**Name of journal: World Journal of Radiology**

**ESPS Manuscript NO: 9641**

**Columns: Minireviews**

**Nuclear imaging in detection and monitoring of cardiotoxicity**

D’Amore C *et al*. Nuclear imaging and cardiotoxicity

Carmen D’Amore, Paola Gargiulo, Stefania Paolillo, Angela Maria Pellegrino, Tiziana Formisano, Antonio Mariniello, Giuseppe Della Ratta, Elisabetta Iardino, Marianna D’Amato, Lucia La Mura, Irma Fabiani, Flavia Fusco, Pasquale Perrone Filardi

**Carmen D’Amore, Stefania Paolillo, Angela Maria Pellegrino, Tiziana Formisano, Antonio Mariniello, Giuseppe Della Ratta, Elisabetta Iardino, Marianna D’Amato, Lucia La Mura, Irma Fabiani, Flavia Fusco, Pasquale Perrone Filardi,** Department of Advanced Biomedical Sciences, Federico II University, 80131 Naples, Italy

**Paola Gargiulo,** SDN Foundation, Institute of Diagnostic and Nuclear Development, 80129 Naples, Italy

**Author contributions**: D’Amore C and Gargiulo P contributed to this work, generated the tables and wrote the manuscript; Paollillo S, Pellegrino AM, Formisano T and Mariniello A contributed to the writing of the manuscript; Della RattaG, IardinoE, D’AmatoM, La MuraL, FabianiI and FuscoF contributed to med-line; and Perrone FilardiP reviewed the manuscript.

**Correspondence to: Pasquale Perrone Filardi, MD, PhD,** Department of Advanced Biomedical Sciences, Federico II University, Via Pansini, 5, 80131, Naples, Italy. [fpperron@unina.it](mailto:fpperron@unina.it)

**Telephone:** +39-081-7462224 **Fax:** +39-081-7462224

**Received:** February 21, 2014 **Revised:** April 21, 2014

**Accepted:** May 29, 2014

**Published online:**

**Abstract**

Cardiotoxicity due to cancer treatment is a novel and a serious public health issue that has a significant impact on cancer patient’s management and outcome. The coexistence of cancer and cardiac disease in the same patients is more common due to the aging population and improvement of antitumor agents effectiveness. Left ventricular dysfunction is the most typical manifestation and can lead to heart failure. Left ventricular ejection fraction measurement by echocardiography and multigated radionuclide angiography is the most common diagnostic approach to detect cardiac damage, but it identifies a late manifestation of myocardial injury. Early non-invasive imaging techniques are needed to the diagnosis and monitoring of cardiotoxic effects. Although echocardiography and cardiac magnetic resonance are the most commonly used imaging techniques for cardiotoxicity assessment, greater attention is focused on new nuclear cardiologic techniques, which identify high-risk patients in the early stage visualizing pathophysiologic process at the tissue level before the clinical manifestation. The aim of this review is to summarize the role of nuclear imaging techniques in the non-invasive detection of myocardial damage related to antineoplastic therapy at reversible stage, focusing on the current role and future perspectives of nuclear imaging techniques and molecular radiotracers in detection and monitoring of cardiotoxicity.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Cardiotoxicity; Cardiac nuclear imaging; Early diagnosis; Scintigraphy; Positron emission tomography

**Core tip:** Cardiomyopathy is a potential complication of various anticancer drugs, like anthracyclines and biological therapy. Left ventricular dysfunction is the most common manifestation of cardiotoxicity and it is monitored with left ventricular ejection fraction measurement, but it is a late manifestation of myocardial injury. So, the cardiologist and oncologist should collaborate to identify new non-invasive techniques to detect cardiac dysfunction at the early and potentially reversible stage, before the onset of clinical manifestation. To achieve this aim, nuclear imaging technique may offer good future perspectives to early detection of myocardial damage using novel molecular tracers.

D’Amore C, Gargiulo P, Paolillo S, Pellegrino AM, Formisano T, Mariniello A, Della Ratta G, Iardino E, D’Amato M, La Mura L, Fabiani I, Fusco F, Perrone Filardi P. Nuclear imaging in detection and monitoring of cardiotoxicity. *World J Radiol* 2014; In press

**Available from:**

**DOI:**

**INTRODUCTION**

Over the last decades, early diagnosis and development of new antitumor agents have significantly improved the survival of cancer patients. However, conventional and new oncologic drugs can frequently have a wide range of cardiac adverse effects, in particular myocardial toxicity. Anthracyclines (doxorubicin, epirubicin), cyclophosphamide, monoclonal antibodies (trastuzumab) and other tyrosine kinase inhibitors (TKIs) are antineoplastic drugs more frequently associated with cardiotoxicity[1]. These drugs may cause irreversible damage, like that induced by anthracyclines, through free radicals production, adrenergic function alteration and cardiac myocytes death for calcium overload[2,3], or potential complete reversible dysfunction, like that related to TKIs administration[4].

