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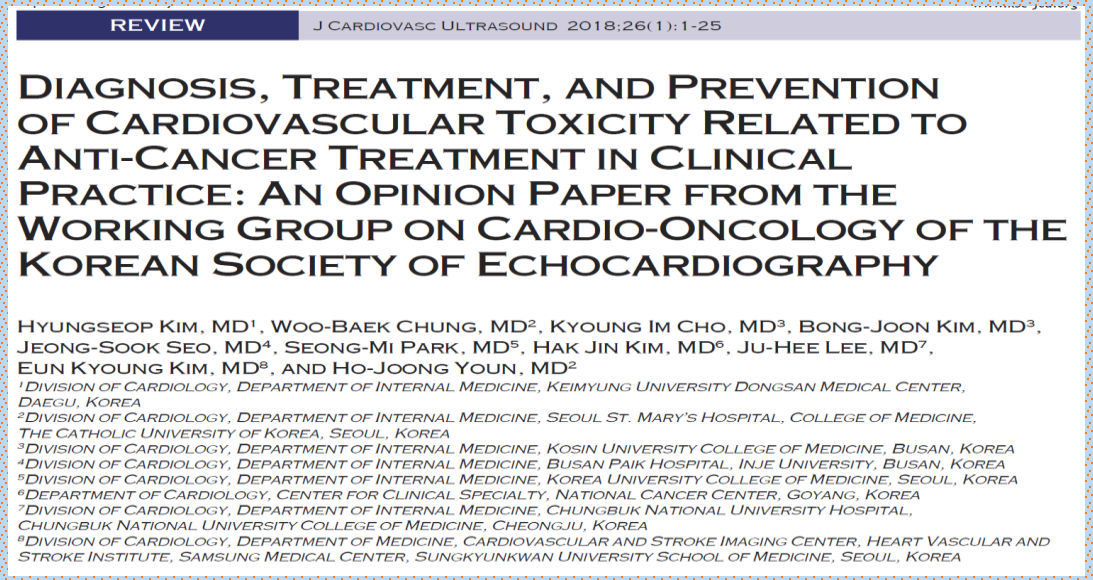
Dott. Matteo Salgarello
Dipartimento delle Alte Tecnologie
Ospedale Sacrocuore Don Calabria Negrar-VR

RM cardiaca ed Imaging Medico Nucleare

Biomarcatori e Imaging nella valutazione del danno miocardico



REVIEW J Cardiovasc Ultrasound 2018;26(1):1-25

Diagnosis, Treatment, and Prevention of Cardiovascular Toxicity Related to Anti-Cancer Treatment in Clinical Practice: An Opinion Paper from the Working Group on Cardio-Oncology of the Korean Society of Echocardiography

Hyungseop Kim, MD[1], Woo-Baek Chung, MD[2], Kyoung Im Cho, MD[3], Bong-Joon Kim, MD[3], Jeong-Sook Seo, MD[4], Seong-Mi Park, MD[5], Hak Jin Kim, MD[6], Ju-Hee Lee, MD[7], Eun Kyoung Kim, MD[8], and Ho-Joong Youn, MD[2]

[1]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
[2]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Division of Cardiology, Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea
[4]Division of Cardiology, Department of Internal Medicine, Busan Paik Hospital, Inje University, Busan, Korea
[5]Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[6]Department of Cardiology, Center for Clinical Specialty, National Cancer Center, Goyang, Korea
[7]Division of Cardiology, Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
[8]Division of Cardiology, Department of Medicine, Cardiovascular and Stroke Imaging Center, Heart Vascular and Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Imaging anatomo-funzionale di II e III livello nella valutazione del danno miocardico

Table 1. Common chemotherapeutic agents related with cardiomyopathy

Group	Agent
Anthracyclines	Doxorubicin*
	Epirubicin
	Idarubicin*
Alkylating agents	Cyclophosphamide*
	Ifosfamide*
Antimetabolites	Clofarabine*
Antimicrotuble agents	Docetaxel*
Monoclonal antibody-based tyrosine kinase inhibitors	Bevacizumab*
	Trastuzumab*
Proteasome inhibitors	Bortezomib
Small molecular tyrosine kinase inhibitors	Sunitinib*
	Imatinib mesylate
	Lapatinib
	Dasatinib

