Review Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.2018513-10

Breast Cancer Treatment and Cardiovascular Considerations

Maryam Mehrpooya*[a], Jeyran Zebardast[b], Mahdi Aghili[c]

[a] Cardiology Department, Tehran University of Medical Sciences, Tehran, Iran
[b] MS, E-learning in Medical Education, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Radiation Oncology, Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Received:
06 January 2018
Revised:
17 January 2018
Accepted:
26 January 2018

Key words:
Breast cancer treatment, cardiovascular, cardiovascular complications

ABSTRACT

Background: Breast cancer is the most frequently occurring cause of cancer-related mortality in women all around the world. However, the risk of cardiovascular diseases increases in parallel with dramatic improvements in target-specific treatment for breast cancer. The aim of this review was to show the importance of cardiovascular involvement in patients with breast cancer.

Methods: Published literature, regarding breast cancer and cardiovascular involvements, as well as cardiovascular complications of current treatments for breast cancer, including chemotherapy and radiotherapy, was reviewed.

Results: Review of our data revealed that there are extensive direct and indirect impacts of breast cancer on the cardiovascular system. Cardiovascular complications of breast cancer are common and range from cardiomyopathy, pericardial involvement, venous thromboembolism, and arterial thrombosis to some uncommon problems.

Conclusion: Early detection of cardiovascular damages from breast cancer is strongly recommended. Considering the significant cardiovascular complications of both breast cancer and its treatment, early recognition, prevention, and management of these complications, even the minor ones, improve prognosis and survival of patients with breast cancer.

Introduction

Breast cancer is the most frequently occurring cause of cancer mortality in women all around the world (in developed countries as well as low- and middle-income countries).[1] Most of the newly diagnosed cases, as well as the largest number of breast cancer deaths, happen in less developed areas of the world,[2] which is mostly due to economic and financial situations. Therefore, the development of effective but less expensive therapies is necessary.[3] After lung cancer, it is the second leading cause of cancer death in women.[4] On the one hand, screening for breast cancer has led to mortality reduction, but on the other, breast cancer incidence has increased.[4] Globally, it is estimated that 1.4 million women are diagnosed with breast cancer each year, and 458 000 die as the result of the disease.[5] Finally, mortality reduction in breast cancer after screening mammography was remarkably due to diagnosis in earlier stages and improving in systemic therapy.[6]

The risk of cardiovascular diseases increases in parallel with the dramatic improvement in target-specific treatment of breast cancer. This suscepti-bility to cardiovascular complications is potentially due to the fact that these therapies include radiotherapy and chemotherapy drugs.[7, 8] This risk is aggravated remarkably after 65 years of age.[7,9,10]

Consequently, considering the cardiovascular complications in breast cancer survivors, recognition, prevention, and management of this critical event is a very important clinical issue. We will discuss these cardiovascular issues in this review. We will look at cardiovascular complications

Address for correspondence:
Maryam Mehrpooya, M.D.
Address: No 144, Emdad Alley., Sheikh Bahaei St., Tehran, Iran.
Tel: +98 21 88605521
Fax:+98 21 66939537
Email: maryammehrpooya1@gmail.com

of breast cancer irrespective of chemotherapy or radiotherapy. In the second section, we will talk about cardiovascular complications of radiotherapy or chemotherapy in patients treated for breast cancer.

Methods

A literature search was performed for the years 1989 through 2017. We searched PubMed, Elsevier, MEDLINE, and Google Scholar. We considered scientific publications relevant to breast cancer for inclusion in our work.

First of all, we searched with "breast cancer," and again with the "breast cancer and cardiovascular." Then we select some of the articles obtained from the first search strategy, but most of them were related to the second search strategy.

Published literature regarding breast cancer and cardiovascular involvements, as well as cardiovascular complications of the current treatments for breast cancer, including chemotherapy and radiotherapy, were reviewed.

We used review articles (n = 22), cohort studies (n = 5), cross-sectional studies (n = 27), population-based case-control studies (n = 1), case reports (n = 6), guidelines (n = 2), case-control studies (n = 2), experimental studies (n = 3), and RCTs (n = 5).