Left ventricular (LV) dysfunction is the most typical manifestation of cardiotoxicity and it contributes to increased mortality during chemotherapy[5]. Cardiotoxicity has been defined by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials[6] as characterized by: (1) decrease in cardiac LV ejection fraction (EF), either global or more severe in septum; (2) onset of symptoms associated with congestive heart failure (HF); (3) presence of signs associated with congestive HF; and (4) reduction in LVEF from baseline of at least 5% to below 55% with signs and symptoms of congestive HF, or a decline in LVEF of at least 10% to below 55% without signs and symptoms of congestive HF. The serial assessment of LVEF is the most common modality for detection of cardiotoxicity and reduction more than 10% from baseline or the decrease of LVEF below 50% are considered interruption criteria of anticancer drugs administration[7-9]. Notwithstanding, guidelines do not specify the timing and the duration of follow-up and what technique is preferable to assess LV function during and after cancer treatment[10].

Echocardiography (ECHO) plays an important role in evaluation and monitoring of cancer patients treated with cardiotoxic antineoplastic drugs due to availability and repeatability. Conversely, inter- and intra-observer variability during serial measurement of LVEF and underestimation of myocardial contractile dysfunction should be considered. To overcome these limits, novel echocardiographic techniques, like as tissue velocity imaging and strain imaging, could be used to detect the presence of myocardial contractile dysfunction before the impairment of LVEF[11].

In addition, cardiac magnetic resonance imaging (CMR) is a well recognized imaging technique to screen chemotherapy-related cardiomyopathy[12]. It provides reproducible and noninvasively assessment of LV volume, mass and function[13,14]. Moreover, several studies[13,15,16] emphasized its role in early detection of myocardial damage, however high cost and low availability limit clinical routine use.

Although ECHO and CMR are the two most commonly used imaging techniques for non-invasive chemioterapic myocardial toxicity assessment, nuclear imaging may still have a role in the evaluation and monitoring of cancer patients treated with cardiotoxic drugs. Besides to provide sensitive and accurate estimation of LVEF, nuclear imaging techniques using specific radiotracer molecules represents an emerging tool for non-invasive detection of biological processes preceding anatomical involvement and physiological consequences of myocardial damage induced by antineoplastic drugs (Tables 1 and 2).

In this review we will summarize the role of nuclear cardiology in the non-invasive detection of myocardial damage related to antineoplastic therapy, focusing on the current role and future perspectives of nuclear imaging and molecular radiotracers in the assessment of cardiac toxicity.

**99MTC-MUGA**

Multigated radionuclide angiography (MUGA) is a non-invasive technique using 99mTc-erythrocyte to visualize cardiac blood pool through γ camera gating acquisition[17]. The series of heart planar images at each stage of the cardiac cycle permit accurate and high reproducible quantification of LV volumes and LVEF during cancer therapy[18]. However, its use may be hampered by soft-tissue attenuation artifacts and may expose patients to ionizing radiations[14,19]. In 28 patients treated with increasing cumulative doses of doxorubicin for non-Hodgkin lymphoma, Nousianen et al.[20] documented that MUGA scan had 90% sensitivity and 72% specificity for predicting development of chronic HF. However, the results of this little prospective study were not confirmed by large retrospective study[21] conducted on 630 patients randomized to increasing dose of doxorubicin or placebo. In fact, Swain et al. observed that 66% of patients experiencing doxorubicin-related chronic HF showed not clinical relevant decline in LVEF value assessed by MUGA scan from baseline levels (ranging from 0 and 30% of absolute value), suggesting that it is not accurate in HF prediction.

**99mTC GBPS**

99mTC Gated Blood-Pool SPECT (Single Photon Emission Computed Tomography) is nuclear technique enable to obtain 3-dimensional scanned images. 99mTC Gated blood-pool SPECT provides information on LVEF, right ventricular EF and wall motion useful in monitoring and personalizing of therapy in HF patients[21]. A good correlation between GBPS and MUGA in the LVEF estimation was documented[22]. However, compared to MUGA (41% ± 14%, *P* = 0.001), first-pass radionuclide ventriculography (45% ± 13%, *P* < 0.0001) and echocardiography (37% ± 15%, *P* = 0.004), GBPS tends to underestimate LVEF values (33% ± 13%)[23].

**111-INANTIMYOSIN SPECT**

The immunoscintigraphic agent 111-Inantimyosin is a specific marker for myocardial cell injury and necrosis, binding to intracellular myosin when sarcolemma disruption occurs and the cell is irreversibly damaged. It has been studied in myocardial infarction, myocarditis, cardiac transplant rejection and anthracycline cardiotoxicity[24].

