Review Article

Critical Analysis and Applicability of Imaging Methods in Monitoring and Diagnosing Ventricular Dysfunction in Patients with Cancer

Claudio Tinoco Mesquita,[1,2] Marcelo Dantas Tavares de Melo,[3] Ariane Binoti Pacheco Leal,[4] André Luiz Cerqueira de Almeida[5]

Hospital Universitário Antonio Pedro/Ebserh – Universidade Federal Fluminense,[1] Niterói, RJ – Brazil
Hospital Pró-Cardíaco,[2] Rio de Janeiro, RJ – Brazil
Universidade Federal da Paraíba,[3] João Pessoa, PB – Brazil
Multiscan Inteligência Diagnóstica,[4] Vila Velha, ES – Brazil
Santa Casa de Misericórdia de Feira de Santana,[5] Feira de Santana, BA – Brazil

Abstract

Cardio-oncology is a subspecialty of cardiology that has become necessary as a consequence of the favorable impact of cancer treatment, which increases patients' survival rates, but makes them more prone to the cardiovascular side effects of cancer therapies in the short and long term. The presence of predisposing factors such as pre-existing cardiovascular disease, cardiovascular risk factors, genetic predisposition, previous antineoplastic therapies, and increased patient age is associated with a higher risk of cardiotoxicity in cancer treatment and may aggravate its complications. The use of imaging methods is fundamental in the management and detection of complications in cancer treatment. Echocardiography is considered the standard method for assessing left ventricular function and should be used in all patients. Magnetic resonance imaging is the best alternative for evaluation in patients with other associated conditions, especially advanced coronary disease, and in cases where it is difficult to obtain adequate echocardiographic images. Nuclear medicine offers options for patients for whom the use of echocardiography and magnetic resonance imaging is limited and for patients whose clinical and laboratory assessments conflict. Judicious use of imaging techniques leads to better patient outcomes during cancer treatment.

Introduction

Cardio-oncology is a subspecialty of cardiology that has become necessary as a consequence of the favorable impact of cancer treatment, which increases patients' survival rates, but makes them more prone to the cardiovascular side effects of cancer therapies in the short and long term. The presence of predisposing factors such as pre-existing cardiovascular disease, cardiovascular risk factors, genetic predisposition, previous antineoplastic therapies, and increased patient age is associated with a higher risk of cardiotoxicity in cancer treatment and may aggravate its complications.[1-3] The new European Society of Cardiology guideline defines cancer therapy-related toxicity in different stages. The mildest form of involvement is identified by the presence of elevated cardiac biomarkers (such as cardiac troponin) and/or abnormalities in cardiac strain with preserved left ventricular ejection fraction (LVEF) in asymptomatic patients. Accordingly, it is possible to observe that, for the detection of abnormalities resulting from cancer treatment, it is necessary to continuously monitor symptoms, biomarkers, and changes in imaging tests. The correct understanding of the use of these methods and their applicability, advantages, disadvantages, and limitations is crucial for good outcomes in cancer treatment.[2,4,5]

Keywords

Heart Failure; Echocardiography; Computed Tomography; Magnetic Resonance; Scintigraphy; Cardiotoxicity

Mailing Address: Claudio Tinoco Mesquita •
R. Mario Santos Braga, 30. Postal Code 24020-140, Centro, Niterói, RJ – Brazil
E-mail: claudiotinocomesquita@id.uff.br
Manuscript received December 14, 2022, revised manuscript January 19, 2023, accepted January 19, 2023

DOI: https://doi.org/10.36660/abchf.20220087

General principles for using cardiovascular imaging methods in assessment of cardiotoxicity

There are fundamental points about the use of imaging methods in the assessment of cardiotoxicity. Firstly, clinical evaluation prior to the beginning of cancer treatment is important to identify and treat cardiovascular risk factors and pre-existing cardiovascular diseases. Based on this information, a strategy involving adequate prevention and monitoring of patients should be developed for early identification of potential complications of cancer treatment (Figure 1). In addition to monitoring complications during cancer treatment, a strategy should also be drawn up for long-term patient follow-up, as a significant number of complications may arise after an active phase of cancer treatment. The use of reproducible, easily accessible techniques that have expertise and local familiarity and that cause the least number of risks for the patient should be taken into account when defining which technique should be used in the follow-up of patients.[2,3,6]

Echocardiogram

Chemotherapy-related cardiotoxicity, despite the recent growing interest, was first described in 1967.[7] For analyzing patients who will begin treatment with potentially cardiotoxic drugs, an overvaluation of the ejection fraction as a criterion of chemotherapy-related cardiotoxicity has been observed. This leads to a loss of diagnostic accuracy, since, depending on the treatment performed, the target lesion is unique. Therefore, the first Brazilian position statement on the use of multimodal cardiovascular imaging considers cardiotoxicity as any injury

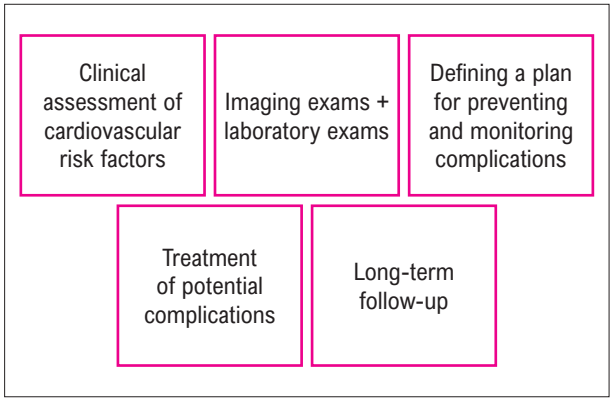

Figure 1 – *General principles for managing patients in cardio-oncology.*

to the cardiovascular system within a pathophysiological plausibility, which could range from pulmonary hypertension (desatinib), QT prolongation (arsenic trioxide), venous thrombosis (thalidomide), coronary disease (5-fluorouracil), myocarditis (checkpoint inhibitors), and others.[6]

