Supplement submission

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Cardiovascular imaging in the diagnosis and monitoring of cardiotoxicity: cardiovascular magnetic resonance and nuclear cardiology

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Chemotherapy-induced cardiotoxicity (CTX) is a determining factor for the quality of life and mortality of patients administered potentially cardiotoxic drugs and in long-term cancer survivors. Therefore, prevention and early detection of CTX are highly desirable, as is the exploration of alternative therapeutic strategies and/or the proposal of potentially cardioprotective treatments. In recent years, cardiovascular imaging has acquired a pivotal role in this setting. Although echocardiography remains the diagnostic method most used to monitor cancer patients, the need for more reliable, reproducible and accurate detection of early chemotherapy-induced CTX has encouraged the introduction of second-line advanced imaging modalities, such as cardiac magnetic resonance (CMR) and nuclear techniques, into the clinical setting. This review of the Working Group on Drug Cardiotoxicity and Cardioprotection of the Italian Society of Cardiology aims to afford an overview of the most important findings from the literature about the role of CMR and nuclear techniques in the management of chemotherapy-treated patients, describe conventional and new parameters for detecting CTX from both diagnostic and prognostic perspectives and provide integrated insight into the role of CMR and nuclear techniques compared with other imaging tools and versus the positions of the most important international societies.

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Introduction

The use of chemotherapy has largely improved the prognosis of cancer patients in recent decades. However, chemotherapy-induced cardiotoxicity (CTX) shows an increased incidence[1] and represents a significant determinant of quality of life and mortality during on-going treatment and in long-term survivors of cancer. Thus, the prediction of CTX in this setting is highly desirable, such that alternative therapeutic strategies can be explored and/or potentially preventive cardio-active treatment can be instituted.

However, a universally accepted definition of CTX is not available to date. The recent joint consensus document of the European Association of Cardiovascular Imaging and American Society of Echocardiography redefined CTX as a drop in the left ventricular ejection fraction (LVEF) more than 10% below the value of 53%, as assessed by two-dimensional echocardiography (2DE).[2] Accordingly, LVEF still represents the parameter most used in the follow-up of oncologic patients.

In addition, 2DE is the most exploited diagnostic tool because of its feasibility, repeatability, availability, safety and low cost. However, 2DE-calculated LVEF suffers from suboptimal reproducibility and depends on the acoustic window; furthermore, the use of contrast imaging can only partially improve inter-observer variability.[3] Three-dimensional echocardiography (3DE) demonstrates better reproducibility[4]; however, it is not yet widely implemented in current practice (the role of echocardiography in the diagnosis and monitoring of CTX is extensively addressed in a dedicated article within this Special Issue).

Moreover, a decrease of LVEF occurs only after a relevant ultrastructural injury, and thus it does not represent a marker of early CTX and cannot predict the development of future heart failure.[5,6] Therefore, the need for a reliable and accurate detection method for early CTX has encouraged the introduction of second-line advanced imaging modalities into the evaluation of chemotherapy-treated patients, including cardiac magnetic resonance (CMR) and nuclear techniques.

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Cardiac magnetic resonance and chemotherapy-induced cardiotoxicity

Standard and new function parameters

CMR is a ionizing radiation free imaging method accepted as the gold standard for quantifying biventricular parameters because of the lack of acoustic window limits and the need for geometric model assumption, high contrast to noise ratio and good temporal resolution.[7] The excellent reproducibility of this approach has been confirmed in multicentre observational studies[8] and is valuable for detecting an early cardiac injury, monitoring patients over time and significantly reducing sample size in the research setting.

These characteristics can be very useful in chemotherapy-treated patients, whose management depends on minimal variations in systolic function. CMR has demonstrated a good correlation with echocardiography and radionuclide ventriculography. However, the absolute cut-off values are different,[9] and when monitoring CTX, it is strongly recommended that the same patients be followed with the same technique over time.

The standard CMR approach for quantifying biventricular function parameters uses contiguous short-axis slices covering the entire ventricles acquired from a cine steady-state free precession (SSFP) sequence (Fig. 1).

CMR demonstrates higher sensitivity compared with 2DE and 3DE in detecting values of LVEF less than 50%,[10] suggesting a preferential use of CMR in cases of ventricular dysfunction by echocardiography.

Two small CMR studies have demonstrated a significant early decrease in LVEF at 3–6 months after chemotherapy.[11] With regard to late CTX, Ylanen studied 62 subjects and found an overly decreased LVEF (<45%) in 18% and a suboptimal LVEF (45–55%) in 61% at a mean follow-up time of 7.8 years.[12] Unfortunately, none of these studies reported prognostic data.

CTX may also involve the right ventricle, and CMR is the most accurate method for the determination of its morphological and functional parameters because the irregular shape of the right ventricle cannot be derived by geometrical formulas and requires 3D acquisition. Regrettably, few and small studies in the literature have investigated right ventricle parameters in oncologic patients, and no prognostic data are available.[13]

A decrease in myocardial mass has been identified in many long-term survivors of childhood cancer, suggesting that it could be considered as a late CTX manifestation.[10,14] In particular, a study by Neilan highlighted that indexed left ventricular mass is the strongest predictor of major cardiovascular events.[14] Conversely, echocardiography failed to detect functional and structural alterations in most patients in this group.[10]

The fact that LVEF does not take into account the relationship between mass and chamber dimensions may partly explain its limited sensitivity.[15,16] The LV global function index is a new CMR parameter that combines left ventricular stroke volume, end-systolic and end-diastolic volumes, and mass, and a value less than 37% has been shown to be associated with the occurrence of cardiovascular events in a more powerful way.[16] However, no data are available on this promising index in monitoring CTX.

Diastolic function

Contrasting opinions have been reported on the predictive value of diastolic dysfunction in chemotherapy-treated patients.