Papers without full text, presented at conferences, or published in languages other than English were excluded.

Results

Cardiovascular complications of metastatic breast cancer

Cardiovascular complications of breast cancer included metastasis to the heart, superior vena cava syndrome, pericardial involvement, vascular problems, and cardiac function deterioration in a background of paraneoplastic syndrome.

Cardiac metastases

Cardiac metastases are detected in 6–20% of autopsies of patients with malignant neoplasms such as lung cancer, mediastinal tumors, breast cancer, melanoma, and esophageal cancer.[11] Although intracavitary growth of secondary heart tumors is rare, the important point is that symptomatic heart metastasis can occur even many years after diagnosis.[12] According to Bussani *et al.*, cardiac metastasis (more commonly pericardial metastasis, and rarely direct myocardial and endocardial metastasis) could be as high as 15.5% in patients with breast cancer.[12]

From pathophysiological viewpoint, multiple mechanisms have been proposed for breast cancers that are able to induce heart metastasis. For instance, breast-tumor cells in brain and heart metastases express high levels of endoglin, a cell-surface disulfide-linked homodimeric glycoprotein which binds to integrins and is a co-receptor for TGF-β.[13,14] These ligands and mediators participate in heart metastasis. Two-dimensional transthoracic and transesophageal echocardiography are easy, quick, and sensitive techniques for detection of cardiac metastasis. Computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose integrated with computed tomography (18F-FDG PET/CT), and PET-MRI as confirming methods could be helpful when there is any suspicion as to excluding cardiac involvement during clinical follow-up of these patients.[15-17]

Superior vena cava syndrome (SVCS)

Approximately 87% to 97% of SVCS cases are caused by primary intrathoracic malignancies. Breast cancer is one of the solid tumors causing SVCS, but not as much as other tumors like non-Hodgkin lymphoma, lung, or testicular cancer.[18] The most common nonmalignant cause of SVCS in cancer patients is thrombosis associated with venous access devices, especially patients with breast cancer who have long term central venous port catheter. There are some noninvasive therapeutic measures for SVCS, but endovascular revascularization of complete occlusion of the SVC is considered the therapy of choice.[19,20]

Pericardial involvement

Breast cancer could cause significant pericardial effusion or tamponade. This kind of pericardial involvements impairs quality of life. Recurrent pericardial effusion along with the development of dyspnea or tachycardia may necessitate repetitive hospitalization. Percutaneous pericardiocentesis with extended catheter drainage can be safely and effectively implemented as the primary treatment for pericardial effusion in cancer patients, including in those with thrombocytopenia.[21]

Venous thromboembolism (VTE)

Cancer patients constitute about 20% of all cases of VTE, and are also 4- to 7-fold more likely to develop VTE compared with patients without cancer.[22-24] Patients with cancer often show abnormalities in each component of Virchow's triad, leading to hypercoagulability.[23] Breast cancer is not a common cause of primary VTE per se, but patients with multiple metastasis or immobile ones, or who are under hormone therapy with tamoxifen or aromatase inhibitors, have higher risk for VTE and should receive VTE prophylaxis.[24]

Arterial thrombosis

Arterial thrombosis and its resultant clinical syndromes, such as cerebrovascular events or peripheral ischemia, could happen in cancer patients, and the most common reported malignancy in this setting is metastatic breast cancer.[25]

Thrombosis may be related to cancer itself or its treatment. The paraneoplastic process leads to hypercoagulability with changes in levels of factor VII and proteins C and S. Tissue factor and cancer procoagulant levels may rise. Thrombocytosis, increased fibrinogen levels and reduced fibrinolysis, endothelial damage, and stasis may also contribute to thrombosis. Premenopausal breast cancer patients who receive both chemotherapy and tamoxifen are more likely to present with arterial thrombosis compared with those who receive chemotherapy alone.[26,27]

Heart failure (HF) or cardiac function deterioration also occurs in a background of paraneoplastic syndrome of breast cancer.[28]

Complications of therapy for breast cancer

Here we explain more about anti-human epidermal growth factor receptor 2 (HER2) agents, especially trastuzumab.