111-Inantimyosin SPECT can play a role in subclinical assessment of LV dysfunction as documented in several studies[24,25]. Estorch *et al*[25] showed an increased uptake of 111-Inantimyosin after anthracycline chemotherapy (doxorubicin or mitoxantrone) in breast cancer patients without cardiovascular risk factors or previous chemotherapy exposition or mediastinal radiotherapy and the degree of myocardial antimyosin uptake was associated with changes in LVEF. Moreover, the presence in some patients of radiotracer uptake not associated with a significant reduction of LVEF after chemotherapy suggested the potential use of this technique to detect cellular damage before the onset of LV functional impairment, allowing the identification of patients at risk of HF. Similar results have been also obtained by Carrió *et al*[24], who documented a significant reduction of LVEF value after chemotherapy in patients treated with anthracycline dose of 420-600 mg/m2 (*P* < 0.001) and a not significant change in patients treated with dose of 240-300 mg/m2. Moreover, patients with heart-to-lung ratio (HLR) ≥ 1.90 at a cumulative anthracycline dose of 240-300 mg/m2 developed LVEF reduction greater 10% at subsequent cumulative doxorubicin dose of 420-600 mg/m2. These evidences encourage the use of antimyosin scintigraphy in order to identify patients with high risk to develop systolic LV dysfunction when treated with increasing dose of chemotherapeutic drugs. In addition, Valdes Olmos *et al*[26] observed that patients with persistent reduction of LVEF after chemotherapy had a significant higher value (1.83 ± 0.37) of HLR than patients with transient LVEF decrease (1.52 ± 0.21) (*P* < 0.01), revealing that cardiac uptake of 111-Inantimyosin could be also useful to discriminate between patients with transient and persistent LV dysfunction and to guide clinical decision about discontinuation of anthracycline therapy.

**123I-METAIODOBENZYLGUANIDINE SPECT**

123I-Metaiodobenzylguanidine (123I-MIBG) SPECT is a promising technique to detect early anthracyclines injury and to identify patients at high risk of developing cardiotoxicity.

Chemotherapy-induced cardiomyopathy actives compensatory response that increases adrenergic sympathetic and renin-angiotensin system activity to preserve organs perfusion[27]. In patients with chronic HF increased norepinephrine (NE) release, depletion of NE deposits and down regulation of human norepinephrine transporter (hNET1) have been shown[28]. 123I-MIBG is a norepinephrine analogue, showing the same uptake, storage and release mechanisms of NE. Unlike NE, MIBG is not metabolized by catechol-o-methyl transferase and monoamine oxidase[29]; so, labelled with 123I it can be used to generate scintigraphic images of cardiac efferent sympathetic innervation. After 123I-MIBG administration, early (15 min) and late (4 h) post injection images are acquired to determinate heart to mediastinal ratio (H/M) and washout rate (WR). Consequently, the NE increasing in cardiac synaptic space and reduction in presynaptic space, induced by HF, cause reduction of MIBG cardiac uptake and acceleration of washout rate.

Studies[30,31] conducted in asymptomatic patients treated with anthracyclines revealed that 123I-MIBG is useful to assess myocardial adrenergic derangement and identify patients at risk of develop cardiotoxicity. In addition, in 36 patients with diagnosis of sarcoma and without history of cardiac disease or previous cancer treatment, undergoing to MIBG scintigraphy, Carriò *et al*[30] documented not significant decrease of LVEF and of MIBG uptake at intermediate cumulative dose of doxorubicin (240-300 mg/mg2). Instead, when high cumulative dose of doxorubicin 420-600 mg/m2 was used, the experimenters documented significant impairment of 123I-MIBG uptake (*P* < 0.001) and reduction of LVEF (*P* < 0.05), proposing that the degree of H/M reduction is also correlated with the dose of anthracyclines administrated.

**111-INTRASTUZUMAB SPECT**

In cancer patients, the anthracyclines can increase the levels of human epidermal growth factor receptor 2 (HER2) expressed by myocytes. In patients pre-treated with anthracyclines, trastuzumab, a chemotherapic agent with direct effect on HER2, often cause cardiotoxicity, likely due to the inhibition of cardiac HER2,that activates the apoptotic pathways and amplifies anthracycline oxidative stress. Thus, 111-InTrastuzumab (111In-Tz) SPECT can be used to evaluate the HER2 myocyte expression and the risk of development LV dysfunction in patients treated with this drug[32].

In a little study, Behr *et al*[33] underwent to 111In-Tz scintigraphy 20 patients with metastatic breast cancer expressing the HER2/neu receptor, pre-treated with anthracyclines and scheduled for administration of Tz as second line therapy. They documented myocardial 111In-Tz uptake prior to Tz in 7 patients; of these, 6 developed clinical HF (II-IV NYHA class), whereas none of 13 patients without uptake had adverse cardiac events, suggesting that pre-treatment scanning with 111In-Tz could predict cardiotoxicity. In contrast to these results, Perik *et al*[34] documented increased 111In-Tz uptake at the start of trastuzumab therapy only in 1of 17 studied patients, who had received extensive anthracyclines pre-treatment, and normal 111In-Tz uptake at baseline scintigraphy in the 3 patients developing Tz-induced cardiomyopathy.

**99MTC-ANNESSIN V SPECT**

Apoptosis of myocardial cells plays a critical role in the onset of cardiomyopathy and has been observed in several conditions, like hypoxia, ischemia, cardiac overload, acute myocardial infarction, anthracycline-induced cardiomyopathy and end-stage of HF. In apoptotic cells, the early stage is characterized by activation of proteases and sphingomyelinases and consequent exposure of phosphatidylderine molecules on the outer surface of the cell membrane. 99mTc-annessin V has a high affinity for the exposed phosphatidylserine molecule and thus allows imaging of apoptotic cell death[35].