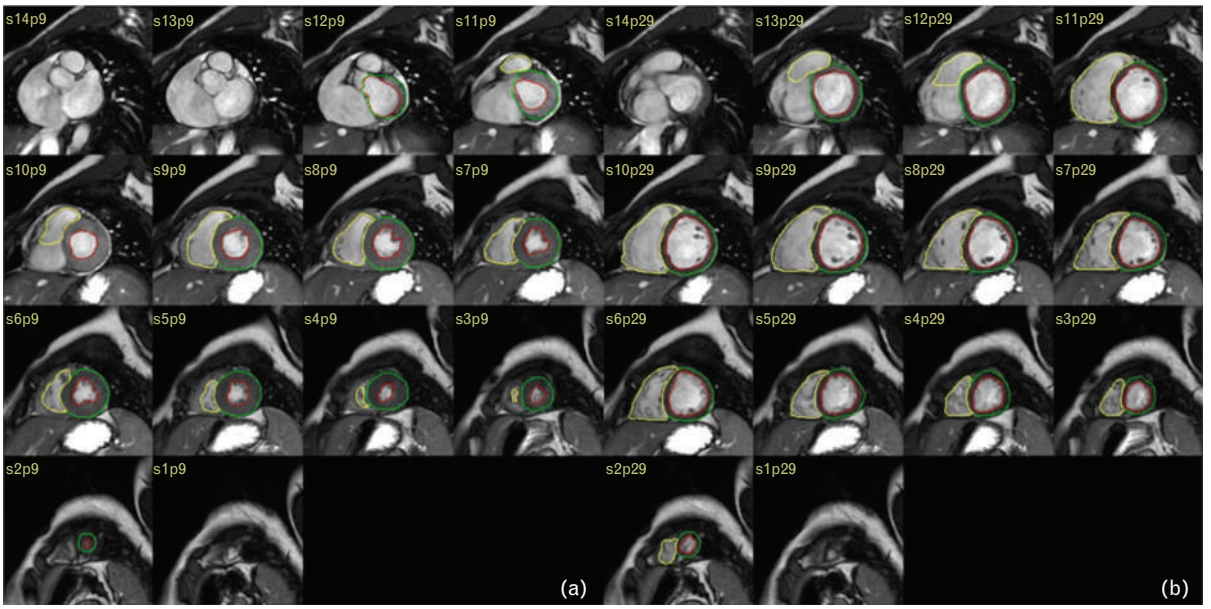
In general, 2DE and Doppler represent the most useful instruments for detecting diastolic function. However, in oncologic patients, diastolic dysfunction is not specific and in large studies, has failed to predict a late decrease in LVEF less than 50% within 3 years.[17] Additionally, the use of the E/e′ ratio remains questionable, as fluctuation in E and e′ velocities could be significantly influenced by changes in loading conditions associated with chemotherapy. Although diastolic parameters can be derived by CMR using the variation rate of the atrial volume[18] and phase contrast sequences to evaluate mitral inflow,[19] these techniques are typically time-consuming, and a clear advantage over Doppler has not been demonstrated. Consequently, diastolic function by CMR is not usually recommended in current practice.[2]

Myocardial deformation

Early changes in LV mechanical deformation typically precede a drop in LVEF in patients undergoing chemotherapy, representing an early marker of myocardial damage.[20,21] CMR is able to provide an accurate and reliable evaluation of myocardial deformation by tagging techniques and, more recently, by using phase contrast imaging and CMR feature tracking. In the technique most frequently used, the myocardium is tagged with a grid of magnetic saturation lines at end diastole, allowing the analysis of deformation by tracking the distortion of the grid during systole.

Only few and small studies evaluating myocardial deformation parameters by tagging in the monitoring of early CTX have demonstrated a significant decrease in longitudinal and circumferential deformation compared with controls.[11,21] However, deformation analysis did not demonstrate an incremental value versus the LVEF in early CTX detection. Indeed, only Toro-Salazar, in a study including 46 long-term childhood cancer survivors treated with anthracycline doses of 200 mg/m^2 or more, was able to show a significant decrease in circumferential and longitudinal strain and regional peak circumferential strain, despite a normal LVEF by 2DE and CMR. Unfortunately, the study did not report a predictive

Fig. 1



Contiguous short-axis SSFP images in end-systolic (a) and end-diastolic (b) phases covering the entire ventricles in quantification of biventricular function parameters.

role.[22] Although tagging CMR is promising, larger studies including long-term follow-up data are needed to clarify the real predictive value of this method. The suboptimal sequence efficiency for creating the tag lines and the time-consuming image analysis limit the introduction of the method into current practice and make tagging CMR a focus of research.

Stress cardiac magnetic resonance

Some chemotherapeutic agents such as 5-fluorouracil and tyrosine kinase inhibitors show an association with myocardial ischaemia.[23] Some studies performed with echocardiography reported an additional role of stress imaging, revealing that patients treated with chemotherapy have reduced contractile reserve in comparison to healthy subjects.[24,25] However, none of these studies demonstrated a prognostic value, whereas other studies did not report an incremental value of stress imaging in patients without suspicion of myocardial ischaemia.[26,27] Therefore, when myocardial ischaemia secondary to chemotherapy is clinically suspected, CMR can be used, as indicated by the current Guidelines of the European Society of Cardiology on stable coronary artery disease.[28] In patients with an intermediate pre-test probability of stable coronary artery disease, stress imaging testing is preferred to exercise ECG.[29] Specifically, the advantages of CMR include the absence of radiation exposure, higher spatial resolution and higher diagnostic performance compared with SPECT,[30,31] as well as independence from the acoustic window and the opportunity to evaluate wall motion abnormalities, myocardial perfusion and necrosis/fibrosis in the same test. In addition to the classical contraindications of performing a basal CMR exam, the main limitations for stress CMR to date are local expertise and availability.

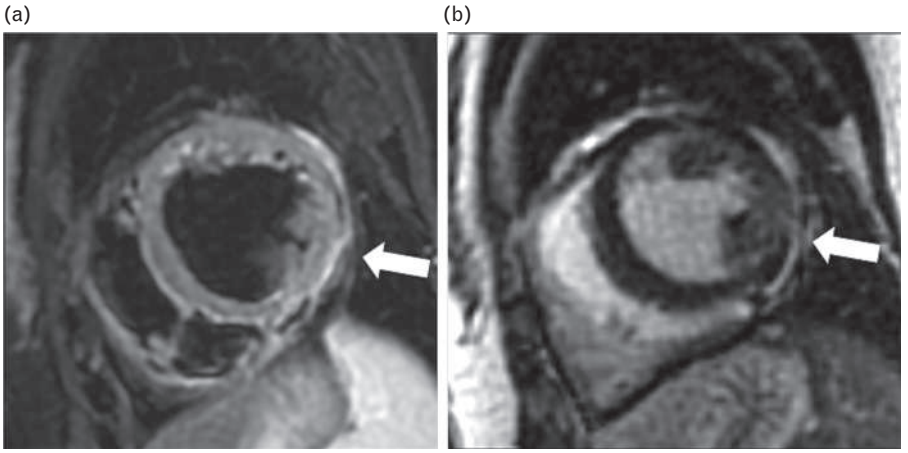
Tissue characterization

In the evaluation of CTX, the additive and incremental value of CMR is the unique possibility of providing information on tissue characterization. As expected, chemotherapeutic agents can cause oedema and hyperaemia, and even cellular necrosis and subsequent fibrosis.