Novel chemotherapy agents and related cardiac toxicity

The overexpression of HER2 in breast cancer is associated with more aggressive disease with a poor prognosis.[2 9, 30] Trastuzumab, pertuzumab, and other anti-HER2 agents are monoclonal antibodies against the extracellular domain of HER2 that have been shown to be effective in metastatic breast cancer as monotherapy or combining with other chemotherapy agents.[31, 32] These agents have proved to be effective in both metastatic and early-stage breast cancers when combined with chemotherapy, and reduce relapse rates by 50% irrespective of age and other relevant prognostic factors.[33,34]

As mentioned by the American Society of Clinical Oncology, in contrast to anthracycline-related cardiac toxicity (type 2/irreversible), trastuzumab does not result in myocyte loss. In trastuzumab-induced cardiac dysfunction, myocytes appear normal histologically and alterations may be noticed only by using electron microscopy.[35]

In a study by Swain *et al.*, the addition of pertuzumab to trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer significantly increased the median overall survival to 56.5 months—an improvement of 15.7 months over survival in the control group.[30]

As mentioned before, these novel biologic therapies improve disease-free and overall survival, but increase the risk of cardiotoxicity,[36] as has been shown in many studies.[29, 34] The cardiotoxicity of these agents could involve any part of the heart's structure, and the ongoing studies are assessing these damages to heart using various methods and parameters.

Recently, we compared cardiomyopathy-related findings before and after trastuzumab therapy in patients with breast cancer and found that diastolic function was significantly impaired after treatment (25.9% versus 43.6 %).[37] After the therapy, left ventricular ejection fraction (LVEF) was reduced significantly, and troponin levels were increased remarkably (0% versus 6.7 %); however, no significant differences were observed for CRP and NT-pro-BNP levels. This study showed the importance of troponin for trastuzumab-induced cardiomyopathy.

In a study by Rossner and colleagues[38] in 28 female patients with metastatic HER2-positive breast cancer, blood samples were drawn before and 30 min after intravenous trastuzumab infusion, and EF and NT-pro-BNP levels before and after the initiation of trastuzumab were compared. According to higher median 3-month mortality in cases with elevated levels of NT-pro-BNP, this marker could be considered as a prognostic factor in these patients.

In one study by Cardinale *et al.*,[39] the incidence rate of trastuzumab-induced cardiotoxicity (TIC) in breast cancer patients was reported to be 17%, and TIC was significantly associated with elevated levels of troponin I (TNI) (62% in TNI+ vs 5%; P < .001). They suggested that increased TNI levels can identify trastuzumab-treated patients who are at risk for cardiotoxicity and who are unlikely to recover from cardiac dysfunction despite HF therapy.

In another study by Goel *et al.*, serum troponin I and NT-pro-BNP were assayed immediately before and 24 hours after trastuzumab infusion in patients with breast cancer. A significant proportion of the patients with normal LVEF who received trastuzumab experienced elevated levels of NT-pro-BNP , but that was not the case for troponin I levels.[40]

Lamot *et al.* reported evaluated trastuzumab treatment-induced cardiac toxicity in 30 breast cancer patients.[41] Cardiac toxicity was assessed based on LV function. LVEF showed a significant decrease after trastuzumab adjuvant therapy.

In a large cohort study by Chavez-MacGregor *et al.*,[42] 2203 older breast cancer patients under trastuzumab therapy were evaluated. They observed a chronic heart failure rate of 29.4% among trastuzumab users, compared with 18.9% in non-trastuzumab users (P < 0.001).

In addition to ejection fraction (EF) and cardiac biomarkers, a few studies have also shown adverse effect of this drug on left atrium. A recently published observational study revealed changes in atrial diameter and geometry during the early periods of trastuzumab treatment.[43] Ongoing studies are evaluating precisely the effect of these monoclonal antibodies on atrial structure and function.

