Sadeq IA, Mohammed MQ, AL-Timimi AA, Al Enbari AA. Detection of subclinical left-ventricular systolic dysfunction in patient treated with anthracycline chemotherapy: A comparative analysis between different left-ventricular systolic echocardiographic parameters. *International Journal of Adv Research in Biological Sciences* 2019; 6(8): 137-147. doi: http://dx.doi.org/10.22192/ijarbs.2019.06.08.019.
16. Jeyaprakash P, Sangha S, Ellenberger K, Sivapathan S, Pathan F, Negishi K. Cardiotoxic Effect of Modern Anthracycline Dosing on Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Placebo Arms From Randomized Controlled Trials. *J Am Heart Assoc* 2021; 10(6): e018802. doi: 10.1161/JAHA.120.018802.
17. Boyd A, Stoodley P, Richards D, Hui R, Harnett P, Vo K, *et al*. Anthracyclines induce early changes in left ventricular systolic and diastolic function: A single centre study. *PLoS One* 2017; 12(4): e0175544. doi: 10.1371/journal.pone.0175544.
18. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, *et al*; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation* 2018; 137(8): e30-e66. doi: 10.1161/CIR.0000000000000 556.
19. Screever EM, Meijers WC, Moslehi JJ. Age-Related Considerations in Cardio-Oncology. J Cardiovasc Pharmacol Ther 2021; 26(2): 103-113. doi: 10.1177/1074248420968689.
20. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology* 2009; 150(6): 2537-42. doi: 10.1210/en.2009-0070.
21. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, *et al*. Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in

Breast Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol* 2016; 34(26): 3157-3165. doi: 10.120 0/JCO.2016.67.4846.

22. de Azambuja E, McCaskill-Stevens W, Francis P, Quinaux E, Crown JPA, Vicente M, *et al*. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: The experience of 02-98 trial. *Breast Cancer Res Treat* 2009; *119*(1): 145-153. doi: 10.1007/s10549-009-0512-0.
23. Reding KW, Ghemigian K, Carbone S, D'Agostino RJr, Jordan JH, Melendez G, et al. The relationship between abdominal fat and change in left-ventricular ejection fraction in cancer patients. *Obes Sci Pract* 2020; *7*(1): 82-90. doi: 10.1002/osp4.454.
24. Kotwinski P, Smith G, Cooper J, Sanders J, Ma L, Teis A, *et al*. Body Surface Area and Baseline Blood Pressure Predict Subclinical Anthracycline Cardiotoxicity in Women Treated for Early Breast Cancer. *PLoS One* 2016; 11(12): e0165262. doi: 10.1371/ journal.pone.0165262.
25. Philip LJ, Findlay SG, Gill JH. Baseline blood pressure and development of cardiotoxicity in patients treated with anthracyclines: A systematic review. *Int J Cardiol Cardiovasc Risk Prev* 2022; 15: 200153. doi: 10.1016/j.ijcrp.2022.200153.
26. Reinbolt RE, Patel R, Pan X, Timmers CD, Pilarski R, Shapiro CL, *et al*. Risk factors for anthracycline-associated cardiotoxicity. *Support Care Cancer* 2016; 24(5): 2173-2180. doi: 10.1007/s00520-015-3008-y.
27. Zhang M, Yang H, Xu C, Jin F, Zheng A. Risk Factors for Anthracycline-Induced Cardiotoxicity in Breast Cancer Treatment: A Meta-Analysis. *Front Oncol* 2022; 12: 899782. doi: 10.3389/fonc.2022.899782.
28. Kang DW, Wilson RL, Christopher CN, Normann AJ, Barnes O, Lesansee JD, *et al*. Exercise Cardio-Oncology: Exercise as a Potential Therapeutic Modality in the Management of Anthracycline-Induced Cardiotoxicity. *Front Cardiovasc Med* 2022; 8: 805735. doi: 10.3389/fcvm.2021.805735.
29. Antunes P, Esteves D, Nunes C, Amarelo A, Fonseca-Moutinho J, Afreixo V, *et al*. Effects of exercise on cardiac function outcomes in women receiving anthracycline or trastuzumab treatment for breast cancer: A systematic review and meta-analysis. *Applied Sciences* 2021; 11(18): 8336. https://doi.org/10.3390/app11188336.
30. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; *28*(1): 1-39.e14. doi: 10.1016/j.echo.2014. 10.003.