Myocardial oedema

Myocardial oedema leads to an overall increase in the water burden of the affected tissue, resulting in elongation of T2 relaxation times. In the clinical setting, the most common approach for the evaluation of myocardial oedema is the qualitative analysis of T2-weighted short tau inversion recovery fast spin echo (FSE) sequences, in which oedema appears hyper-intense (Fig. 2a). However, the disadvantages of the qualitative approach are a coil sensitivity and the inability to monitor serial progress. Moreover, oedema may be global and thus not recognizable to the naked eye. Consequently, semi-quantitative analysis by normalizing the signal intensity of the myocardium to that of skeletal muscle, using a cut-off of more than 1.9, is strongly recommended.[31]

Fig. 2



(a) Short-axis T2-weighted short tau inversion recovery image showing hyperintensive signal (oedema) in the mid infero-lateral wall in an onco-haematological patient early after anthracycline treatment (3 weeks). (b) The corresponding short-axis view using the late gadolinium enhancement technique, showing enhancement in the mid infero-lateral wall.

Only two small studies have demonstrated the early presence of myocardial oedema by CMR in patients treated with cardiotoxic chemotherapy.[13,32] Specifically, Grover *et al.* found a significant relationship between the presence of oedema (myocardium/skeletal ratio ≥ 2) and a lower RVEF at 12 months. Conversely, Jordan *et al.*[33] did not find differences in myocardial oedema during 3 months of chemotherapy; however these authors only evaluated a mid-short axis view, and this could have influenced the negative result. Regardless, no prognostic data are available regarding the detection of oedema by CMR after chemotherapy.

Several groups are promoting quantitative T2 mapping as being more sensitive than qualitative and semi-quantitative analyses.[34] Indeed, T2 mapping allows monitoring the inflammatory state regionally and serially as well as across subjects. However, we are still in the research phase, and no data have been published in cardiac oncology; due to technical challenges, translation to the clinical area is pending.

Myocardial hyperaemia

The increased blood volume in an inflamed area leads to higher uptake of contrast agent during the early vascular phase. Myocardial hyperaemia is usually assessed using T1 FSE pulse sequences, acquired before and shortly after gadolinium-based contrast administration, by the demonstration of an increased signal intensity ratio between the myocardium and skeletal muscle.

In a small study on 22 patients, early enhancement of the myocardium increased significantly at the end of doxorubicin; this was negatively correlated with the LVEF and returned to the same value of the skeletal muscle within 6 months.[35]

T1 FSE sequences are time-consuming and vulnerable to inconsistent image quality. Conversely, cine SSFP images used to quantify biventricular parameters acquired shortly after gadolinium-based contrast administration may provide a valid and rapid alternative for the evaluation of myocardial hyperaemia.[36] Regrettably, no data for oncologic patients are available in the literature.

Macroscopic necrosis/fibrosis

CMR is a unique non-invasive technique validated for the detection of myocardial necrosis/fibrosis by acquiring T1 inversion recovery sequences after approximately 10 min following gadolinium-based contrast injection. Using this approach, which is called late gadolinium enhancement (LGE), the necrotic/fibrotic areas that retain the contrast appear hyper-intense (Fig. 2b), and their presence is strongly correlated with prognosis in all cardiomyopathies.[37]

Although many gadolinium-based contrasts for the heart are at present designated as off-label use by the U.S. Food and Drug Administration and in many European countries, the incidence of adverse reactions in the off-label setting of CMR was found to not be different from the incidence in the FDA-approved general radiology setting.[38] The use of these agents was proved to be relatively safe[39] and should be limited only in patients with severe renal insufficiency due to the potential risk of nephrogenic systemic fibrosis and in patients with previous severe allergic reactions to gadolinium.[40]

Two small studies failed to detect the presence of LGE[11,12] in chemotherapy-treated patients. Conversely, other relatively small studies have reported the presence of non-ischaemic areas of LGE with a prevalence between 6 and 100%.[41,42] The potential prognostic

value of LGE was weakly shown in two retrospective studies, in which approximately 40% of patients with LGE had no improvement or further decline in LVEF.[42,43] Moreover, in a single, small prognostic study, the presence of LGE was not an independent predictor of adverse cardiovascular outcomes, though the incidence of the events was low.[14]

The amount of fibrosis depends on many variables, such as cumulative dose, individual response, age and presence of comorbidities. Thus, larger studies with longer follow-up are needed for an understanding of the prevalence and prognostic impact of LGE in monitoring CTX.

Finally, when using the LGE technique, it is also possible to evaluate pericardial enhancement as a sign of pericardial inflammation, with the imposition of aggressive anti-inflammatory therapy to prevent late constrictive pericarditis.[44]

Diffuse myocardial fibrosis

LGE is able to detect only macroscopic fibrosis. However, chemotherapy-treated patients can develop mild diffuse myocardial fibrosis that can be detected by T1 mapping with the evaluation of the extracellular volume (ECV).

T1 values of the myocardium and blood pool before and after the 15-min administration of gadolinium-based contrast are necessary to estimate the myocardial ECV according to the formula $ECV = [1/T1(myocardium_{post}) - 1/T1(myocardium_{pre})]/[1/T1(blood_{post}) - 1/T1(blood_{pre})] (1\text{-}Hct)$, where Hct is the blood haematocrit.[45,46]

Some small studies have reported encouraging results on the use of T1 mapping in chemotherapy-induced heart damage. Toro-Salazar *et al.*[22] measured the mean T1 values of 46 long-term survivors in comparison with volunteers and found that T1 values after contrast administration were significantly lower in the study subjects, revealing mild diffuse fibrosis. Tham *et al.*[47] studied 30 paediatric patients at least 2 years after anthracycline administration, showing that increased ECV correlated with a decreased mass/volume ratio, decreased LV wall thickness/height ratio, lower peak VO(2), and higher cumulative dose.

