Editorial

Radiotherapy-Induced Heart Disease: What Can We Evaluate?

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Radiotherapy (RT) has been part of oncological treatment since 1899 and is currently used with more than 50% of all patients.[1] Breast, lung, esophagus, and lymphoma tumors are commonly submitted to RT treatment, showing improvements in the total survival and freedom from diseases. By contrast, when including mediastinal structures, such as the heart and blood vessels, in 10% to 30% of the patients, adverse cardiovascular events were observed after 5 and 10 years, defined as Radiation-Induced Heart Disease (RIHD).[2,3]

The RIHD spectrum includes pericardial diseases, coronary artery disease, valvar heart disease, cardiomyopathy, as well as conduction abnormality and dysautonomia, leading to an increase in the cardiovascular morbidity and mortality of the survivors.[4]

High-risk patients were those submitted to anterior chest RT, whose therapeutic planning involves the heart and the presence of one or more factors related to the patient, such as a person under 50 years of age, previous cardiovascular disease, cardiovascular risk factors, a tumor located close the heart, and factors related to the treatment itself, including total accumulated dose (> 30 Gy), total dose upon the heart (increase in cardiovascular risk from 1.5% to 7% for each 1 Gy), association with anthracyclines and the absence of cardioprotection.[2,5]

Ionizing radiation can damage all heart tissues and be responsible for micro and macrovascular lesions. The loss of endothelial cells, inflammatory response, and vascular lesion were detected early on, resulting in capillary rarefaction with a consequent ischemia, fibrosis, and systolic and diastolic dysfunctions. The macrovascular lesion appears through accelerated atherosclerosis, with endothelial dysfunction, macrophagic infiltration, inflammation, and intraplaque hemorrhage, which makes it more prone to rupture.[2]

The pre-RT evaluation should include, in addition to the anamnesis and physical exam, the multimodality of imaging exams in the study of the pre-existing cardiovascular disease. In the staging or therapeutic planning, a chest computed tomography (CT) is commonly taken, in which one can evaluate the presence of coronary calcification. The identification of this shows a good correlation with research dedicated to the study of calcium scores and to the stratification of the cardiovascular risk.[4] The transthoracic echocardiogram (TTE) should be considered in all patients to evaluate the ventricular dysfunction and to study the valvar and pericardial heart disease. Whenever possible, medical professionals should evaluate myocardial deformities by means of the global longitudinal strain.[4]

The presence of cardiovascular risk and coronary disease in women with breast cancer submitted to RT was associated with a 2-fold and 6-fold higher risk, respectively, of severe cardiovascular events during follow-up.[6] One study, conducted with patients with atherosclerotic plaque in the anterior descending artery, demonstrated that, when submitted to RT (average dose applied to the left ventricle > 5 Gy), the patients presented a high risk of cardiovascular events after an average follow-up of 9 years.[5] All of the patients identified as high risk prior to RT should be treated according to the cardiovascular prevention and treatment guidelines.

Faced with the high risk of RIHD, a wide range of imaging exams can be used for follow-up and diagnosis of cardiotoxicity. The choice for complementary exams will depend on the experience of each center and of the individual characteristics of the patient, such as comorbidities, RT characteristics, association or not with anthracycline, and the emergence of symptoms.

In the majority of asymptomatic cases, the TTE is recommended to evaluate abnormalities, in addition to the study of ischemia after 5 to 10 years and every 5 years thereafter. In patients considered to be of high risk, an earlier evaluation is recommended, between 6 and 24 months after the end of RT.[7] More recently, the evaluation of non-obstructive coronary artery disease by coronary CT angiography enabled the early implementation of preventive pharmacological measures, such as the use of statins.[1] In symptomatic patients, medical exams should follow the recommendation set forth in the guidelines for each pathology.