Finally, regarding the research on cardiotoxicity of trastuzumab, most recent and valuable studies some of which have been mentioned above, have demonstrated the adverse effect of newer biologic therapies on heart system, but their cardiotoxicity is significantly lower than the older agents such as anthracyclines.[4]

Contemporary radiotherapy and related cardiac toxicity

Like chemotherapy, radiation causes mainly a series of toxic effects and hemodynamic and structural damages to the cardiovascular system, affecting the long-term survival.[44, 45] Radiation to the chest can damage the pericardium, myocardium, heart valves, and coronary vessels.[46, 47] According to available evidence, the damage to the cardiovascular system is directly related to the dose of radiation and the volume of heart irradiated, especially if combined with chemotherapy.[48] The extent of damage will be doubled in patients with preexisting cardiac diseases. In radiation-induced vascular damage, endothelial dysfunction is the first sign.[49] After starting radiation therapy, , large myocardial perfusion defects were detected in single-photon emission computerized tomography scans (even in 55% of asymptomatic patients),[50, 51] and radiotherapy has even been accompanied by HF in these patients; overall, however, HF is not common in patients undergoing radiation therapy and is usually a late effect of radiation therapy. The mechanism responsible for radiation-induced injury to heart could be myocardial fibrosis resulting from collagen disruption.[52] Radiation can cause injury to the intima of the coronary arteries and initiate a cascade of atherosclerotic events. The left anterior descending and the right coronary arteries are most often involved in patients undergoing mediastinal radiation for Hodgkin's disease.[53]

Progressive fibrosis following radiation-induced myocardial collagen synthesis results in valvular heart disease by increasing the valvular thickness, and in left ventricular dysfunction by increasing ventricular wall thickness.[54] Ongoing studies are evaluating radiotherapy-induced LV dysfunction by new imaging methods and parameters like (18F-FDG PET/CT) and PET-MRI, as mentioned.

In spite of all the mentioned complications, the absolute risk of radiation therapy is small and seems to be cancelled out by the advantages for patients receiving radiation therapy.

Discussion

Approach to cardiac toxicity of chemotherapeutic agents in patients with breast cancer

Risk factors for trastuzumab-induced cardiomyopathy

Epidemiologic evidence indicates that, even without a clear LVEF at the time of treatment, early treatment of breast cancer with trastuzumab presents a substantial long-term risk of HF, especially for women older than 65 years.[55]

Diagnosis of trastuzumab-induced cardiomyopathy

Echocardiographic evolution of EF using Simpson's method is recommended for assessment of left ventricular function.[56-58] Abnormalities of right ventricular contractility, ventricular dilation, and abnormal left ventricular contractility are the earliest presentations of myocardial damage diagnosed by echocardiography.

Strain rate imaging (SRI) is a new echocardiographic modality that enables accurate measurement of regional myocardial function and is recommended especially for chemotherapy- and radiotherapy-induced cardiotoxicity in breast cancer patients.[59]

There are some recommendations by experts and in reported articles from tertiary centers, and almost all of them agree that treatment with trastuzumab must be stopped if clinical symptoms of HF are present.[35,60,61]

In the event of an asymptomatic decrease in LVEF by 15% or more, discontinuation of trastuzumab therapy is mandatory.[62, 63] Patients receiving chemotherapy may be considered to be at elevated risk of developing cardiac dysfunction —Stage A heart failure in ACC/AHA guidelines.[64]