In addition, Neilan *et al.*[48] showed that the ECV of 42 patients previously treated with anthracyclines was significantly higher in comparison to age-matched controls, with the ECV being positively correlated with the left atrial volume and negatively correlated with diastolic function.

T1 mapping represents a very useful technique that is able to detect changes in the molecular features of the myocardium prior to the occurrence of functional alterations. Nevertheless, its role in the detection of the early CTX should be further investigated to provide a prognostic role for these findings and to ascertain whether this technique can improve the management of patients.

The emerging role of iron

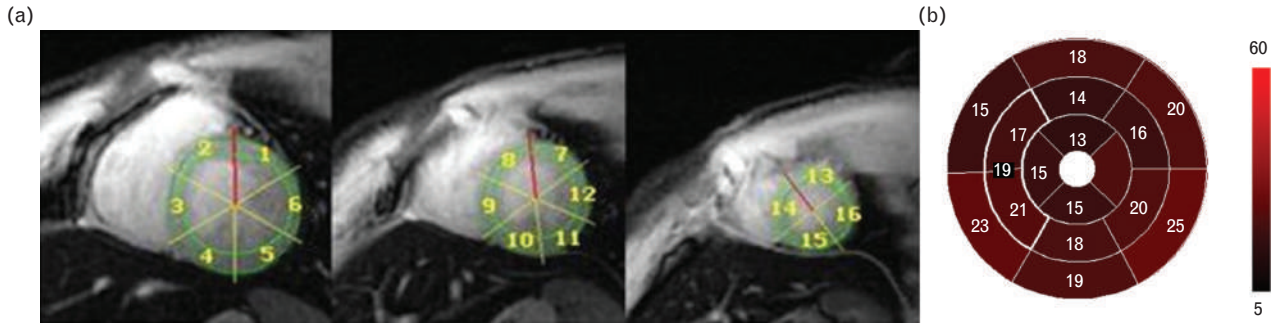
Cardiac damage induced by anthracyclines appears to be partially dependent on the alteration of intracellular iron metabolism. Recent evidence has revealed that CTX is mitigated by iron chelators and not by antioxidants, suggesting that anthracycline iron-mediated damage relies on complicated alterations of the intracellular metabolic pathways involved in the inhibition of iron regulatory proteins.[49] Cascales *et al.*[50] demonstrated that the post-mortem iron concentration in patients with genetic haemochromatosis is strongly related to the cumulative doxorubicin dose, independently from liver iron overload and transfusion therapy. Miranda *et al.*[51] found that mice affected by genetic haemochromatosis were more susceptible to anthracycline-mediated myocardial damage and burdened with a poor survival in comparison to wild-type subjects. CMR is a unique approach for quantifying non-invasive myocardial iron overload (MIO) by exploiting the paramagnetic properties of iron, which shortens the T2$*$ relaxation time.[52] The multi-slice multi-echo T2$*$ technique (Fig. 3) is a validated method for detecting global and segmental MIO in haemochromatosis,[53,54] allowing the identification of different MIO patterns and correlating with an increased risk of heart failure and biventricular dysfunction.[55] Although evaluations of MIO in patients treated with anthracyclines has not yet been performed, patients at risk of increased MIO (primary and secondary haemocromatosis also due to multiple blood transfusions) should be screened for MIO before starting anthracyclines and in the follow-up. In fact, new oral iron chelation agents[56] could have a potential role in cardioprotection strategies.

Nuclear imaging techniques and cardiotoxicity

Although echocardiography and CMR are the two most commonly used imaging techniques for non-invasive CTX, nuclear imaging may still have a role in the evaluation and monitoring of cancer patients treated with cardiotoxic drugs. In fact, nuclear imaging techniques employing specific radiotracer molecules represent an emerging tool for the non-invasive detection of biological processes preceding anatomical involvement and physiological consequences of myocardial damage induced by antineoplastic drugs.

The role of nuclear techniques for evaluating LVEF is limited and principally based on 99m Technetium (Tc)-erythrocyte multi-gated radionuclide angiography (MUGA), a non-invasive technique using 99mTc to visualize the cardiac blood pool through a γ camera with gated acquisition.[57] Although MUGA provides accurate and highly reproducible quantification of LV volumes and LVEF during cancer therapy,[58] it can be

Fig. 3



(a) Three short-axis slices (basal, medium and apical) acquired using T2∗ multi-echo sequences with endocardial and epicardial contours of the manually traced left ventricular. (b) Representative bull's eye maps identifying a heterogeneous pattern of myocardial iron overload with a global heart T2∗ value greater than 20 ms (normal cut-off 20 ms) in an onco-haematological patient treated with anthracyclines and requiring multiple red blood cell transfusions.

hampered by soft tissue attenuation artefacts and also exposes the patient to ionizing radiation.[59] As a consequence, in clinical practice, this technique is preferred when echocardiography as a first-line or CMR as a second-line approach are not feasible or available. However, the capability of MUGA to accurately assess diastolic dysfunction in patients with breast cancer treated with trastuzumab (Tz) has been documented,[60] suggesting the potential role of a diastolic parameter, the diastolic time to peak filling rate, in the early screening of CTX.

Moreover, new cadmium-zinc-telluride camera allows obtaining 3D MUGA with low dose (dose $<$ 2mSv) and thus the possibility to achieve information with high safety, about right and left ventricular function (ejection fraction, systolic and diastolic volumes), intra-ventricular and inter-ventricular dyssynchrony (Fig. 4). Nevertheless, further clarification about the additive predictive value of this parameter is needed.

Very promising results were been obtained with 123Iodio (123I)-metaiodobenzylguanidine (123I-MIBG) single-photon emission computed tomography (SPECT). 123I-MIBG is a 123I-labelled norepinephrine analogue used in the non-invasive assessment of sympathetic myocardial innervation. Because 123I-MIBG is not metabolized, it reflects neuronal integrity and cardiac status.[61] Studies conducted in asymptomatic patients treated with anthracyclines have revealed that assessment of myocardial adrenergic derangement with 123I-MIBG SPECT was able to identify patients at risk of developing CTX[62,63] and that the degree of myocardial adrenergic impairment was related to anthracycline dose.[62] These findings suggest new potential applications of nuclear cardiac innervation assessment in the early detection of CTX. However, such evidence requires confirmation in larger studies.