The TTE (Figure 1), as it is a widely available method that is non-invasive and does not use ionizing radiation, has quickly become the first option for port-RT patient follow-up. The use of diverse modalities and resources, such as the M mode, Doppler 2D and 3D, ultrasound contrast, stress echocardiography, and transesophageal echocardiography, enables the detection of critical structural and functional changes in the diagnosis of RIHD. The reduction of the global longitudinal strain in the segment exposed to RT (Figure 1.C) can be observed early and present a subclinical dysfunction with a worse diagnosis.[1,8,9] The appearance of a pericardial stroke (Figure 1.B) a few weeks after the end of RT was significantly diminished after the reduction in the total dose in more modern protocols; however, 10% to 20% of the cases can evolve into chronic and constrictive forms after 20 years. The findings that suggest constrictive

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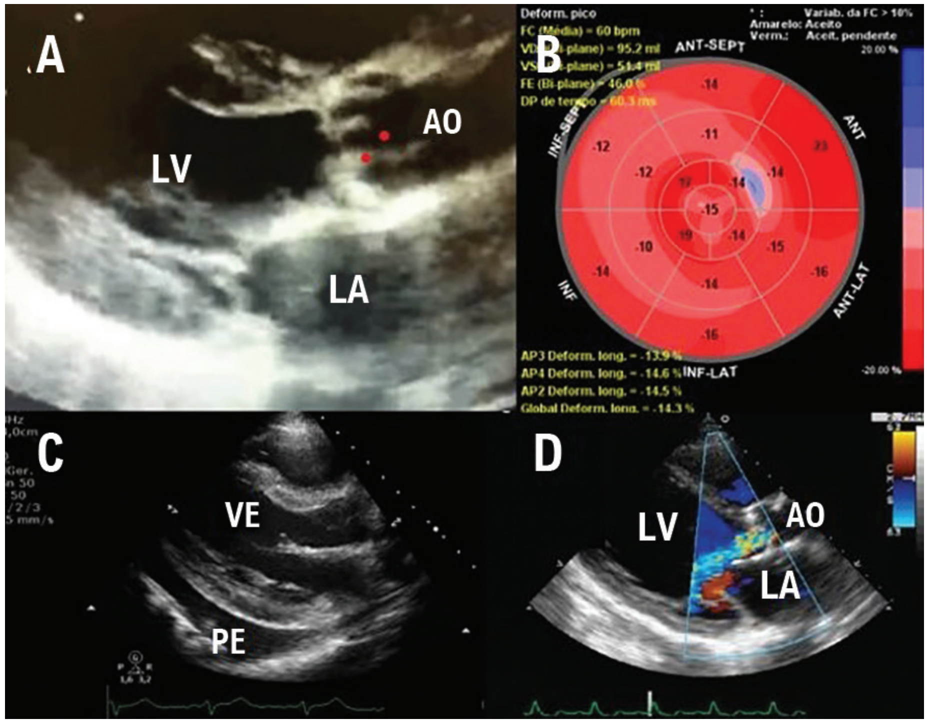

Figure 1 – *A) Longitudinal parasternal cut, valve-aortic calcification, mitroaortic fibrosis and anterior leaflet of the mitral valve, 72-year-old patient with a breast neoplasm; B) Polar Map of a 57-year-old patient and esophagogastric transition tumor; C) Longitudinal parasternal cut, presence of pericardial stroke, 32-year-old patient with Hodgkin lymphoma; D) longitudinal parasternal cut, presence of aortic insufficiency, 65-year-old patient with Hodgkin lymphoma. LV: left ventricle; PE: Pleural Effusion; AO: aorta; LA: left atrium*