In animals Annexin V scintigraphy has been used to assess acute and chronic doxorubicin-induced cardiomyopathy based on early apoptosis. Increased 99mTc-annessin V uptake was observed in the myocardium of doxorubicin-treated animals and cardiac oxidative stress was confirmed by histological analysis histological[36,37].

Further studies are needed for the clinical use of this radiotracer, in particular for early identification of myocardial damage antineoplastic-drugs related.

**123I-15-(P-IODOPHENYL)-3-(R,S)-METHYLPENTADECANOIC ACIDSPECT**

Taxanes are used in the treatment of breast, lung and ovarian cancer and they can cause ischemia, arrhythmias and HF. Taxanes can impair microtubular transport system in cardiomyocytes, resulting in failure to store free fatty acids in cytosol lipid poll and impaired mitochondrial free fatty acids uptake for beta-oxidation. 123I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (123I-BMIPP) scintigraphy has been used to assess this biochemical perturbation in free fatty acid oxidation[38]. Saito *et al*[38] showed a significant lower BMIPP uptake scores after chemotherapy than those before treatment (23.4 ± 3.4 *vs* 26.6 ± 0.8, *P* < 0.001). Moreover, 6 of 25 studied patients, who developed LV dysfunction, had also significant decrease in total BMIPP uptake scores, suggesting the use of 123I-BMIPP SPECT for detecting of taxan-induced cardiotoxicity. The value of 123I-BMIPP in prediction of cardiotoxicity was also documented in 36 patients with various malignancies treated with doxorubicin[39]. In this study, Saito *et al*[39] showed a significant dose-related reduction of 123I-BMIPP uptake (0.095 ± 0.25 *vs* 0.071 ± 0.019; *P* < 0.001) after doxorubicin chemotherapy and higher rate of LV dysfunction development in patients with decreased uptake, but with normal LVEF at echocardiography.

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography (PET) is the gold standard technique to assess myocardial metabolism and perfusion, due to high spatial and temporal resolution and high diagnostic sensibility and accuracy. Cardiac PET radiotracers are divided in two categories, those evaluating myocardial perfusion and those myocardial metabolism.

In cardio-oncologic field, PET is useful to the diagnosis of metastatic lesion and to assess response chemotherapy. However, fluorine-18-fluorodeoxyglucose (18F-FDG)-PET imaging is used to monitor the response to treatment of primary cardiac lymphoma[40,41] and to evaluate metastatic pericardial involvement[42]. The PET role in the early detection of cardiotoxicity is still debated. Whereas, Novy *et al*[43] showed significant decrease in LVEF (*P* = 0.046) assessed by radionuclide angiography after treatment with doxorubicin, but no significant effect was observed in myocardial blood flow evaluated with PET in 6 cancer woman without heart disease. Recently, Borde *et al*[44] analyzed changes in myocardial glucose metabolism using FDG-PET and hypothesized increased glucose utilization as evidence of cellular alteration that precede the cardiotoxicity cascade in patients treated with adriamycin.

Like SPECT, PET imaging can play a key role in the evaluation of cardiac autonomic dysfunction associated with HF[45]. PET provides several advantages over SPECT, as higher spatial and temporal resolution and routinely available attenuation correction. In addition, PET radiotracers more closely resemble the endogenous neurotransmitters than 123MIBG used for SPECT imaging and the variety of available tracers may allow for more detailed analysis of neuronal signalling[46]. There are two types of presynaptic positron-emitting tracers to assess the presynaptic sympathetic integrity in the heart, radiolabeled catecholamines and radiolabeled catecholamine analogs. The first type behaves identically to endogenous neurotransmitters, thus it is metabolically active and can complicate kinetic data analysis. Instead catecholamine analogs work as false neurotransmitters and are incapable of following the entire metabolic pathway of true catecholamines. Instead, postsynaptic tracers transmit the sympathetic signal to target tissue. Compared with the availability of presynaptic tracer, only a small number of tracers for postsynaptic neuronal imaging are clinically used. Experimental studies showed a significant reduction in the amount of LV β-adrenoceptors[47] and 11C-Hydroxyephedrine (HED) in HF catecholamine uptake[48,49] associated with LV dysfunction. Thus, studies are needed to validate this new radiotracer in the cardio-oncology field.

However, the complexity of the most of the ligands radiolabeling, the requirement of laboriousus and specific knowledges, the high cost and the low availability limit clinical use of PET.

**CONCLUSION**

Cardiotoxicity is one of the most principal adverse effects of anticancer therapy due to clinical and prognostic importance. LVEF reduction is the most validate criterion to assess the presence of myocardial damage during or after chemotherapy. However, changes in LVEF occur when a critical amount of myocardial damage has taken place and compensatory mechanisms are exhausted[50]. Thus, cardiologists and oncologists should work together to identify new non-invasive, sensitive and not expensive diagnostic tool that accurately recognize cardiotoxicity at subclinical stage to reduce cardiac morbidity and mortality in cancer patients. More interesting future perspectives in early detection of myocardial damage are offered by nuclear imaging that using new molecular tracers may be able to identify high risk patients to develop LV dysfunction during and after cancer treatment.