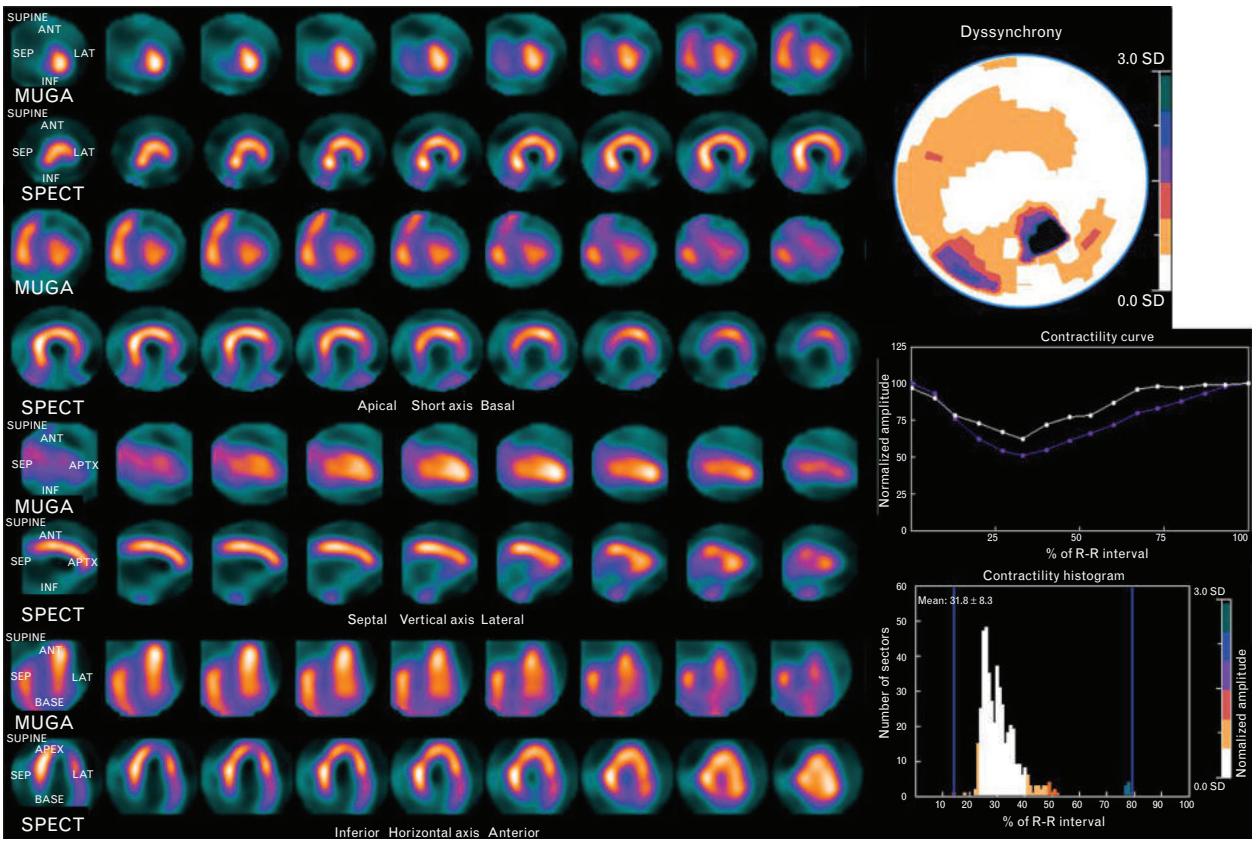
Interesting results have also been obtained using specific radiotracer molecules, such as ^{111}indium (In)-antimyosin, ^{99m}Tc-annexin V, ^{123}I-15-(P-iodophenyl)-3-(R,S)-methylpentadecanoic and ^{111}In-Tz.

The immunoscintigraphic agent ^{111}In-antimyosin is a specific marker of myocardial cell injury and necrosis, and its role in assessing subclinical impairment of LV function in patients treated with anthracyclines was already well documented approximately 20 years ago.[64–66] In patients affected by breast cancer without cardiovascular risk factors, it has been demonstrated that the uptake of ^{111}In-antimyosin increases after anthracycline chemotherapy and that the degree of uptake is correlated with changes in LVEF[65] and anthracycline dosage.[64] Moreover, in some patients, the radiotracer uptake was found to be independent of a significant reduction in LVEF, suggesting that this technique may be used to recognize cellular damage prior to the onset of LV functional impairment.[64] In addition, ^{111}In-antimyosin could also be useful in discriminating between patients with transient and persistent LV dysfunction and in guiding clinical decisions about the discontinuation of anthracycline therapy.[66]

Annexin V shows high affinity for the phosphatidylserine molecules exposed on the outer surface of the myocardial cell membrane at the early stages of anthracycline-induced cardiomyopathy. In in-vivo studies, annexin V labelled with ^{99m}Tc has been used to assess acute and chronic doxorubicin-induced cardiomyopathy.[67,68] However, studies in humans are needed to clarify the role of ^{99m}Tc-annexin V scintigraphy in the nuclear imaging of CTX.

Taxanes, antineoplastic drugs used in the treatment of several tumours, can induce CTX, impairing myocardial microtubular transport system and producing a significant perturbation in the free fatty acid oxidation system.[69]

Fig. 4



3D MUGA obtained by new cadmium-zinc-telluride camera and myocardial perfusion imaging in the patient with silent myocardial infarction and previous non-Hodgkin lymphoma: information about right and left ventricular function (ejection fraction, systolic and diastolic volumes), intra-ventricular and inter-ventricular dyssynchrony (courtesy of Dr Alessia Gimelli, U.O.C. Medicina Nucleare, Fondazione Toscana G. Monasterio C.N.R., Pisa, Italy).