The knowledge acquired in recent decades has allowed for changes in some important paradigms, including the classification of type I and type II cardiotoxicity. In the latter, the myocardial injury is said to be reversible (trastuzumab, for example), whereas, in the former, it is irreversible (anthracyclines). In 2010, Cardinale et al. demonstrated that, among patients with cardiotoxicity due to anthracyclines undergoing pharmacological intervention during the first 2 months, 64% had lesion reversibility.[8] Therefore, the aforementioned classification is in disuse. The first echocardiographic definition of chemotherapy-related cardiotoxicity in a clearer and more objective manner was proposed in 2014, described as an absolute drop in LVEF by 10 percentage points to values below 53%, assessed by the modified Simpson's biplane method, for example, a reduction of LVEF from 61% to 50%. Reassessment of LVEF after 2 to 3 weeks is recommended.[4] The rationale for recommending this reassessment is associated with two main points: a) the intrinsic temporal variability of the method, which can vary by up to 10 percentage points using the 2-dimensional technique;[5] b) the clinical conditions of patients with cancer, who usually present great variability of left ventricular (LV) preload and afterload, for example, dehydration, tachycardia, polypharmacy, anemia, infections, surgeries, diarrhea, vomiting, bleeding, exacerbated inflammatory response, etc. Accordingly, an attempt is made to minimize the effects of method variability. There is a concept that every systolic dysfunction presents associated diastolic dysfunction and that this precedes the reduced ejection fraction, mainly due to the pathophysiological model of the ischemia cascade. However, to the surprise of imaging specialists, the use of diastolic classification to assess cardiotoxicity according to the latest guideline of the American Society of Echocardiography remains controversial to this day, probably due to the clinical dynamics of these patients, in which there is constant lability of LV preload and afterload during treatment, as mentioned above.[9] Recently, in a cohort with breast cancer, it was demonstrated that a persistent change or worsening of diastolic dysfunction had little association with the subsequent risk of developing systolic dysfunction.[10] In 1998, the clinical application of myocardial strain analysis was demonstrated for the first time.[11] Only after the first decade of the 2000s, the first studies supported the use of LV global strain as a tool capable of diagnosing subclinical myocardial injury and predicting a drop in LVEF.[12,13] The CECCY Trial demonstrated that the use of beta-blockers to prevent cardiotoxicity was associated with an incidence of cardiotoxicity of 13.5% to 14.5%. Although carvedilol did not lead to a reduction in the early incidence of reduced LVEF, there was a significant reduction in troponin levels and in diastolic dysfunction.[14] On the other hand, in the first randomized, multicenter study evaluating the clinical impact of guiding therapy by 2-dimensional longitudinal strain in one arm and by the drop in ejection fraction using the 3-dimensional method in the other (SUCCOUR Trial), the patients who were treated in the strain arm had more pharmacological intervention and higher ejection fraction at the end of the study.[12]

In the Brazilian context of positions and guidelines, we have the Second Brazilian Guidelines on Cardio-oncology[6] and the First Brazilian Position Statement on the Use of Multimodal Imaging in Cardio-oncology.[2] Both documents agree on the criteria for follow-up during chemotherapy; they differ, however, on the cutoff point for subclinical cardiotoxicity. The guideline maintained the 15% relative drop in LV global longitudinal strain, while the position statement adopted a cutoff point of 12%, in line with the SUCCOUR Trial, given that it is the most robust study to evaluate the impact of drug intervention guided by the decrease in strain. The critical analysis of these documents is part of the burden of clinical individualization, which translates into cardio-oncology in more cardiotoxic chemotherapy treatment. In other words, if anthracyclines are being used, the image monitoring periods will be guided by that class of medication; if tyrosine kinase inhibitors are used, this class will guide monitoring. Until the publication of these 2 documents, echocardiogram was recommended before treatment and every 3 months in most classes of chemotherapy, with the exception of anthracyclines, with the subsequent echocardiograms at 2 months, 6 months, 1 year, and then annually. It may be performed earlier if the total dose of doxorubicin exceeds 240 mg/m^2, and it is recommended to repeat the echocardiogram at each 50 mg/m^2 increment in the total cumulative dose. Another situation where there is no clarity is monitoring during the use of checkpoint inhibitors. To date, no study has been able to demonstrate the role of echocardiography in predicting cardiotoxicity or myocarditis in this class. In this context, when facing suspicion, it is strongly recommended to perform cardiac resonance. Over the past years, another form of toxicity has been noticed, namely, the excess of imaging tests without clinical impact, especially in patients at a low risk for cardiotoxicity (young patients, no cardiovascular risk factors, low doses of anthracyclines, absence of radiotherapy). In 2022, the European Society of Cardiology published the update to its cardio-oncology guideline.[3] In this document, there is a change of perspective on monitoring patients with cancer who are exposed to chemotherapy. Instead of monitoring according

to the cardiotoxic agent, the recommendation is to monitor through clinical stratification using the HFA-ICOS score, which classifies the risks of cardiotoxicity as low, moderate, high, and very high. Only patients with high/very high risk should be referred to a cardiologist (class I) before starting treatment. Regarding systematic and serial echocardiograms, there has been a change in the performance of the exam, based on clinical stratification, with a baseline echocardiogram being recommended before the start of chemotherapy in all patients. However, serial performance throughout treatment will be guided by the patients' stratification according to the HFA-ICOS score. This rationale is extremely consistent from a clinical and cost-effectiveness point of view. On the other hand, the practicality of using it in daily clinical practice has become challenging, due to the uniqueness of each cancer treatment and each patient's risk stratification (Table 1). This European update has brought an interesting severity classification, considering the patient's functional status or the echocardiogram imaging data in asymptomatic patients.

This classification is important not only for prognostic stratification, but also for guiding therapy, which differentiates it from previous documents that did not categorize asymptomatic and symptomatic patients.