Therefore, several studies are needed to validate the clinical application of several molecular markers for the identification of early cellular damage.

**REFERENCES**

1 **Yeh ET**, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, Durand JB, Gibbs H, Zafarmand AA, Ewer MS. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation* 2004; **109**: 3122-3131 [PMID: 15226229 DOI: 10.1161/01.CIR.0000133187.74800.B9]

2 **Smith LA**, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer* 2010; **10**: 337 [PMID: 20587042 DOI: 10.1186/1471-2407-10-337]

3 **Olivetti G**, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res* 1991; **68**: 1560-1568 [PMID: 2036710 DOI: 10.1161/01.RES.68.6.1560]

4 **Ewer MS**, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol* 2005; **23**: 2900-2902 [PMID: 15860848 DOI: 10.1200/JCO.2005.05.827]

5 **Kendal WS**. Dying with cancer: the influence of age, comorbidity, and cancer site. *Cancer* 2008; **112**: 1354-1362 [PMID: 18286532 DOI: 10.1002/cncr.23315]

6 **Seidman A**, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, Keefe D. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**: 1215-1221 [PMID: 11870163 DOI: 10.1200/JCO.20.5.1215]

7 **Schwartz RG**, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, Schwartz PE, Berger HJ, Setaro J, Surkin L. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. *Am J Med* 1987; **82**: 1109-1118 [PMID: 3605130 DOI: 10.1016/0002-9343(87)90212-9]

8 **van Royen N**, Jaffe CC, Krumholz HM, Johnson KM, Lynch PJ, Natale D, Atkinson P, Deman P, Wackers FJ. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol* 1996; **77**: 843-850 [PMID: 8623737 DOI: 10.1016/S0002-9149(97)89179-5]

9 **Mitani I**, Jain D, Joska TM, Burtness B, Zaret BL. Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era. *J Nucl Cardiol* 2003; **10**: 132-139 [PMID: 12673177 DOI: 10.1067/mnc.2003.7]

10 **Eschenhagen T**, Force T, Ewer MS, de Keulenaer GW, Suter TM, Anker SD, Avkiran M, de Azambuja E, Balligand JL, Brutsaert DL, Condorelli G, Hansen A, Heymans S, Hill JA, Hirsch E, Hilfiker-Kleiner D, Janssens S, de Jong S, Neubauer G, Pieske B, Ponikowski P, Pirmohamed M, Rauchhaus M, Sawyer D, Sugden PH, Wojta J, Zannad F, Shah AM. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2011; **13**: 1-10 [PMID: 21169385 DOI: 10.1093/eurjhf/hfq213]

11 **Yu CM**, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. *J Am Coll Cardiol* 2007; **49**: 1903-1914 [PMID: 17498573 DOI: 10.1016/j.jacc.2007.01.078]

12 **Hendel RC**, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Kramer CM, Lesser JR, Martin ET, Messer JV, Redberg RF, Rubin GD, Rumsfeld JS, Taylor AJ, Weigold WG, Woodard PK, Brindis RG, Hendel RC, Douglas PS, Peterson ED, Wolk MJ, Allen JM, Patel MR; [American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group](http://www.ncbi.nlm.nih.gov/pubmed?term=American%20College%20of%20Cardiology%20Foundation%20Quality%20Strategic%20Directions%20Committee%20Appropriateness%20Criteria%20Working%20Group%5BCorporate%20Author%5D); [American College of Radiology](http://www.ncbi.nlm.nih.gov/pubmed?term=American%20College%20of%20Radiology%5BCorporate%20Author%5D); [Society of Cardiovascular Computed Tomography](http://www.ncbi.nlm.nih.gov/pubmed?term=Society%20of%20Cardiovascular%20Computed%20Tomography%5BCorporate%20Author%5D); [Society for Cardiovascular Magnetic Resonance](http://www.ncbi.nlm.nih.gov/pubmed?term=Society%20for%20Cardiovascular%20Magnetic%20Resonance%5BCorporate%20Author%5D); [American Society of Nuclear Cardiology](http://www.ncbi.nlm.nih.gov/pubmed?term=American%20Society%20of%20Nuclear%20Cardiology%5BCorporate%20Author%5D); [North American Society for Cardiac Imaging](http://www.ncbi.nlm.nih.gov/pubmed?term=North%20American%20Society%20for%20Cardiac%20Imaging%5BCorporate%20Author%5D); [Society for Cardiovascular Angiography and Interventions](http://www.ncbi.nlm.nih.gov/pubmed?term=Society%20for%20Cardiovascular%20Angiography%20and%20Interventions%5BCorporate%20Author%5D); [Society of Interventional Radiology](http://www.ncbi.nlm.nih.gov/pubmed?term=Society%20of%20Interventional%20Radiology%5BCorporate%20Author%5D). ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006; **48**: 1475-1497 [PMID: 17010819 DOI: 10.1016/j.jacc.2006.07.003]