One free fatty acid, 15-(*p*-iodophenyl)-3-(*R*,*S*)-methyl-pentadecanoic acid, labelled with ^{123}I (^{123}I-BMIPP) has been used to assess taxane-induced cardiomyopathy.[70,71] In these studies, the BMIPP uptake score was reduced after chemotherapy compared with that measured before treatment,[70] and the degree of reduction was related to the administered dose of the drug and was also directly associated with the development of LV dysfunction.[71]

Attractive results were also obtained with ^{111}In-labelled Tz in patients with metastatic breast cancer. Tz, a chemotherapeutic agent with a direct effect on human epidermal growth ^{70}factor receptor 2 (HER2) is often used as second-line therapy.[72] It has been demonstrated that anthracyclines can increase the levels of HER2 expressed by myocytes; as a consequence, such patients with high myocyte expression of HER2 as candidates for receiving Tz have a high risk of developing CTX, likely as a result of the inhibition of cardiac HER2, which activates the apoptotic pathways and amplifies anthracycline oxidative stress.[72]

^{111}In-Tz SPECT was been used to identify patients with high myocardial levels of HER2 receptors and at an elevated risk of developing LV dysfunction.[73,74] However, contrasting results have been obtained in studies of ^{111}In-Tz SPECT. In a small preliminary study, Behr *et al.*[73] investigated ^{111}In-Tz scintigraphy in 20 metastatic breast cancer patients expressing the HER2/neu receptor, pre-treated with anthracyclines, and scheduled for Tz administration as second-line therapy. These authors documented myocardial ^{111}In-Tz uptake in seven patients; of these, six developed clinical heart failure, whereas none of 13 patients without uptake had adverse cardiac events, suggesting that pre-treatment scanning with ^{111}In-Tz could predict CTX. Opposite results were obtained by Perik *et al.*[74] These authors enrolled 15 breast cancer patients that were candidates for receiving Tz as second-line therapy and performed ^{111}In-Tz SPECT scintigraphy within 24 h after the first Tz infusion and again after 12 h; the results showed myocardial uptake at the start of Tz in only one patient who had

received extensive anthracycline pre-treatment and had cardiac ventricular arrhythmias before the Tz treatment. However, no myocardial uptake was observed in the three patients who developed severe symptomatic left ventricular dysfunction during Tz and paclitaxel treatment. It should be noted that these data are from single-centre studies of limited sample size. Indeed, there could be mechanisms not yet elucidated that in addition to HER2 receptor inhibition, are involved in Tz-CTX, which might explain these conflicting results.

PET is the gold standard technique for assessing myocardial metabolism and perfusion. However, the role of PET in the early detection of CTX is still debated.[75] Nony *et al.*[76] showed a significant decrease in LVEF assessed by radionuclide angiography after treatment with doxorubicin, but no significant effect was observed in myocardial blood flow evaluated with PET in six female cancer patients without heart disease. Recently, Borde *et al.*[77] analysed changes in myocardial glucose metabolism using FDG-PET and suggested that a greater utilization of this substrate constitutes evidence of a cellular alteration preceding the CTX cascade in patients treated with adriamycin. Similarly to SPECT, PET imaging can play a key role in the evaluation of cardiac autonomic dysfunction associated with heart failure,[78] providing several advantages over SPECT, with higher spatial and temporal resolution and routinely available attenuation correction. In addition, PET radiotracers more closely resemble endogenous neurotransmitters than the ^{123}MIBG used for SPECT imaging, and the variety of available tracers may allow more detailed analysis of neuronal signalling.[79] Regardless, studies are needed to validate these new radiotracers in the field of cardio-oncology, in addition to the complexity of radiolabeling ligands, requirements of labour and specific knowledge, the high cost and the low availability limit the clinical use of PET.[80]

Conclusion

Based on the recent joint consensus document of the European Association of Cardiovascular Imaging and American Society of Echocardiography, the use of CMR is recommended for the quantification of LVEF when the quality of echocardiogram is suboptimal. Furthermore, CMR is suggested for confirming a LVEF less than 53%. In follow-up assessments, CMR is recommended for the quantification of LVEF in cases of possible discontinuation of chemotherapeutic regimens as a result of CTX or when LVEF estimation by echocardiography is controversial or unreliable due to technical constrains.[2]

Nonetheless, in the evaluation of CTX, the additive and incremental value of CMR is represented by its unique competence for providing information on tissue characterization, such as oedema, iron overload, hyperaemia and diffuse fibrosis, which have all been associated with early CTX. The early appreciation of these findings can play a crucial role in the management of patients treated with chemotherapy because it may allow the implementation of a timely and optimal cardioprotective regimen, thereby justifying the relatively higher cost of CMR compared with echocardiography. Future studies should explore the role of CMR upstream to the diagnostic algorithm for the management of CTX using as gatekeepers either biomarkers, a high-risk profile for CTX or a borderline dysfunction by 2DE.

Standard safety precautions for CMR must be observed, taking into account the electromagnetic interference, among others. A major limitation is the restricted availability of CMR laboratories with standardized quality criteria.[81]

Finally, larger and prospective studies are necessary to definitively introduce CMR into current clinical practice and to define its role in the management of CTX based on a cost/effectiveness balance.

MUGA, though also providing highly reproducible quantification of LVEF during cancer therapy, retains its principal limitation: radiation exposure. Therefore, this technique should be considered only when echocardiography as the front line or CMR as the second line are not feasible or available.[2] However, owing to the use of new molecular tracers, nuclear imaging offers interesting future perspectives in the early detection of myocardial damage and deserves further evaluation in larger studies and in prospective clinical trials.

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References

1 Seidman A, Hudis C, Pierri MK, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**:1215–1221.
2 Plana JC, Galderisi M, Barac A, *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**:1063–1093.
3 Hoffmann R, Barletta G, von Bardeleben S, *et al.* Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. *JASE* 2014; **27**:292–301.
4 Thavendiranathan P, Grant AD, Negishi T, *et al.* Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol* 2013; **61**:77–84.
5 Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? *J Clin Oncol* 2008; **26**:1201–1203.

6 Sawaya H, Sebag IA, Plana JC, *et al.* Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging* 2012; **5**:596–603.

7 Goenka AH. Flamm SD: cardiac magnetic resonance imaging for the investigation of cardiovascular disorders. Part 1: current applications. *Tex Heart Inst J* 2014; **41**:7–20.

8 Marsella M, Borgna-Pignatti C, Meloni A, *et al.* Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. *Haematologica* 2011; **96**:515–520.

9 Alfakih K, Bloomer T, Bainbridge S, *et al.* A comparison of left ventricular mass between two-dimensional echocardiography, using fundamental and tissue harmonic imaging, and cardiac MRI in patients with hypertension. *Eur J Radiol* 2004; **52**:103–109.