The incorporation of new technologies for monitoring cancer therapy-related cardiotoxicity, such as longitudinal global strain, allows for subclinical detection and more accurate monitoring during cardioprotective intervention (Figure 2).

Finally, although several studies have demonstrated that the assessment of LVEF by 3-dimensional echocardiography is quite robust, with values approaching the gold standard of cardiac volumetry (magnetic resonance imaging of the heart),[15] there is no demonstration of the superiority of monitoring cardiotoxicity using 3-dimensional LVEF in relation to the technique of LV global longitudinal strain.[16-18] Nevertheless, we must adopt a critical view of the subject, since cardio-oncology is a relatively recent science. In the other clinical scenarios, the assessment of LVEF using the 3-dimensional technique is a more accurate tool when available. Therefore, we must use as much information as we have available, always combining it with clinical rationale, seeking to improve the survival of these patients, mitigating risks and morbidities.

Table 1 – Cancer therapy-related cardiotoxicity

Symptomatic (HF)	Mild	Patient with mild symptoms, without worsening during cancer treatment
	Moderate	Outpatient requiring diuretic therapy and HF medication
	Severe	Hospitalized patient
	Very severe	Patient requiring inotropic agents or mechanical circulatory support; or under assessment for heart transplantation
Asymptomatic	Mild	Ejection fraction ≥ 50% and new relative drop by more than 15% in LV global longitudinal strain; and/or increase in myocardial injury biomarkers
	Moderate	New drop in ejection fraction to values between 40% and 49%, associated or not with elevated biomarkers and decreased LV global longitudinal strain
	Important	New drop in ejection fraction to values below 40%

HF: heart failure, LV: left ventricle; biomarkers: troponin. Adapted table.[3]

Nuclear cardiology

a) Radionuclide ventriculography in the monitoring of ventricular dysfunction

At the basis of cardio-oncology, the use of nuclear medicine has been one of the structuring forms of the ventricular function assessment protocol. Schwartz et al. used radionuclide ventriculography (often known as multigated acquisition or MUGA) to monitor patients treated with doxorubicin to detect small changes in LV function, in order to avoid elevated doses of doxorubicin and thus prevent significant cardiomyopathy.[19] In a pioneering manner, they demonstrated that the routine use of radionuclide ventriculography was associated with a reduced incidence of clinical heart failure to 2.8%, compared to 20.8% in patients receiving standard care without imaging.[19] Since then, the assessment of ventricular function has been routinely performed in patients treated with anthracyclines, and radionuclide ventriculography is now part of the assessment in a diverse range of patients. For its best use, it is necessary to understand its operational characteristics. The main advantages of radionuclide ventriculography are great intra- and inter-observer reproducibility, semi-automatic processing, widely available performance in nuclear medicine services, accuracy, little dependence on the operator, and the absence of contraindications related to renal dysfunction or allergy. The limitations to radionuclide ventriculography include the use of radiation (especially due to its repeated use) and the fact that the assessment of ventricular function is not accompanied by a structural analysis of the heart, the pericardium, the valves, or the state of the myocardium, as in magnetic resonance imaging.[1,20] It is important to emphasize the fact that the LVEF values obtained by echocardiogram are not consistent with those from radionuclide ventriculography. Some authors found that echocardiogram provides higher LVEF values than radionuclide ventriculography, which could lead echocardiogram to underestimate cardiotoxicity. It is very important to be aware of the specificities of imaging methods and be familiar with them for proper use.[21] In general, radionuclide ventriculography is best used in the following situations: when LVEF values on the echocardiogram are difficult to obtain (poor acoustic window); when LVEF values conflict with other results of clinical or laboratory tests or with clinical evaluation, as radionuclide ventriculography is more accurate and less dependent on operator proficiency; and when the LVEF value obtained by echocardiogram will lead to a significant change in the cancer treatment, such as interruption of a first-line cancer drug, in order to confirm the need for a change in strategy.[1,3,20,22]

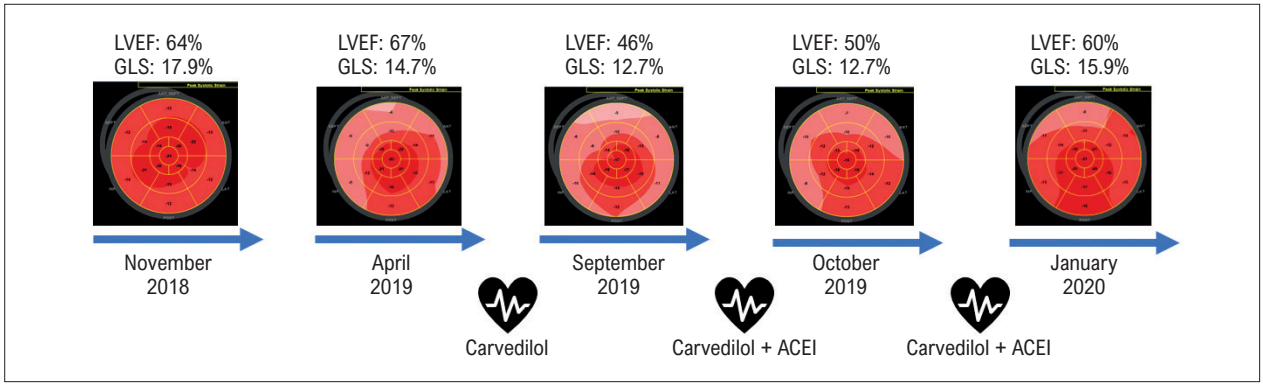

Figure 2 – *A 67-year-old patient with inoperable abdominal leiomyosarcoma who used docetaxel with gemcitabine as first line, then doxorubicin with dacarbazine, and currently using ifosfamide. In April 2019, she was asymptomatic, and a beta-blocker was prescribed due to subclinical cardiotoxicity (drop in global longitudinal strain greater than 15%), but the patient did not use the medication, returning 5 months later with heart failure and reduced ejection fraction. At that time, the patient was medicated with enalapril and carvedilol, evolving with clinical and echocardiographic improvement. ACEI: angiotensin-converting enzyme inhibitor; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction.*