pericarditis include pericardial thickening, septal bounce, restrictive patterns of diastolic filling, variation > 25% of the mitral inflow, plethora of inferior vena cava, and reversal of the expiratory diastolic flow in the hepatic veins.[2,7,11] The more common findings in the myocardial dysfunction are the change in the segmental contractility (normally on the lower wall), general hypokinesia, and signs of diastolic dysfunction. Changes in the segmental contractility are not necessarily related to the presence of coronary artery disease and the added evaluation by means of the stress echocardiogram can aid in the diagnosis.[12] It is important to remember that, to calculate the ejection fraction (EF), if possible, one should use 3D echocardiography, and, if this is not possible, always use the Simpson method in 2D. Despite the importance of EF, both in the diagnosis and in the follow-up of cardiotoxicity, one should not disregard the intraobserver and interobserver variability inherent to the method, as well as the influence of the pre-load and post-load. The subclinical dysfunction evaluated by the study of myocardial deformity, more commonly using the 2D speckle-tracking technique, presents more sensitive and earlier results, earlier even than the change in the EF. The study of the diastolic function is of utmost importance, as the emergence of heart failure with the EF preserved due to fibrosis and endothelial dysfunction is much more commonly observed.[2,4,8,10] The prevalence of moderate or severe valvar heart disease is rare in the first 10 years, with the preferential involvement being to that of the aortic valve, followed by the mitral valve. The echocardiographic findings range from the discrete thickening and calcification of the valve leaflets to more characteristic findings, such as the thickening and calcification of the mitroaortic curtain, a more significant involvement of the valve leaflets (aortic and anterior leaflets of the mitral valve) without commissural fusion, which enables a differential diagnosis with rheumatic carditis (Figure 1.A). Functionally, the regurgitant lesions (Figure 1.D) are more common; however, after 20 years, an increase in the incidence of valvar stenosis can be observed.[2,4,7,12,13]

Cardiac magnetic resonance Imaging (CMRI) is especially useful in cases in which the echocardiograph window is limited, and the evaluation of the ventricular function is adopted as the gold standard. The use of delayed enhancement by gadolinium injection, T1 map, and the increase in the extracellular volume, allow for the myocardial tissue characterization of the presence of fibrosis. The pericardial thickness, enhancement after contrast, the presence of a stroke, and findings suggestive of constriction in the cine-RM images suggest pericardial involvement. Evaluation of valvar heart lesions is also possible, with a higher precision for regurgitant lesions.[1,2,4]

Nuclear medicine (NM) can contribute to relevant information about the function and myocardial perfusion, both at rest and with stress (physical or pharmacological).

The need to use radiation and the possible evaluation of the ventricular function by other methods has limited the use of NM to the study of perfusion, preferentially with ^{201}Tl and ^{99m}Tc. The prevalence of the defects of post-RT myocardial perfusion vary from 1% to 64%, depending on the irradiated ventricular volume, age, post-RT time, and methodology of the perfusion study. The distribution of the changes in the perfusion are not always correlated with obstructive coronary artery disease, often corresponding to changes in microcirculation. When changes in perfusion occur, an association among a deterioration of the ventricular function, the need for myocardial revascularization, and adverse cardiovascular events can be observed.[1,2,4]

As seen above, the identification of coronary calcification in studies performed for the staging of the oncological disease or the planning of RT, provides important information referent to the presence of atherosclerotic disease and the need to control cardiovascular risk factors. The use of CT angiography of the coronary arteries in the post-RT follow-up is still limited. In a study conducted with 31 patients with lymphomas after 24 years of RT treatment, CT angiography identified the presence of coronary disease in 12 patients and in the obstructive form in 3 patients, with only 1 identified in the functional exam used to study ischemia. The best moment for screening and the possibility of benefits in repeating the exam are still under debate. CT angiography appears to present a greater benefit than the isolated study of the calcium score, and the use of CT studies themselves can highlight false negative results.[1,2,4]

Despite the progress of RT techniques, RIHD is still common and can appear many years after the termination of the therapy. The simultaneous involvement of diverse heart structures, the comorbidities, and the limitations for invasive cardiovascular treatment reinforce the need for a rigorous control of cardiovascular risk factors, strategies of cardioprotection during RT, and the use of multimodality imaging (Figure 2) to reach an early diagnosis aimed at improving clinical results.[1,2,4,14]