Baseline cardiac evaluation through history taking, physical examination, and electrocardiography should be done for all patients before they are given trastuzumab.[61] Five main randomized trials have demonstrated the survival advantages of adjuvant trastuzumab in early breast cancer patients.[35, 60] Recently, guidelines were developed for cardiac monitoring of metastatic breast cancers receiving trastuzumab treatment.[61] Since trastuzumab-associated cardiac toxicity is a great concern in making all the adjuvant trials, strict cardiac evaluation is necessary in these trials prior designing and monitoring at regular intervals during therapy. In National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, trastuzumab-induced symptoms were monitored and patients who developed clinically significant cardiac symptoms while receiving anthracycline treatment were excluded from subsequent trastuzumab therapy. The initiation or continuation of trastuzumab treatment in asymptomatic patients required an LVEF equal to or exceeding the lower limit of normal range.[65] In North Central Cancer Treatment Group (NCCTG) N9831, pooled with NSABP B-31, 6.7% of the enrolled patients were not allowed to start trastuzumab treatment because their LVEF had declined to a subnormal level or had been decreased by ≥ 16% from baseline after completion of anthracycline treatment.[65, 66] Jones *et al.*, published cardiology assessment and monitoring methods in *British Journal of Cancer*,[35] and Saad *et al.* presented the second recommendations and their related demonstrations.[60]

The newest accepted guidelines are developed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[61]

Table 1. Assessment of LVEF and Cardiac Toxicity Criteria in Adjuvant Trials of Trastuzumab

Trial	Method of LVEF assessment
NSABP B31	MUGA scanning
NCCTG N9831	MUGA scanning or echocardiography
HERA67	MUGA scanning or echocardiography
FinHer 68	MUGA scanning or echocardiography

LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NCI–CTC = National Cancer Institute–Common Toxicity Criteria; NYHA = New York Heart Association

Baseline evaluation of LVEF by 2D or 3D echocardiography, global longitudinal strain (GLS), and troponin I should be determined at the initiation of any regimen potentially associated with type 1 toxicity.

At the initiation of trastuzumab, baseline evaluation of LVEF should be done by 2D or 3D echocardiography, GLS, and troponin I assessment. If LVEF is less than 53%, GLS is near the lower limit of normal, and troponin test is positive, cardiology consultation should be recommended, and if these three parameters are in normal range, follow-up by measurement of LVEF, GLS, and troponin every 3 months is recommended.

At the initiation of trastuzumab after a regimen associated with type I toxicity, such as anthracycline (cell apoptosis and irreversible cell damage) the assessment is similar to above guidelines.[61] Follow-up by measurement of LVEF, GLS, and troponin every 3 months during therapy, and 6 months after therapy, is recommended. As in trastuzumab monitoring, if parameters are abnormal, cardiology consultation would be necessary; and if parameters are within normal range, follow-up at the completion of therapy and 6 months later should be considered. For early detection of subclinical LV dysfunction GLS is the optimal parameter: a relative percentage reduction of < 8% from baseline is not significant, but those >15% are probably abnormal.

Today, cardiovascular magnetic resonance (CMR) imaging is widely used in patients with breast cancer for detecting both the acute and chronic complications of cardiotoxic chemotherapeutic agents. CMR is recommended when the quality of the echocardiogram is suboptimal. With the introduction of late gadolinium enhancement (LGE), CMR is considered the gold standard for myocardial viability imaging accompanied by positron emission tomography.[61]

Aerobic training (AT) is a non-pharmacological strategy to attenuate or even counteract acute and chronic cardiovascular abnormalities in the context of early breast cancer. It can improve systolic and diastolic function and reduce pathologic cardiac remodeling.[69, 70] This may lead to enhanced exercise tolerance and resistance to fatigue during exertion in patients with known cardiovascular disease.[71] Cardioprotective properties of AT in the context of early breast cancer has been well explained in an important study by Scott *et al.*[72] They proposed an exercise paradigm based on the principles of AT to facilitate a personalized medicine approach that may optimize prevention or attenuation of breast cancer therapy-associated cardiovascular disease.

Echocardiography can be utilized as a routine method for monitoring cardiac side effects. It helps in assessment of parameters for systolic and diastolic function and anatomical cardiac dimensions as well.

The remarkable improvements in screening and adjuvant therapy for breast cancer, combined with close surveillance of cancer survivors, have led to a significant decrease in recurrence rate. Currently, cardiovascular disease is one of the leading causes of death in many patients who have been treated for breast cancer.