10 Armstrong GT, Plana JC, Zhang N, *et al.* Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. *J Clin Oncol* 2012; **30**:2876–2884.

11 Drafts BC, Twomley KM, D'Agostino R Jr, *et al.* Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging* 2013; **6**:877–885.

12 Ylanen K, Poutanen T, Savikurki-Heikkila P, *et al.* Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyclines among long-term survivors of childhood cancer. *J Am Coll Cardiol* 2013; **61**:1539–1547.

13 Oberholzer K, Kunz RP, Dittrich M, Thelen M. Anthracycline-induced cardiotoxicity: cardiac MRI after treatment for childhood cancer. *Rofo* 2004; **176**:1245–1250.

14 Neilan TG, Coelho-Filho OR, Pena-Herrera D, *et al.* Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines. *Am J Cardiol* 2012; **110**:1679–1686.

15 Gulati A, Jabbour A, Ismail TF, *et al.* Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013; **309**:896–908.

16 Mewton N, Opdahl A, Choi EY, *et al.* Left ventricular global function index by magnetic resonance imaging–a novel marker for assessment of cardiac performance for the prediction of cardiovascular events: the multi-ethnic study of atherosclerosis. *Hypertension* 2013; **61**:770–778.

17 Tassan-Mangina S, Codorean D, Metivier M, *et al.* Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. *Eur J Echocardiogr* 2006; **7**:141–146.

18 Grassedonio E, Todiere G, La Grutta L, *et al.* Assessment of atrial diastolic function in patients with hypertrophic cardiomyopathy by cine magnetic resonance imaging. *Radiol Med* 2015; **120**:714–722.

19 Buss SJ, Krautz B, Schnackenburg B, *et al.* Classification of diastolic function with phase-contrast cardiac magnetic resonance imaging: validation with echocardiography and age-related reference values. *Clin Res Cardiol* 2014; **103**:441–450.

20 Mercuro G, Cadeddu C, Piras A, *et al.* Early epirubicin-induced myocardial dysfunction revealed by serial tissue Doppler echocardiography: correlation with inflammatory and oxidative stress markers. *Oncologist* 2007; **12**:1124–1133.

21 Lunning MA, Kutty S, Rome ET, *et al.* Cardiac magnetic resonance imaging for the assessment of the myocardium after doxorubicin-based chemotherapy. *Am J Clin Oncol* 2015; **38**:377–381.

22 Toro-Salazar OH, Gillan E, O'Loughlin MT, *et al.* Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. *Circ Cardiovasc Imaging* 2013; **6**:873–880.

23 Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009; **53**:2231–2247.

24 Yildirim A, Sedef Tunaoglu F, Pinarli FG, *et al.* Early diagnosis of anthracycline toxicity in asymptomatic long-term survivors: dobutamine stress echocardiography and tissue Doppler velocities in normal and abnormal myocardial wall motion. *Eur J Echocardiogr* 2010; **11**:814–822.

25 Jarfelt M, Kujacic V, Holmgren D, *et al.* Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2007; **49**:835–840.

26 Bountioukos M, Doorduijn JK, Roelandt JR, *et al.* Repetitive dobutamine stress echocardiography for the prediction of anthracycline cardiotoxicity. *Eur J Echocardiogr* 2003; **4**:300–305.

27 Lanzarini L, Bossi G, Laudisa ML, *et al.* Lack of clinically significant cardiac dysfunction during intermediate dobutamine doses in long-term childhood cancer survivors exposed to anthracyclines. *Am Heart J* 2000; **140**:315–323.

28 Task Force Members. Montalescot G, Sechtem U, *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; **34**:2949–3003.

29 Greenwood JP, Maredia N, Younger JF, *et al.* Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012; **379**:453–460.

30 Schwitter J, Wacker CM, Wilke N, *et al.* MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013; **34**:775–781.

31 Abdel-Aty H, Boye P, Zagrosek A, *et al.* Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. *J Am Coll Cardiol* 2005; **45**:1815–1822.

32 Grover S, Leong DP, Chakrabarty A, *et al.* Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: a prospective study using novel cardiac imaging and biochemical markers. *Int J Cardiol* 2013; **168**:5465–5467.

33 Jordan JH, D'Agostino RB Jr, Hamilton CA, *et al.* Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2014; **7**:872–879.

34 Giri S, Chung YC, Merchant A, *et al.* T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson* 2009; **11**:56.

35 Wassmuth R, Lentzsch S, Erdbruegger U, *et al.* Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging-a pilot study. *Am Heart J* 2001; **141**:1007–1013.

36 Perfetti M, Malatesta G, Alvarez I, *et al.* A fast and effective method to assess myocardial hyperemia in acute myocarditis by magnetic resonance. *Int J Cardiovasc Imaging* 2014; **30**:629–637.

37 Mahrholdt H, Wagner A, Judd RM, *et al.* Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J* 2005; **26**:1461–1474.

38 Bruder O, Schneider S, Nothnagel D, *et al.* Acute adverse reactions to gadolinium-based contrast agents in CMR: multicenter experience with 17,767 patients from the EuroCMR Registry. *JACC Cardiovascular Imaging* 2011; **4**:1171–1176.

39 Meloni A, Favilli B, Positano V, *et al.* Safety of cardiovascular magnetic resonance gadolinium chelates contrast agents in patients with hemoglobinopathies. *Haematologica* 2009; **94**:1625–1627.

40 Thomsen HS. European Society of Urogenital R. European Society of Urogenital Radiology guidelines on contrast media application. *Curr Opin Urol* 2007; **17**:70–76.

41 Fallah-Rad N, Walker JR, Wassef A, *et al.* 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.

42 Fallah-Rad N, Lytwyn M, Fang T, *et al.* Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson* 2008; **10**:5.

43 Wadhwa D, Fallah-Rad N, Grenier D, *et al.* Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast Cancer Res Treat* 2009; **117**:357–364.

44 Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. *J Cardiovasc Magn Reson* 2009; **11**:14.

45 Moon JC, Messroghli DR, Kellman P, *et al.* Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013; **15**:92.

46 Dabir D, Child N, Kalra A, *et al.* Reference values for healthy human myocardium using a T1 mapping methodology: results from the International T1 Multicenter cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2014; **16**:69.

47 Tham EB, Haykowsky MJ, Chow K, *et al.* Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson* 2013; **15**:48.

48 Neilan TG, Coelho-Filho OR, Shah RV, *et al.* Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. *Am J Cardiol* 2013; **111**:717–722.