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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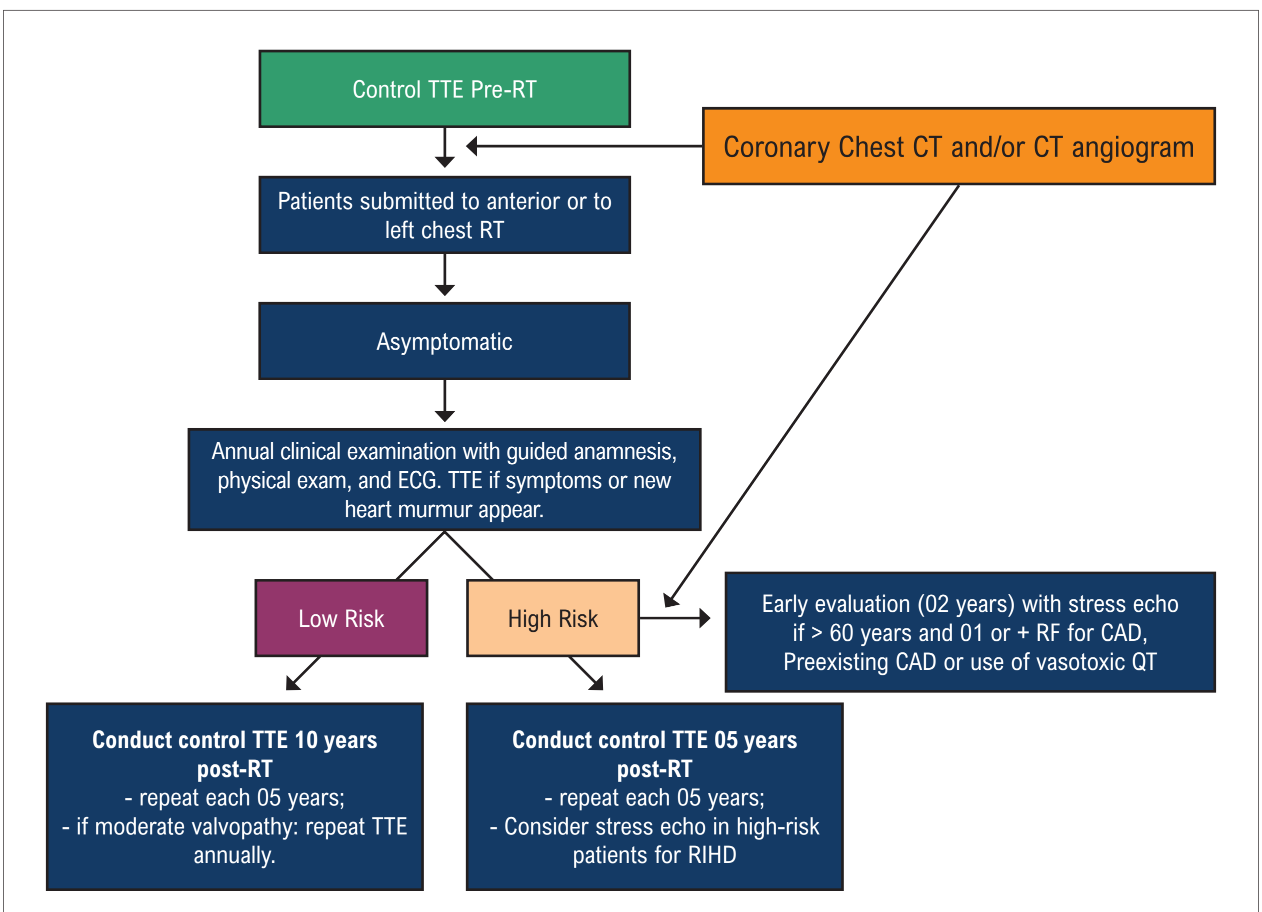

Figure 2 – *Adapted from the Brazilian Position Statement concerning the Use of Multimodal Imaging in Cardio-Oncology – 2021.7 RT: radiotherapy; TTE: transthoracic echocardiogram; ECG: electrocardiogram; CAD: coronary artery disease; RF: risk factor; QT: chemotherapy; RIHD: Radiation-Induced Heart Disease; CT: computed tomography.*