13 **Fallah-Rad N**, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson* 2008; **10**: 5 [PMID: 18272009 DOI: 10.1186/1532-429X-10-5]

14 **Walker J**, Bhullar N, Fallah-Rad N, Lytwyn M, Golian M, Fang T, Summers AR, Singal PK, Barac I, Kirkpatrick ID, Jassal DS. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. *J Clin Oncol* 2010; **28**: 3429-3436 [PMID: 20530277 DOI: 10.1200/JCO.2009.26.7294]

15 **Fallah-Rad N**, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick ID, Singal PK, Krahn M, Grenier D, Jassal DS. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol* 2011; **57**: 2263-2270 [PMID: 21616287 DOI: 10.1016/j.jacc.2010.11.063]

16 **Wassmuth R**, Lentzsch S, Erdbruegger U, Schulz-Menger J, Doerken B, Dietz R, Friedrich MG. Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging-a pilot study. *Am Heart J* 2001; **141**: 1007-1013 [PMID: 11376317 DOI: 10.1067/mhj.2001.115436]

17 **Hesse B**, Lindhardt TB, Acampa W, Anagnostopoulos C, Ballinger J, Bax JJ, Edenbrandt L, Flotats A, Germano G, Stopar TG, Franken P, Kelion A, Kjaer A, Le Guludec D, Ljungberg M, Maenhout AF, Marcassa C, Marving J, McKiddie F, Schaefer WM, Stegger L, Underwood R. EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging* 2008; **35**: 851-885 [PMID: 18224320 DOI: 10.1007/s00259-007-0694-9]

18 **Altena R**, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol* 2009; **10**: 391-399 [PMID: 19341970 DOI: 10.1016/S1470-2045(09)70042-7]

19 **Corapçioglu F**, Sarper N, Berk F, Sahin T, Zengin E, Demir H. Evaluation of anthracycline-induced early left ventricular dysfunction in children with cancer: a comparative study with echocardiography and multigated radionuclide angiography. *Pediatr Hematol Oncol* 2006; **23**: 71-80 [PMID: 16326416 DOI: 10.1080/08880010500313603]

20 **Nousiainen T**, Jantunen E, Vanninen E, Hartikainen J. Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. *Br J Cancer* 2002; **86**: 1697-1700 [PMID: 12087452 DOI: 10.1038/sj.bjc.6600346]

21 **Swain SM**, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003; **97**: 2869-2879 [PMID: 12767102 DOI: 10.1002/cncr.11407]

22 **Groch MW**, DePuey EG, Belzberg AC, Erwin WD, Kamran M, Barnett CA, Hendel RC, Spies SM, Ali A, Marshall RC. Planar imaging versus gated blood-pool SPECT for the assessment of ventricular performance: a multicenter study. *J Nucl Med* 2001; **42**: 1773-1779 [PMID: 11752072]

23 **Hacker M**, Hoyer X, Kupzyk S, La Fougere C, Kois J, Stempfle HU, Tiling R, Hahn K, Störk S. Clinical validation of the gated blood pool SPECT QBS processing software in congestive heart failure patients: correlation with MUGA, first-pass RNV and 2D-echocardiography. *Int J Cardiovasc Imaging* 2006; **22**: 407-416 [PMID: 16328851 DOI: 10.1007/s10554-005-9031-1]

24 **Carrió I**, Lopez-Pousa A, Estorch M, Duncker D, Berná L, Torres G, de Andrés L. Detection of doxorubicin cardiotoxicity in patients with sarcomas by indium-111-antimyosin monoclonal antibody studies. *J Nucl Med* 1993; **34**: 1503-1507 [PMID: 8355070]

25 **Estorch M**, Carrió I, Martínez-Duncker D, Berná L, Torres G, Alonso C, Ojeda B. Myocyte cell damage after administration of doxorubicin or mitoxantrone in breast cancer patients assessed by indium 111 antimyosin monoclonal antibody studies. *J Clin Oncol* 1993; **11**: 1264-1268 [PMID: 8315423]

26 **Valdés Olmos RA**, ten Bokkel Huinink WW, ten Hoeve RF, van Tinteren H, Bruning PF, van Vlies B, Hoefnagel CA. Usefulness of indium-111 antimyosin scintigraphy in confirming myocardial injury in patients with anthracycline-associated left ventricular dysfunction. *Ann Oncol* 1994; **5**: 617-622 [PMID: 7993837]

27 **Francis GS**, Cohn JN. The autonomic nervous system in congestive heart failure. *Annu Rev Med* 1986; **37**: 235-247 [PMID: 2871803 DOI: 10.1146/annurev.me.37.020186.001315]

28 **Triposkiadis F**, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol* 2009; **54**: 1747-1762 [PMID: 19874988 DOI: 10.1016/j.jacc.2009.05.015]

29 **Strashun A**. Adriamycin, congestive cardiomyopathy, and metaiodobenzylguanidine. *J Nucl Med* 1992; **33**: 215-222 [PMID: 1732443]