We recommend screening and surveillance for early detection of subclinical cardiovascular complications of breast cancer itself, or cardiotoxicity associated with its treatment. Early detection and treatment of even the smallest cardiac damages will improve prognosis and life expectancy of patients with breast cancer.

Conflict of Interest

None to declare.

References

1. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, *et al.* Breast-cancer screening—viewpoint of the IARC Working Group. New England Journal of Medicine. 2015;372(24):2353-8.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al.* GLOBOCAN 2012 v 1.0, Cancer Incidence and Mortality Worldwide. 2013. Lyon, International Agency for Research on Cancer IARC CancerBase. 2015(11).
3. Coates A. PG 0.1 Evolution of the St. Gallen Consensus process for the optimal treatment of women with breast cancer. The Breast. 2015;24:S1.
4. Ban KA, Godellas CV. Epidemiology of breast cancer. Surgical oncology clinics of North America. 2014;23(3):409-22.
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. 2010;127(12):

2893-917.
6. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, andmammography screening effectiveness. New England Journal of Medicine. 2016;375(15): 1438-47.
7. Anthony FY, Jones LW. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. Cardio-Oncology. 2016;2(1):1.
8. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, *et al.* A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA cardiology. 2017;2(1):88-93.
9. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Research. 2011;13(3):R64.
10. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, Rouzier R, Broglio KR, Hortobagyi GN, *et al.* Overall survival and cause-specific mortality of patients with stage T1a, bN0M0 breast carcinoma. J Clin Oncol. 2007;25(31):4952-60.
11. Cheruvu B, Cheruvu P, Boyars M. An unusual case of metastasis to the left side of the heart: a case report. J Med Case Rep. 2011;5:23.
12. Katalinic D, Stern-Padovan R, Ivanac I, Aleric I, Tentor D, Nikolac N, *et al.* Symptomatic cardiac metastases of breast cancer 27 years after mastectomy: a case report with literature review-pathophysiology of molecular mechanisms and metastatic pathways, clinical aspects, diagnostic procedures and treatment modalities. World J Surg Oncol. 2013;11(1):1.
13. Oxmann D, Held-Feindt J, Stark A, Hattermann K, Yoneda T, Mentlein R. Endoglin expression in metastatic breast cancer cells enhances their invasive phenotype. Oncogene. 2008;27(25): 3567-75.
14. Hancox RA, Allen MD, Holliday DL, Edwards DR, Pennington CJ, Guttery DS, *et al.* Tumour-associated tenascin-C isoforms promote breast cancer cell invasion and growth by matrix metalloproteinase-dependent and independent mechanisms. Breast Cancer Res. 2009; 11(2):R24.
15. Johnson TR, Becker CR, Wintersperger BJ, Herzog P, Lenhard MS, Reiser MF. Detection of Cardiac Metastasis by Positron-Emission Tomography–Computed Tomography. Circulation. 2005;112(4):e61-e2.
16. Houck RC, Cooke JE, Gill EA. Live 3D echocardiography: a replacement for traditional 2D echocardiography? American Journal of Roentgenology. 2006;187(4):1092-106.
17. Ohnishi M, Niwayama H, Miyazawa Y, Kondo N, Imai H, Nishimoto Y, *et al*. [Echocardiography in patients with malignant metastatic neoplasms of the heart and great vessels]. J Cardiol. 1989;20(2):377-84.
18. Escalante CP, Manzullo E, Weiss M, Bonin S. Oncologic emergencies and paraneoplastic syndromes. Cancer Management: A Multidisciplinary Approach, Ninth Edition Melville, NY: The Oncology Group, FA Davis Company. 2005:982-6.
19. Dağdelen S. Superior vena cava syndrome arising from subclavian vein port catheter implantation and paraneoplastic syndrome. Turk Kardiyol Dern Ars. 2009;37:125-7.
20. Tonak J, Fetscher S, Barkhausen J, Goltz J. Endovascular recanalization of a port catheter-associated superior vena cava syndrome. J Vasc Access. 2015;16(5):434-6.
21. El Haddad D, Iliescu C, Yusuf SW, William WN, Khair TH, Song J, *et al.* Outcomes of cancer patients undergoing percutaneous pericardiocentesis for pericardial effusion. Journal of the American College of Cardiology. 2015;66(10):1119-28.
22. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Archives of Internal Medicine. 2000;160(6):809-15.
23. Blann AD, Dunmore S. Arterial and venous thrombosis in cancer patients. Cardiol Res Pract. 2011;2011:394740.
24. Connolly GC, Francis CW. Cancer-associated thrombosis. ASH Education Program Book. 2013;2013(1):684-91.
25. Du Toit JM. Upper limb ischaemia: a twelve year experience: University of Cape Town; 2014.
26. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.
27. Kwaan HC, Parmar S, Wang J, editors. Pathogenesis of increased risk of thrombosis in cancer. Seminars in thrombosis and hemostasis; 2003.
28. Pelosof LC, Gerber DE, editors. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010:85(9), 838-854.
29. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti–HER-2 therapy and personalized medicine. The oncologist. 2009;14(4):320-68.
30. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, *et al.* Pertuzumab, trastuzumab, and docetaxel in HER2-positive