Figure 3 shows the example of a patient whose echocardiogram showed doubtful LVEF values making radionuclide ventriculography necessary to define management.

b) 123I-MIBG scintigraphy in the detection of cardiotoxicity

Changes in LV contractility function are relatively late in the cascade of damage secondary to cancer treatment. Earlier means of detecting cardiotoxicity have been proposed, such as the use of hyperstimulation of the adrenergic system, which is secondary to ventricular damage caused by antineoplastic agents. The tracer 123-iodine metaiodobenzylguanidine (MIBG) has demonstrated value in identifying patients with hyperstimulation of the adrenergic system and who are at increased risk of adverse events when suffering from heart failure with reduced LVEF.[23] An experimental study demonstrated that, after treatment with doxorubicin, cardiac 123I-MIBG uptake was significantly reduced 2 weeks later, followed by a decrease in LV end-diastolic volume and increased 18F-FDG uptake at 4 weeks, and, finally, by an increase in LV end-systolic volume and a decrease in LVEF at 6 weeks. Imaging of cardiac innervation is, thus, the earliest marker of anthracycline cardiotoxicity.[24] In Brazil, Guimarães et al. demonstrated that, in women with breast cancer undergoing chemotherapy, the evaluation of cardiac sympathetic activity with 123I-MIBG was an early marker of cardiotoxicity.[25] These data were recently reinforced by a systematic review with 12 studies using 123I-MIBG that indicated the value of the technique as an earlier method than echocardiogram in detecting cardiotoxicity; however, due to the methodological variability of the studies, further studies are recommended to confirm these findings.[26]

c) 18F-FDG PET CT in the assessment of cardiotoxicity

Increased myocardial uptake of 18-fluorine fluorodeoxyglucose (18F-FDG) appears to be a marker of early myocardial damage in cancer therapy. Experimental studies using radiotherapy in the cardiac area have shown that high uptake of FDG in an irradiated field appears to be related to myocardial damage in the microcirculation associated with mitochondrial damage.[27] Positron emission tomography (PET) with 18F-FDG is mentioned in the cardio-oncology position statement of the Brazilian Society of Cardiology as a means of diagnosing cardiotoxicity induced by immune checkpoint inhibitors, since it makes it possible to detect, evaluate the extent, and even quantify the inflammatory process of multiple cardiovascular conditions, such as myocarditis, pericarditis, and vasculitis.[28] Figure 4 displays how the main applications of nuclear medicine in cancer-related cardiotoxicity have expanded beyond the assessment of LV function.[29]

Cardiac magnetic resonance imaging

The improvement of cardiac magnetic resonance imaging techniques and the increasingly available access have expanded the role of cardiac magnetic resonance imaging into cardio-oncology. Recently, myocardial strain imaging and native T1 and T2 mapping have offered information beyond the quantification of ejection fraction, improving early detection of cardiotoxicity and predicting cardiac dysfunction without the use of contrast and radiation exposure.

Echocardiography is the first-line approach in the initial assessment of cardiac function, in the risk stratification of pre-existing cardiovascular disease, and in the imaging surveillance of cardiotoxicity during cancer treatment.[3,6] In some situations, echocardiographic evaluation is a challenge, for instance, in patients undergoing treatment for breast cancer who have breast implants, or in patients who have already undergone pulmonary lobectomy due to lung cancer with consequent displacement of the heart (Figure 5), making echocardiographic assessment difficult or even impossible.

In patients with a limited echocardiographic window or with doubtful echocardiographic findings, cardiac magnetic resonance imaging is recommended, and it is able to add important information to stress imaging in the risk stratification of coronary disease and in the suspicion of acute myocarditis related to cardiotoxicity.[3]

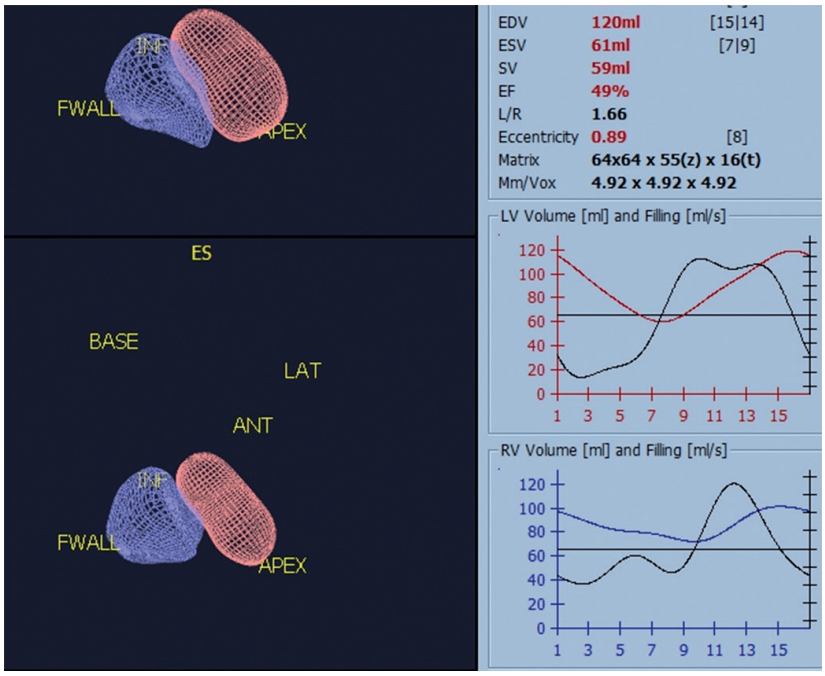

Figure 3 – *A 52-year-old patient undergoing treatment for breast cancer with doxorubicin and trastuzumab. After the second cycle, the echocardiogram showed a worsening of the left ventricular ejection fraction from 67% to 45%. Radionuclide ventriculography confirmed that left ventricular ejection fraction had dropped to less than 50% (49%), leading to temporary suspension of trastuzumab.*

a) Magnetic resonance imaging in the detection of early myocardial damage

Waiting for LVEF to drop during cancer treatment may imply irreversible cardiovascular damage and it may be too late for protective measures. The alteration of regional myocardial deformation occurs before myocardial dysfunction in these patients.[2,3]

Accordingly, the use of myocardial strain by cardiac magnetic resonance imaging has shown to be an effective tool not only in the early detection of cardiotoxicity, before the reduction of the ejection fraction, but also a tool capable of identifying patients at risk of developing cardiotoxicity and those with chances of recovery after established cardiotoxicity.