Study Association

This study is not associated with any thesis or dissertation work.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript for intellectual content: Paiva MG.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J, et al. Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification. JACC CardioOncol. 2021;3(3):343-59. doi: 10.1016/j.jaccao.2021.06.007.
2. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, et al. Expert Consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2013;26(9):1013-32. doi: 10.1016/j.echo.2013.07.005.
3. Ganatra S, Chatur S, Nohria A. How to Diagnose and Manage Radiation Cardiotoxicity. JACC CardioOncol. 2020;2(4):655-60. doi: 10.1016/j.jaccao.2020.07.010.
4. Mitchell JD, Cehic DA, Morgia M, Bergom C, Toohey J, Guerrero PA, et al. Cardiovascular Manifestations from Therapeutic Radiation: A Multidisciplinary Expert Consensus Statement from the International Cardio-Oncology Society. JACC CardioOncol. 2021;3(3):360-80. doi: 10.1016/j.jaccao.2021.06.003.
5. van den Bogaard VAB, Spoor DS, van der Schaaf A, van Dijk LV, Schuit E, Sijtsema NM, et al. The Importance of Radiation Dose to the Atherosclerotic Plaque in the Left Anterior Descending Coronary Artery for Radiation-Induced Cardiac Toxicity of Breast Cancer Patients? Int J Radiat Oncol Biol Phys. 2021;110(5):1350-9. doi: 10.1016/j.ijrobp.2021.03.004.
6. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of Ischemic Heart Disease in Women After Radiotherapy for Breast Cancer. N Engl J Med. 2013;368(11):987-98. doi: 10.1056/NEJMoa1209825.
7. Melo MDT, Paiva MG, Santos MVC, Rochitte CE, Moreira VM, Saleh MH, et al. Brazilian Position Statement on the Use of Multimodality Imaging in Cardio-Oncology - 2021. Arq Bras Cardiol. 2021;117(4):845-909. doi: 10.36660/abc.20200266.
8. Yu AF, Ho AY, Braunstein LZ, Thor ME, Lee Chuy K, Eaton A, et al. Assessment of Early Radiation-Induced Changes in Left Ventricular Function by Myocardial Strain Imaging After Breast Radiation Therapy. J Am Soc Echocardiogr. 2019;32(4):521-8. doi: 10.1016/j.echo.2018.12.009.
9. Villarraga HR, Herrmann J, Nkomo VT. Cardio-Oncology: Role of Echocardiography. Prog Cardiovasc Dis. 2014;57(1):10-8. doi: 10.1016/j.pcad.2014.05.002.
10. Hamza A, Tunick PA, Kronzon I. Echocardiographic Manifestations of Complications of Radiation Therapy. Echocardiography. 2009;26(6):724-8. doi: 10.1111/j.1540-8175.2008.00878.x.
11. Heidenreich PA, Schnittger I, Strauss HW, Vagelos RH, Lee BK, Mariscal CS, et al. Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease. J Clin Oncol. 2007;25(1):43-9. doi: 10.1200/JCO.2006.07.0805.
12. Hering D, Faber L, Horstkotte D. Echocardiographic Features of Radiation-Associated Valvular Disease. Am J Cardiol. 2003;92(2):226-30. doi: 10.1016/s0002-9149(03)00546-0.
13. Malanca M, Cimadevilla C, Brochet E, Iung B, Vahanian A, Messika-Zeitoun D. Radiotherapy-Induced Mitral Stenosis: A Three-Dimensional Perspective. J Am Soc Echocardiogr. 2010;23(1):108.e1-2. doi: 10.1016/j.echo.2009.08.006.
14. Dolmaci OB, Farag ES, Boekholdt SM, van Boven WJP, Kaya A. Outcomes of Cardiac Surgery After Mediastinal Radiation Therapy: A Single-Center Experience. J Card Surg. 2020;35(3):612-9. doi: 10.1111/jocs.14427.