metastatic breast cancer. New England Journal of Medicine. 2015;372(8):724-34.
31. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Annals of oncology. 2007;18(6):977-84.
32. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. New England Journal of Medicine. 2005;353(16):1659-72.
33. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74.
34. Adamo V, Ricciardi GRR, Adamo B, Ferraro G, Franchina T, Rossello R, *et al.* The risk of toxicities from trastuzumab, alone or in combination, in an elderly breast cancer population. Oncology. 2013;86(1):16-21.
35. Jones A, Barlow M, Barrett-Lee P, Canney PA, Gilmour I, Robb S, *et al.* Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. British journal of cancer. 2009; 100(5):684-92.
36. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. Journal of the American College of Cardiology. 2012;60(24): 2504-12.
37. Mehrpooya M, Emadi SH, Sattarzadeh-Badkoobeh R, Shahi F, Parsa AFZ, Mohagheghi A, *et al.* Trastuzumab-Induced Cardiomyopathy Evaluation by Combined Echocardiography and Biomarkers in Patients with Breast Cancer. Iranian Heart Journal 2015؛ 15(4) : 26-31.
38. Rossner D, Knobloch K, Lichtinghagen R, Lichtenberg A, Kuehnle H, Lueck H, editors. NT-pro-BNP and CA 125 as potential markers of mortality during long-term immunetherapy with trastuzumab in HER-2-positive metastatic breast cancer. ASCO Annual Meeting Proceedings; 2004.
39. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, *et al.* Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. Journal of clinical oncology. 2010;28(25):3910-6.
40. Goel S,Simes RJ, Beith JM. Exploratory analysis of cardiac biomarkers in women with normal cardiac function receiving trastuzumab for breast cancer. Asia-Pacific Journal of Clinical Oncology. 2011;7(3):276-80.
41. Lamot C, Rottey S, De Backer T, Van Bortel L, Robays H, Van Belle S, *et al.* Cardiac toxicity of trastuzumab: experience at the Ghent University Hospital, Belgium. Acta Clinica Belgica. 2010;65(5):300-4.
42. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, *et al.* Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013;31(33):4222-8.
43. Chang C-M, Cheng FT-F, Yang T-L, Wen W-C. Cardiotoxicity Associated with Trastuzumab Therapy in Taiwan: A Single Medical Center's 5-Year Experience. Journal of Cancer Research and Practice. 2015;2(2):139-50.
44. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2006;366(9503):2087-106.
45. Højris I,Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. The Lancet. 1999;354(9188):1425-30.
46. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, *et al.* Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. Journal of the National Cancer Institute. 2007;99(5):365-75.
47. Correa CR,Litt HI, Hwang W-T, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. Journal of clinical oncology. 2007;25(21):3031-7.
48. Prosnitz RG, Chen YH, Marks LB, editors. Cardiac toxicity following thoracic radiation. Semin Oncol. 2005;32(2 Suppl 3):S71-80.
49. Landau D, Adams EJ, Webb S, Ross G. Cardiac avoidance in breast radiotherapy: a comparison of simple shielding techniques with intensity-modulated radiotherapy. Radiotherapy and Oncology. 2001;60(3):247-55.
50. Hatoum OA, Otterson MF, Kopelman D, Miura H, Sukhotnik I, Larsen BT, *et al.* Radiation induces endothelial dysfunction in murine intestinal arterioles via enhanced production of reactive oxygen species. Arteriosclerosis, thrombosis, and vascular biology. 2006;26(2): 287-94.
51. Seddon B, Cook A, Gothard L, Salmon E, Latus K, Underwood SR, *et al.* Detection of defects in myocardial perfusion imaging in patients with early breast cancer treated with radiotherapy. Radiotherapy and Oncology. 2002;64(1):53-63.
52. Paris F, Fuks Z, Kang A, Capodieci P, Juan G, Ehleiter D, *et al.* Endothelial apoptosis as the