30 **Carrió I**, Estorch M, Berná L, López-Pousa J, Tabernero J, Torres G. Indium-111-antimyosin and iodine-123-MIBG studies in early assessment of doxorubicin cardiotoxicity. *J Nucl Med* 1995; **36**: 2044-2049 [PMID: 7472595]

31 **Valdés Olmos RA**, ten Bokkel Huinink WW, ten Hoeve RF, van Tinteren H, Bruning PF, van Vlies B, Hoefnagel CA. Assessment of anthracycline-related myocardial adrenergic derangement by [123I]metaiodobenzylguanidine scintigraphy. *Eur J Cancer* 1995; **31A**: 26-31 [PMID: 7695974 DOI: 10.1016/0959-8049(94)00357-B]

32 **de Korte MA**, de Vries EG, Lub-de Hooge MN, Jager PL, Gietema JA, van der Graaf WT, Sluiter WJ, van Veldhuisen DJ, Suter TM, Sleijfer DT, Perik PJ. 111Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: a clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. *Eur J Cancer* 2007; **43**: 2046-2051 [PMID: 17719768]

33 **Behr TM**, Béhé M, Wörmann B. Trastuzumab and breast cancer. *N Engl J Med* 2001; **345**: 995-996 [PMID: 11575295 DOI: 10.1056/NEJM200109273451312]

34 **Perik PJ**, Lub-De Hooge MN, Gietema JA, van der Graaf WT, de Korte MA, Jonkman S, Kosterink JG, van Veldhuisen DJ, Sleijfer DT, Jager PL, de Vries EG. Indium-111-labeled trastuzumab scintigraphy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2006; **24**: 2276-2282 [PMID: 16710024 DOI: 10.1200/JCO.2005.03.8448]

35 **Bennink RJ**, van den Hoff MJ, van Hemert FJ, de Bruin KM, Spijkerboer AL, Vanderheyden JL, Steinmetz N, van Eck-Smit BL. Annexin V imaging of acute doxorubicin cardiotoxicity (apoptosis) in rats. *J Nucl Med* 2004; **45**: 842-848 [PMID: 15136635]

36 **Panjrath GS**, Jain D. Monitoring chemotherapy-induced cardiotoxicity: role of cardiac nuclear imaging. *J Nucl Cardiol* 2006; **13**: 415-426 [PMID: 16750786 DOI: 10.1016/j.nuclcard.2006.03.002]

37 **Panjrath GS**, Patel V, Valdiviezo CI, Narula N, Narula J, Jain D. Potentiation of Doxorubicin cardiotoxicity by iron loading in a rodent model. *J Am Coll Cardiol* 2007; **49**: 2457-2464 [PMID: 17599610 DOI: 10.1016/j.jacc.2007.02.060]

38 **Saito K**, Takeda K, Imanaka-Yoshida K, Imai H, Sekine T, Kamikura Y. Assessment of fatty acid metabolism in taxan-induced myocardial damage with iodine-123 BMIPP SPECT: comparative study with myocardial perfusion, left ventricular function, and histopathological findings. *Ann Nucl Med* 2003; **17**: 481-488 [PMID: 14575384 DOI: 10.1007/BF03006439]

39 **Saito K**, Takeda K, Okamoto S, Okamoto R, Makino K, Tameda Y, Nomura Y, Maeda H, Ichihara T, Nakano T. Detection of doxorubicin cardiotoxicity by using iodine-123 BMIPP early dynamic SPECT: quantitative evaluation of early abnormality of fatty acid metabolism with the Rutland method. *J Nucl Cardiol* 2000; **7**: 553-561 [PMID: 11144469 DOI: 10.1067/mnc.2000.108351]

40 **Lee JC**, Platts DG, Huang YT, Slaughter RE. Positron emission tomography combined with computed tomography as an integral component in evaluation of primary cardiac lymphoma. *Clin Cardiol* 2010; **33**: E106-E108 [PMID: 20552627 DOI: 10.1002/clc.20725]

41 **Kaderli AA**, Baran I, Aydin O, Bicer M, Akpinar T, Ozkalemkas F, Yesilbursa D, Gullulu S. Diffuse involvement of the heart and great vessels in primary cardiac lymphoma. *Eur J Echocardiogr* 2010; **11**: 74-76 [PMID: 19759028 DOI: 10.1093/ejechocard/jep111]

42 **Weijs LE**, Arsos G, Baarslag HJ, Wittebol S, de Klerk JM. Pericardial involvement in a non-Hodgkin lymphoma patient: coregistered FDG-PET and CT imaging. *Eur Heart J* 2007; **28**: 2698 [PMID: 17567624]

43 **Nony P**, Guastalla JP, Rebattu P, Landais P, Lievre M, Bontemps L, Itti R, Beaune J, Andre-Fouet X, Janier M. In vivo measurement of myocardial oxidative metabolism and blood flow does not show changes in cancer patients undergoing doxorubicin therapy. *Cancer Chemother Pharmacol* 2000; **45**: 375-380 [PMID: 10803920 DOI: 10.1007/s002800051005]