49 Gammella E, Maccarinelli F, Buratti P, *et al.* The role of iron in anthracycline cardiotoxicity. *Front Pharmacol* 2014; **5**:25.

50 Cascales A, Sanchez-Vega B, Navarro N, *et al.* Clinical and genetic determinants of anthracycline-induced cardiac iron accumulation. *Int J Cardiol* 2012; **154**:282–286.
51 Miranda CJ, Makui H, Soares RJ, *et al.* Hfe deficiency increases susceptibility to cardiotoxicity and exacerbates changes in iron metabolism induced by doxorubicin. *Blood* 2003; **102**:2574–2580.
52 Gossuin Y, Roch A, Muller RN, *et al.* Relaxation induced by ferritin and ferritin-like magnetic particles: the role of proton exchange. *Magn Reson Med* 2000; **43**:237–243.
53 Ramazzotti A, Pepe A, Positano V, *et al.* Multicenter validation of the magnetic resonance T2∗ technique for segmental and global quantification of myocardial iron. *J Magn Reson Imaging* 2009; **30**:62–68.
54 Carpenter JP, Grasso AE, Porter JB, *et al.* On myocardial siderosis and left ventricular dysfunction in hemochromatosis. *J Cardiovasc Magn Reson* 2013; **15**:24.
55 Meloni A, Restaino G, Borsellino Z, *et al.* Different patterns of myocardial iron distribution by whole-heart T2∗ magnetic resonance as risk markers for heart complications in thalassemia major. *Int J Cardiol* 2014; **177**:1012–1019.
56 Pepe A, Meloni A, Capra M, *et al.* Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. *Haematologica* 2011; **96**:41–47.
57 Hesse B, Lindhardt TB, Acampa W, *et al.* EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging* 2008; **35**:851–885.
58 Altena R, Perik PJ, van Veldhuisen DJ, *et al.* Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol* 2009; **10**:391–399.
59 Walker J, Bhullar N, Fallah-Rad N, *et al.* 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.
60 Reuvekamp EJ, Bulten BF, Nieuwenhuis AA, *et al.* Does diastolic dysfunction precede systolic dysfunction in Trastuzumab-induced cardiotoxicity? Assessment with multigated radionuclide angiography (MUGA). *J Nucl Cardiol* 2015.
61 Perrone-Filardi P, Paolillo S, Dellegrottaglie S, *et al.* Assessment of cardiac sympathetic activity by MIBG imaging in patients with heart failure: a clinical appraisal. *Heart* 2011; **97**:1828–1833.
62 Carrio I, Estorch M, Berna L, *et al.* Indium-111-antimyosin and iodine-123-MIBG studies in early assessment of doxorubicin cardiotoxicity. *J Nucl Med* 1995; **36**:2044–2049.
63 Valdes Olmos RA, ten Bokkel Huinink WW, ten Hoeve RF, *et al.* Assessment of anthracycline-related myocardial adrenergic derangement by [123I]metaiodobenzylguanidine scintigraphy. *Eur J Cancer* 1995; **31A**:26–31.
64 Carrio I, Lopez-Pousa A, Estorch M, *et al.* Detection of doxorubicin cardiotoxicity in patients with sarcomas by indium-111-antimyosin monoclonal antibody studies. *J Nucl Med* 1993; **34**:1503–1507.
65 Estorch M, Carrio I, Martinez-Duncker D, *et al.* 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.
66 Valdes Olmos RA, ten Bokkel Huinink WW, ten Hoeve RF, *et al.* Usefulness of indium-111 antimyosin scintigraphy in confirming myocardial injury in patients with anthracycline-associated left ventricular dysfunction. *Ann Oncol* 1994; **5**:617–622.
67 Panjrath GS, Jain D. Monitoring chemotherapy-induced cardiotoxicity: role of cardiac nuclear imaging. *J Nucl Cardiol* 2006; **13**:415–426.
68 Panjrath GS, Patel V, Valdiviezo CI, *et al.* Potentiation of Doxorubicin cardiotoxicity by iron loading in a rodent model. *J Am Coll Cardiol* 2007; **49**:2457–2464.
69 Churchill CD, Klobukowski M, Tuszynski JA. Elucidating the mechanism of action of the clinically-approved taxanes: a comprehensive comparison of local and allosteric effects. *Chem Biol Drug Des* 2015; **86**:1253–1266.
70 Saito K, Takeda K, Imanaka-Yoshida K, *et al.* 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.
71 Saito K, Takeda K, Okamoto S, *et al.* 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.
72 Fedele C, Riccio G, Malara AE, *et al.* Mechanisms of cardiotoxicity associated with ErbB2 inhibitors. *Breast Cancer Res Treat* 2012; **134**:595–602.
73 Behr TM, Behe M, Wormann B. Trastuzumab and breast cancer. *N Engl J Med* 2001; **345**:995–996.
74 Perik PJ, Lub-De Hooge MN, Gietema JA, *et al.* Indium-111-labeled Tz scintigraphy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2006; **24**:2276–2282.
75 Basu S, Borde C, Kand P. Increasing cardiac (1)(8)F-fluorodeoxyglucose (FDG) uptake on PET-CT as a biomarker for cardiotoxicity of chemo-radiotherapy in cancer: a myth or a reality? *Radiother Oncol* 2014; **112**:451–452.
76 Nony P, Guastalla JP, Rebattu P, *et al.* 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.
77 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.
78 Lautamaki R, Tipre D, Bengel FM. Cardiac sympathetic neuronal imaging using PET. *Eur J Nucl Med Mol Imaging* 2007; **34 (Suppl 1)**:S74–S85.
79 Langer O, Halldin C. PET and SPET tracers for mapping the cardiac nervous system. *Eur J Nucl Med Mol Imaging* 2002; **29**:416–434.
80 Yeh ET, Vejpongsa P. Subclinical cardiotoxicity associated with cancer therapy: early detection and future directions. *J Am Coll Cardiol* 2015; **65**:2523–2525.
81 Plein S, Schulz-Menger J, Almeida A, *et al.* Training and accreditation in cardiovascular magnetic resonance in Europe: a position statement of the working group on cardiovascular magnetic resonance of the European Society of Cardiology. *Eur Heart J* 2011; **32**:793–798.