primary lesion initiating intestinal radiation damage in mice. Science. 2001;293(5528):293-7.
53. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005;366(9503):2087-106.
54. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, *et al.* Radiation-related heart disease: current knowledge and future prospects. International journal of radiation oncology, biology, physics. 2010;76(3):656.
55. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol. 2005;23(34):8597-605.
56. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK, editors. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. Mayo Clin Proc. 2008;83(2):197-203.
57. Fox K. The evaluation of left ventricular function for patients being considered for, or receiving Trastuzumab (Herceptin) therapy. British journal of cancer. 2006;95(10):1454.
58. Stoodley PW, Richards DA, Meikle SR, Clarke J, Hui R, Thomas L. The potential role of echocardiographic strain imaging for evaluating cardiotoxicity due to cancer therapy. Heart, Lung and Circulation. 2011;20(1):3-9.
59. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, *et al.* Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. 2013;85(5):1172-8.
60. Saad A, Abraha J. Trastuzumab and cardiac toxicity: monitoring in the adjuvant setting. Community Oncology. 2007;4(12):739-44.
61. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, *et al.* Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2014;27(9):911-39.
62. Duchnowska R, Szmit S, Szczylik C, Opolski G. [Difficulties in echocardiographic monitoring of trastuzumab therapy in breast cancer patients: case report and review of recommendations]. Kardiol Pol. 2008;66(8):895-8.
63. Huszno J, Les D, Sarzyczny-Slota D, Nowara E. Cardiac side effects of trastuzumab in breast cancer patients-single centere experiences. Współczesna Onkologia. 2013;17(2):190.
64. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;62(16):e147-e239.
65. Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2–overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23(31):7811-9.
66. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. New England Journal of Medicine. 2005;353(16):1673-84.
67. De Azambuja E, Procter MJ, Van Veldhuisen DJ, Agbor-Tarh D, Metzger-Filho O, Steinseifer J, *et al.* Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). Journal of clinical oncology. 2014:JCO. 2013.53. 9288.
68. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, Alanko T, Kataja V, Asola R, *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. New England Journal of Medicine. 2006;354(8):809-20.
69. Duquaine D, Hirsch GA, Chakrabarti A, Han Z, Kehrer C, Brook R, *et al.* Rapid-onset endothelial dysfunction with adriamycin: evidence for a dysfunctional nitric oxide synthase. Vascular Medicine. 2003;8(2):101-7.
70. Kotamraju S, Konorev EA, Joseph J, Kalyanaraman B. Doxorubicin-induced apoptosis in endothelial cells and cardiomyocytes is ameliorated by nitrone spin traps and ebselen role of reactive oxygen and nitrogen species. Journal of Biological Chemistry. 2000;275(43):33585-92.
71. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. Canadian medical association journal. 2006;174(6):801-9.
72. Scott JM, Koelwyn GJ, Khouri MG, Douglas PS, Jones LW. Preventing Cardiovascular Complications of Breast Cancer Treatment: The Utility of Effective Exercise Prescription. Current Cardiovascular Risk Reports. 2013;7(4):275-82.