44 **Borde C**, Kand P, Basu S. Enhanced myocardial fluorodeoxyglucose uptake following Adriamycin-based therapy: Evidence of early chemotherapeutic cardiotoxicity? *World J Radiol* 2012; **4**: 220-223 [PMID: 22761982 DOI: 10.4329/wjr.v4.i5.220]

45 **Lautamäki R**, Tipre D, Bengel FM. Cardiac sympathetic neuronal imaging using PET. *Eur J Nucl Med Mol Imaging* 2007; **34 Suppl 1**: S74-S85 [PMID: 17479262 DOI: 10.1007/s00259-007-0442-1]

46 **Langer O**, Halldin C. PET and SPET tracers for mapping the cardiac nervous system. *Eur J Nucl Med Mol Imaging* 2002; **29**: 416-434 [PMID: 12002720 DOI: 10.1007/s002590100640]

47 **Merlet P**, Delforge J, Syrota A, Angevin E, Mazière B, Crouzel C, Valette H, Loisance D, Castaigne A, Randé JL. Positron emission tomography with 11C CGP-12177 to assess beta-adrenergic receptor concentration in idiopathic dilated cardiomyopathy. *Circulation* 1993; **87**: 1169-1178 [PMID: 8096441 DOI: 10.1161/01.CIR.87.4.1169]

48 **Vesalainen RK**, Pietilä M, Tahvanainen KU, Jartti T, Teräs M, Någren K, Lehikoinen P, Huupponen R, Ukkonen H, Saraste M, Knuuti J, Voipio-Pulkki LM. Cardiac positron emission tomography imaging with [11C]hydroxyephedrine, a specific tracer for sympathetic nerve endings, and its functional correlates in congestive heart failure. *Am J Cardiol* 1999; **84**: 568-574 [PMID: 10482157 DOI: 10.1016/S0002-9149(99)00379-3]

49 **Hartmann F**, Ziegler S, Nekolla S, Hadamitzky M, Seyfarth M, Richardt G, Schwaiger M. Regional patterns of myocardial sympathetic denervation in dilated cardiomyopathy: an analysis using carbon-11 hydroxyephedrine and positron emission tomography. *Heart* 1999; **81**: 262-270 [PMID: 10026349]

50 **Popat S**, Smith IE. Therapy Insight: anthracyclines and trastuzumab--the optimal management of cardiotoxic side effects. *Nat Clin Pract Oncol* 2008; **5**: 324-335 [PMID: 18364726 DOI: 10.1038/ncponc1090]

**P-Reviewer:** Vinh-Hung V **S-Editor:** Song XX **L-Editor:** **E-Editor:**

**Table 1 Radiotracer for cardiac nuclear imaging**

|  |  |  |
| --- | --- | --- |
| **Technique** | **tracer** | **Action** |
| **SPECT** |  |  |
|  | 99mTc-erythrocyte | Contractile function |
|  | 111-Inantimyosin | Imaging necrosis/cell death |
|  | 123I-MIBG | Neuronal imaging(presinaptic uptake and storage) |
|  | 111In-Tz | Therapeutic target imaging |
|  | 99mTc-annessin V | Imaging necrosis/cell death |
|  | 123I-BMIPP | Fatty acids use |
| **PET** |  |  |
|  | 18F-FDG | Glucose metabolism |
|  | Presynaptic tracers | Visualize inhibition of neurotrasmission |
|  | true cathecolamines |  |
|  | 18F-6-fluorodopamine |  |
|  | 11C-epinephrine |  |
|  | catecholamine analogs | False neurotransmitters |
|  | 11C-HED |  |
|  | 11C-phenylephrine |  |
|  | 18F-6-fluorometaraminol |  |
|  | Postsynaptic tracers | Visualize transmission of sympathetic signal to target tissue |
|  | 11C-CGP12177 |  |
|  | 11C-CGP12388 |  |
|  | 11C-GB67 |  |

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; HED: Hydroxyephedrine.

**Table 2 Techniques used for detection of anticancer therapy cardiomiopathy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | **Advantagies** | **Limits** | |
| **Echocardiography** | Non-invasive | Inter- and intra-observer variability | |
|  | Absence of adverse effects | Low sensitivity of EF assessment for early diagnosis | |
|  | Analysis of systolic and diastolic function |  | |
|  | Tissue velocity imaging and strain imaging useful for early detection of subclinical alteration | |
| **Magnetic resonance imaging** | Accurate heart anatomic description | Limited availability | |
|  | Absence of radiation exposure | High costs | |
|  | Accurate and reproducible EF assessment | Not applicable in patients with metallic device | |
|  | Cardiac innervation assessment | Low information about its role in the early detection | |
| **Multiple-gated acquisition scintigraphy** | High sensitivity and specificity EF assessment | Low sensitivity of EF for early diagnosis | |
|  | No inter- and intra-observer variability | Less information about diastolic function | |
|  |  | radiation exposure | |
| **Positron emission tomography** | Myocardial metabolic and perfusion evaluation | Limited availability | |

EF: Ejection fraction.