In a longitudinal study of cardiac magnetic resonance imaging, Giusca et al. used fast strain encoded magnetic resonance (fast-SENC) to demonstrate that the percentage of normal myocardium, defined as the number of segments with circumferential and longitudinal strain ≤ −17% divided by 37 (total of segments considered), between 60% and 80% identified patients at risk of developing clinical or subclinical cardiotoxicity, and that early cardioprotective therapies assist in ventricular recovery. On the other hand, patients with a percentage of normal myocardium ≤ 55% had a high risk of cardiotoxicity and a low chance of recovery.[18]

Myocardial deformation by cardiac magnetic resonance imaging can also be calculated using post-processing software (feature tracking) from cine images acquired in the standard protocol, even if the specific sequence of myocardial strain has not been performed. Nevertheless, cine images have lower spatial and temporal resolution for strain calculation by feature tracking than echocardiography using speckle tracking.[13]

b) Magnetic resonance imaging in cardiotoxicity monitoring

The risk of cardiovascular toxicity should be assessed in all patients before initiating cancer treatment to identify individuals with pre-existing cardiovascular disease or multiple risk factors, thus considering prevention strategies, guiding appropriate cancer treatment in high-risk patients, and ultimately mitigating the risk of myocardial injury and heart failure.[1]

The risk of coronary artery disease should be assessed by conventional risk scores, and cardiac magnetic resonance imaging is a good option for cardiovascular stratification with stress perfusion imaging and delayed gadolinium enhancement. Furthermore, cardiac magnetic resonance imaging is the gold standard for measuring left and right ventricular ejection fraction, volumes, and mass. Its ability to detect small changes with low operator dependence may represent early changes in treatment strategy and the initiation of protective measures, thus reducing myocardial injury.[30]

Recent data about damage to the right ventricle related to anticancer therapy have also shown the involvement of this chamber, similar to what occurs with the LV. Corroborating these findings, Souza et al. found a decrease in the right ventricular ejection fraction, an increase in diffuse interstitial

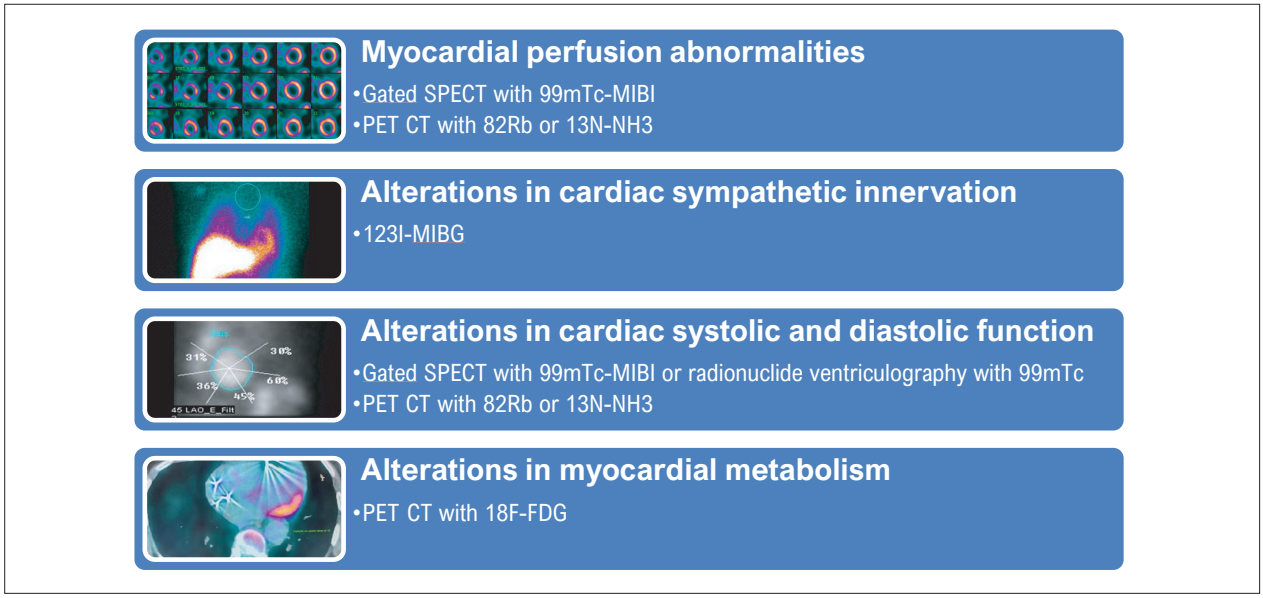

Figure 4 – *Main applications of nuclear medicine in the detection and monitoring of cancer therapy-related cardiotoxicity. 23I-MIBG: 123-iodine metaiodobenzylguanidine; 18F-FDG: 18-fluorine fluorodeoxyglucose; MIBI: sestamibi; NH3: ammonia; PET CT: positron emission tomography coupled with computed tomography; Rb: rubidium; SPECT: single-photon emission computed tomography; Tc: technetium. Adopted from Mesquita et al.*[29]

fibrosis, and a decrease in myocardial mass in 27 women undergoing treatment for breast cancer with anthracyclines, changes similar to those found in the LV.[31]

Conventional sequences of cardiac magnetic resonance imaging during the monitoring of patients undergoing cancer treatment add important information associated with cardiotoxicity or cancer-related complications. Acute pericarditis secondary to chemotherapy or mediastinal radiotherapy, or even involvement of the pericardium due to infiltration or metastatic spread, can be diagnosed with the combination of anatomical dark blood sequences, delayed enhancement, and cine imaging. Real-time cine sequences with free breathing and tagging provide additional information in cases of evolution to constrictive pericarditis.[32]

Although rare, immune checkpoint inhibitor-related myocarditis may be increasingly present in clinical practice due to the increasing use of immunotherapy in the treatment of cancer, and cardiac magnetic resonance imaging is particularly important in this scenario, as it is a non-invasive and accurate diagnostic tool. Parametric maps, although not included in the Lake Louise criteria,[33] when incorporated, have shown an evident gain in diagnostic accuracy, especially in the context of immune checkpoint inhibitor-related myocarditis.[34]

c) New magnetic resonance techniques for detecting cardiotoxicity

Tissue characterization by cardiac magnetic resonance imaging is a promising tool for early identification of cardiotoxicity. Consistent data have shown that edema, inflammation, and extracellular volume expansion occur before myocardial dysfunction in these patients.[30] Increased signal intensity in the myocardium on T2-weighted sequences reveals areas with increased water content that represent myocardial edema. Nonetheless, conventional imaging has some important limitations related to motion artifacts and bright subendocardial rims due to stagnant blood. In contrast, myocardial T2 mapping does not have these limitations and improves edema detection. Some studies have proposed the use of T2 mapping to identify myocardial edema as the first alteration caused by damage to the myocardium related to cardiotoxicity.

Galan-Arriola et al. correlated histopathological findings of doxorubicin-induced myocardial injury with T1 and T2 mapping, quantification of extracellular volume, and LVEF in an animal model. Cardiac magnetic resonance imaging was performed weekly before, during, and after anthracycline treatment, and T2 mapping showed changes prior to T1 mapping, extracellular volume, and LVEF. The histological correlation detected intracardiomyocyte edema without any other evident alteration in the structure of the myocardial tissue, and after suspension of the anthracycline there was no development of clinical or histological alterations.[35]

However, studies in humans have failed to demonstrate the significant role of T2 values in the context of cardiotoxicity. Tahir et al. studied changes in T1 and T2 mapping and myocardial strain in humans in the early detection of cardiotoxicity and found that T1 mapping was better able to detect cardiotoxicity than T2 mapping. The authors believe that this difference is due to the fact that they performed the control cardiac magnetic resonance imaging later and less frequently than Galan-Arriola et al. Therefore, T2 would be smaller or already normalized, while T1 would still be high.[35] This could explain why T1 mapping has a stronger data correlation with cardiotoxicity than T2 mapping.

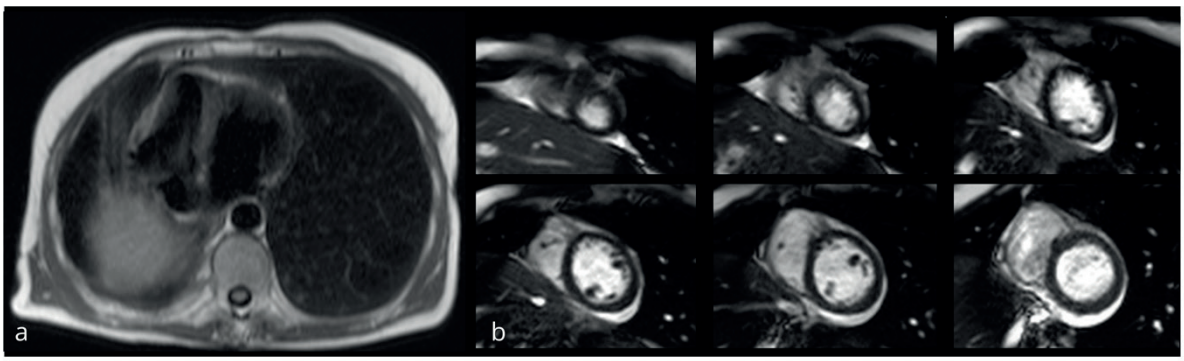

Figure 5 – *A 62-year-old woman with a history of right lower lobectomy due to lung cancer presenting with cardiac arrhythmias. The accentuated displacement of the heart to the right hemithorax seen by locating the chest axial sequence (in a) made echocardiographic evaluation impossible, but there was no limitation to evaluation by cardiac magnetic resonance imaging. In b, cine imaging of the short axis of the heart.*

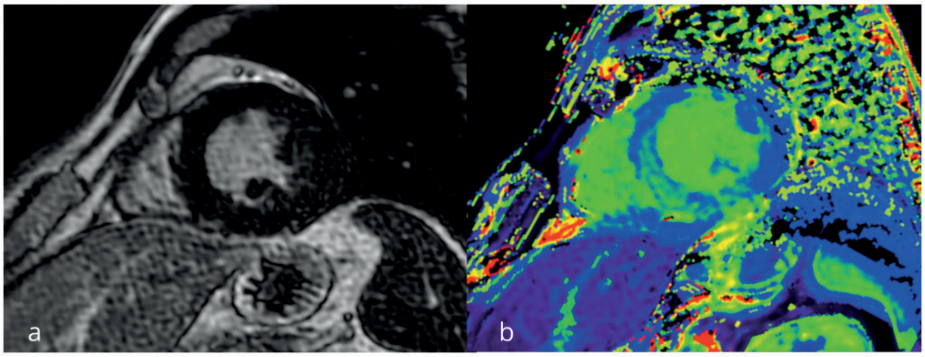

Figure 6 – *Delayed enhancement image without evidence of myocardial fibrosis (in a), but with increased native T1 (in b), in a 53-year-old man undergoing treatment for Hodgkin's lymphoma with doxorubicin, bleomycin, vinblastine, and dacarbazine, in addition to radiotherapy.*

Native T1 sequence identifies focal and/or diffuse myocardial lesion, without the use of contrast, before it can be detected by late gadolinium enhancement.[36] In addition, post-contrast T1 mapping offers the added benefit of quantifying extracellular volume already validated for fibrosis measurement. Considering the diffuse pattern of fibrosis most commonly found in this context, T1 mapping and calculation of extracellular volume are better predictors of the presence of fibrosis than delayed enhancement, seeing that focal fibrosis was detected by delayed enhancement in only 6% of patients treated with anthracycline-based chemotherapy (Figure 6).[37]

Multiple studies have demonstrated the potential of myocardial T1 and T2 mapping and calculation of extracellular volume in the early detection of cardiotoxicity.[18,30,34,36,37] However, the great heterogeneity between acquisition sequences, varying even between manufacturers, limit their use in clinical practice, especially in longitudinal comparison of patients. For patients in monitoring for cardiotoxicity, always performing follow-up with the same type of sequence and respecting the same acquisition parameters can mitigate these limitations.[38]

Conclusion

The care of patients with cancer has evolved substantially in the past decades with the majority of patients surviving the initial treatment. The management of patients with cancer involves planning strategies to monitor the potential complications of this treatment, especially in patients who already have cardiovascular risk factors or manifest cardiovascular diseases. Many cancer treatment survivors will experience various problems related to cancer and the treatment thereof, as well as late effects throughout their lives. Therefore, it is crucial to use reliable techniques to monitor ventricular function for successful treatment, thus ensuring adequate life expectancy and quality of life.

Author Contributions

Conception and design of the research; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Mesquita CT, Melo MDT, Leal ABP, Almeida ALC.

Potential conflict of interest

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

Sources of funding

This study was partially funded by CNPq and FAPERJ.

Study association

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

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. Totzeck M, Aide N, Bauersachs J, Bucerius J, Georgoulias P, Herrmann K, et al. Nuclear Medicine in the Assessment and Prevention of Cancer Therapy-Related Cardiotoxicity: Prospects and Proposal of Use By the European Association of Nuclear Medicine (EANM). Eur J Nucl Med Mol Imaging. 2023;50(3):792-812. doi: 10.1007/s00259-022-05991-7.
2. 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.
3. 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 the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-361. doi: 10.1093/eurheartj/ehac244.
4. 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. Eur Heart J Cardiovasc Imaging. 2014;15(10):1063-93. doi: 10.1093/ehjci/jeu192.
5. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early Detection and Prediction of Cardiotoxicity in Chemotherapy-Treated Patients. Am J Cardiol. 2011;107(9):1375-80. doi: 10.1016/j.amjcard.2011.01.006.
6. Hajjar LA, Costa IBSDSD, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Brazilian Cardio-Oncology Guideline - 2020. Arq Bras Cardiol. 2020;115(5):1006-43. doi: 10.36660/abc.20201006.
7. Tan C, Tasaka H, Yu KP, Murphy ML, Karnofsky DA. Daunomycin, an Antitumor Antibiotic, in the Treatment of Neoplastic Disease. Clinical Evaluation with Special Reference to Childhood Leukemia. Cancer. 1967;20(3):333-53. doi: 10.1002/1097-0142(1967)20:3<333::aid-cncr2820200302>3.0.co;2-k.
8. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-Induced Cardiomyopathy: Clinical Relevance and Response to Pharmacologic Therapy. J Am Coll Cardiol. 2010;55(3):213-20. doi: 10.1016/j.jacc.2009.03.095.
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314. doi: 10.1016/j.echo.2016.01.011.
10. Upshaw JN, Finkelman B, Hubbard RA, Smith AM, Narayan HK, Arndt L, et al. Comprehensive Assessment of Changes in Left Ventricular Diastolic Function With Contemporary Breast Cancer Therapy. JACC Cardiovasc Imaging. 2020;13(1 Pt 2):198-210. doi: 10.1016/j.jcmg.2019.07.018.
11. Heimdal A, Støylen A, Torp H, Skjaerpe T. Real-Time Strain Rate Imaging of the Left Ventricle by Ultrasound. J Am Soc Echocardiogr. 1998;11(11):1013-9. doi: 10.1016/s0894-7317(98)70151-8.
12. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021;77(4):392-401. doi: 10.1016/j.jacc.2020.11.020.
13. Amzulescu MS, De Craene M, Langet H, Pasquet A, Vancraeynest D, Pouleur AC, et al. Myocardial Strain Imaging: Review of General Principles, Validation, and Sources of Discrepancies. Eur Heart J Cardiovasc Imaging. 2019;20(6):605-19. doi: 10.1093/ehjci/jez041.
14. Avila MS, Ayub-Ferreira SM, Wanderley MRB Jr, Cruz FD, Brandão SMG, Rigaud VOC, et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. J Am Coll Cardiol. 2018;71(20):2281-90. doi: 10.1016/j.jacc.2018.02.049.
15. Bottinor W, Trankle CR, Hundley WG. The Role of Cardiovascular MRI in Cardio-Oncology. Heart Fail Clin. 2021;17(1):121-33. doi: 10.1016/j.hfc.2020.08.009.
16. Burrage MK, Ferreira VM. The Use of Cardiovascular Magnetic Resonance as an Early Non-Invasive Biomarker for Cardiotoxicity in Cardio-Oncology. Cardiovasc Diagn Ther. 2020;10(3):610-24. doi: 10.21037/cdt-20-165.
17. Takeuchi M, Nishikage T, Mor-Avi V, Sugeng L, Weinert L, Nakai H, et al. Measurement of Left Ventricular Mass by Real-Time Three-Dimensional Echocardiography: Validation Against Magnetic Resonance and Comparison with Two-Dimensional and M-Mode Measurements. J Am Soc Echocardiogr. 2008;21(9):1001-5. doi: 10.1016/j.echo.2008.07.008.
18. Giusca S, Korosoglou G, Montenbruck M, Geršak B, Schwarz AK, Esch S, et al. Multiparametric Early Detection and Prediction of Cardiotoxicity Using Myocardial Strain, T1 and T2 Mapping, and Biochemical Markers: A Longitudinal Cardiac Resonance Imaging Study During 2 Years of Follow-Up. Circ Cardiovasc Imaging. 2021;14(6):e012459. doi: 10.1161/CIRCIMAGING.121.012459.
19. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, et al. Congestive Heart Failure and Left Ventricular Dysfunction Complicating Doxorubicin Therapy. Seven-year Experience Using Serial Radionuclide Angiocardiography. Am J Med. 1987;82(6):1109-18. doi: 10.1016/0002-9343(87)90212-9.
20. Kahanda MG, Hanson CA, Patterson B, Bourque JM. Nuclear Cardio-Oncology: From its Foundation to its Future. J Nucl Cardiol. 2020;27(2):511-8. doi: 10.1007/s12350-019-01655-6.
21. Fatima N, Zaman MU, Hashmi A, Kamal S, Hameed A. Assessing Adriamycin-Induced Early Cardiotoxicity by Estimating Left Ventricular Ejection Fraction Using Technetium-99m Multiple-Gated Acquisition Scan and Echocardiography. Nucl Med Commun. 2011;32(5):381-5. doi: 10.1097/MNM.0b013e328343ceb9.
22. 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.
23. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial Iodine-123 Meta-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure. Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55(20):2212-21. doi: 10.1016/j.jacc.2010.01.014.
24. Oudot A, Courteau A, Guillemin M, Vrigneaud JM, Walker PM, Brunotte F, et al. [123I]MIBG is a Better Early Marker of Anthracycline Cardiotoxicity Than [18F]FDG: A Preclinical SPECT/CT and Simultaneous PET/MR Study. EJNMMI Res. 2021;11(1):92. doi: 10.1186/s13550-021-00835-1.

25. Guimarães SL, Brandão SC, Andrade LR, Maia RJ, Markman B Filho. Cardiac Sympathetic Hyperactivity after Chemotherapy: Early Sign of Cardiotoxicity? Arq Bras Cardiol. 2015;105(3):228-34. doi: 10.5935/abc.20150075.

26. Arrais TR, Cavalli GD, Santos BT, Pereira GB, Migliavaca CB, Grossman GB, et al. MIBG Cardiac Imaging Compared to Ejection Fraction in Evaluation of Cardiotoxicity: A Systematic Review. J Nucl Cardiol. 2022;29(5):2274-91. doi: 10.1007/s12350-021-02610-0.

27. Yan R, Song J, Wu Z, Guo M, Liu J, Li J, et al. Detection of Myocardial Metabolic Abnormalities by 18F-FDG PET/CT and Corresponding Pathological Changes in Beagles with Local Heart Irradiation. Korean J Radiol. 2015;16(4):919-28. doi: 10.3348/kjr.2015.16.4.919.

28. 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.

29. Mesquita CT, Rezende MF. Precision Medicine: Can 18F-FDG PET Detect Cardiotoxicity Phenotypes? Arq Bras Cardiol. 2022;119(1):109-110. doi: 10.36660/abc.20220393.

30. Tahir E, Azar M, Shihada S, Seiffert K, Goy Y, Beitzen-Heineke A, et al. Myocardial Injury Detected by T1 and T2 Mapping on CMR Predicts Subsequent Cancer Therapy-Related Cardiac Dysfunction in Patients with Breast Cancer Treated by Epirubicin-Based Chemotherapy or Left-Sided RT. Eur Radiol. 2022;32(3):1853-65. doi: 10.1007/s00330-021-08260-7.

31. Souza TF, Silva TQ, Antunes-Correa L, Drobni ZD, Costa FO, Dertkigil SSJ, et al. Cardiac Magnetic Resonance Assessment of Right Ventricular Remodeling after Anthracycline Therapy. Sci Rep. 2021;11(1):17132. doi: 10.1038/s41598-021-96630-y.

32. Saunderson CED, Plein S, Manisty CH. Role of Cardiovascular Magnetic Resonance Imaging in Cardio-Oncology. Eur Heart J Cardiovasc Imaging. 2021;22(4):383-96. doi: 10.1093/ehjci/jeaa345.

33. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009;53(17):1475-87. doi: 10.1016/j.jacc.2009.02.007.

34. Thavendiranathan P, Zhang L, Zafar A, Drobni ZD, Mahmood SS, Cabral M, et al. Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients with Immune Checkpoint Inhibitor-Associated Myocarditis. J Am Coll Cardiol. 2021;77(12):1503-16. doi: 10.1016/j.jacc.2021.01.050.

35. Galán-Arriola C, Lobo M, Vílchez-Tschischke JP, López GJ, Molina-Iracheta A, Pérez-Martínez C, et al. Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity. J Am Coll Cardiol. 2019;73(7):779-91. doi: 10.1016/j.jacc.2018.11.046.

36. Muehlberg F, Funk S, Zange L, von Knobelsdorff-Brenkenhoff F, Blaszczyk E, Schulz A, et al. Native Myocardial T1 Time can Predict Development of Subsequent Anthracycline-Induced Cardiomyopathy. ESC Heart Fail. 2018;5(4):620-29. doi: 10.1002/ehf2.12277.

37. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Ntusi N, et al. T(1) Mapping for the Diagnosis of Acute Myocarditis Using CMR: Comparison to T2-Weighted and late Gadolinium Enhanced Imaging. JACC Cardiovasc Imaging. 2013;6(10):1048-58. doi: 10.1016/j.jcmg.2013.03.008.

38. Fernandesv JL. Cardiac Magnetic Resonance Imaging Perspectives - T1 and T2 Maps: Fundamentals and Clinical Utility. Arq Bras Cardiol: Imagem cardiovasc. 2015;28(3):175-184. doi: 10.5935/2318-8219.20150021.