*Drugs are considered frequent and important for cardiomyopathy

Table 2. Common chemotherapeutic agents related with ischemic heart disease

Group	Agent
Antimetabolites	Capecitabine*
	Fluorouracil*
Antimicrotuble agents	Docetaxel
	Paclitaxel
Monoclonal antibody-based tyrosine kinase inhibitors	Bevacizumab*
Small molecular tyrosine kinase inhibitors	Sorafenib*
	Eriotinib

*Drugs are considered frequent and important for cardiomyopathy

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Imaging anatomo-funzionale di II e III livello nella valutazione del danno miocardico

Table 3. Chemotherapeutic agents associated with cardiac arrhythmias

Arrhythmia	Agent
Sinus bradycardia	Taxane, thalidomide
Atrioventricular block	Taxane, anthracyclines, cyclophosphamide
	5-FU, rituximab
Atrial fibrillation	Alkylating agents, anthracyclines, taxane
	5-FU, gemcitabine
Ventricular tachycardia	Doxorubicin, alkylating agents

5-FU: 5-fluorouracil

Table 4. Chemotherapeutic agents associated with QT prolongation

Group	Agent
Tyrosine kinase inhibitors	Sunitinib, sorafenib, vandetanib, nilotinib
Histone deacetylase inhibitors	Vorinostat, despipeptide (FK-228, romidepsin), panobinostat
Anthracyclines	Doxorubicin
Arsenic trioxide	

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Table 6. Comp

	(mg/m^2)
Doxorubicin	
Doxorubicin	
Doxorubicin	
Doxorubicin	
Doxorubicin	
Epirubicin	
Mitoxantrone	
Daunorubicin	
Idarubicin	
Doxorubicin +	
Doxorubicin, 3	

2005. The estimated incidence of trastuzumab-associated cardiotoxicity is 2–28%: 2–7% with single trastuzumab treatment, 2–13% in combination with paclitaxel, and up to 27% with concomitant treatment with anthracycline/cyclophosphamide.[77-79]

Unlike anthracycline-induced type I toxicity, the cardiac toxicity caused by trastuzumab is considered type II toxicity, which can resolve almost completely if the drug is discontinued. Despite the limited data for Asian patients, the risk factors for cardiac toxicity include old age (> 50 years), a mildly decreased LVEF, underlying CV diseases, and a previous history of accumulated doses of doxorubicin (> 300 mg/m^2).[80-83] Recently, regular evaluation of cardiac function every three months has been recommended in trastuzumab treatment.[3] Furthermore, cardiac Tn-I level and two-dimensional (2D) strain on echocardiography are useful tools for the early detection of LV dysfunction or toxicity and are recommended in every cycle of trastuzumab treatment in high-risk patients.[84-86]

Quando introdurre un test di II e III livello nella diagnostica della cardiotossicità durante trattamenti in oncologia?

Nella prevenzione della HF → non esistono prove scientifiche robuste che giustifichino l'uso di test di questo livello in questo setting clinico

Nella determinazione precoce della HF → in questo caso oltre all'ecografia possono essere proposti test come RM e il MUGA entrambi presentano elevata accuratezza nelle misure con gli svantaggi rispettivamente del costo (RM) e delle radiazioni ionizzanti (MUGA)

La contemporanea presenza di fattori di rischio potrebbe far prendere in considerazione test diversi dal dato ecografico nel monitoraggio della funzione ventricolare →

Table 7. Conventional risk factors of chemotherapy induced cardiotoxicity

Female sex
Age (< 18 years old, > 75 years old)
Uncontrolled hypertension or diabetes mellitus
Renal failure
Previous history of cardiotoxicity
Pre-existing heart disease: LV hypertrophy, coronary artery disease
Cardiomyopathy: reduced LV ejection fraction
Concomitant or previous radiation therapy involving heart
Concomitant chemotherapy: anthracyclines/trastuzumab

LV: left ventricular

Quale introdurre un test di II e III livello nella diagnostica della cardiotossicità durante trattamenti in oncologia?

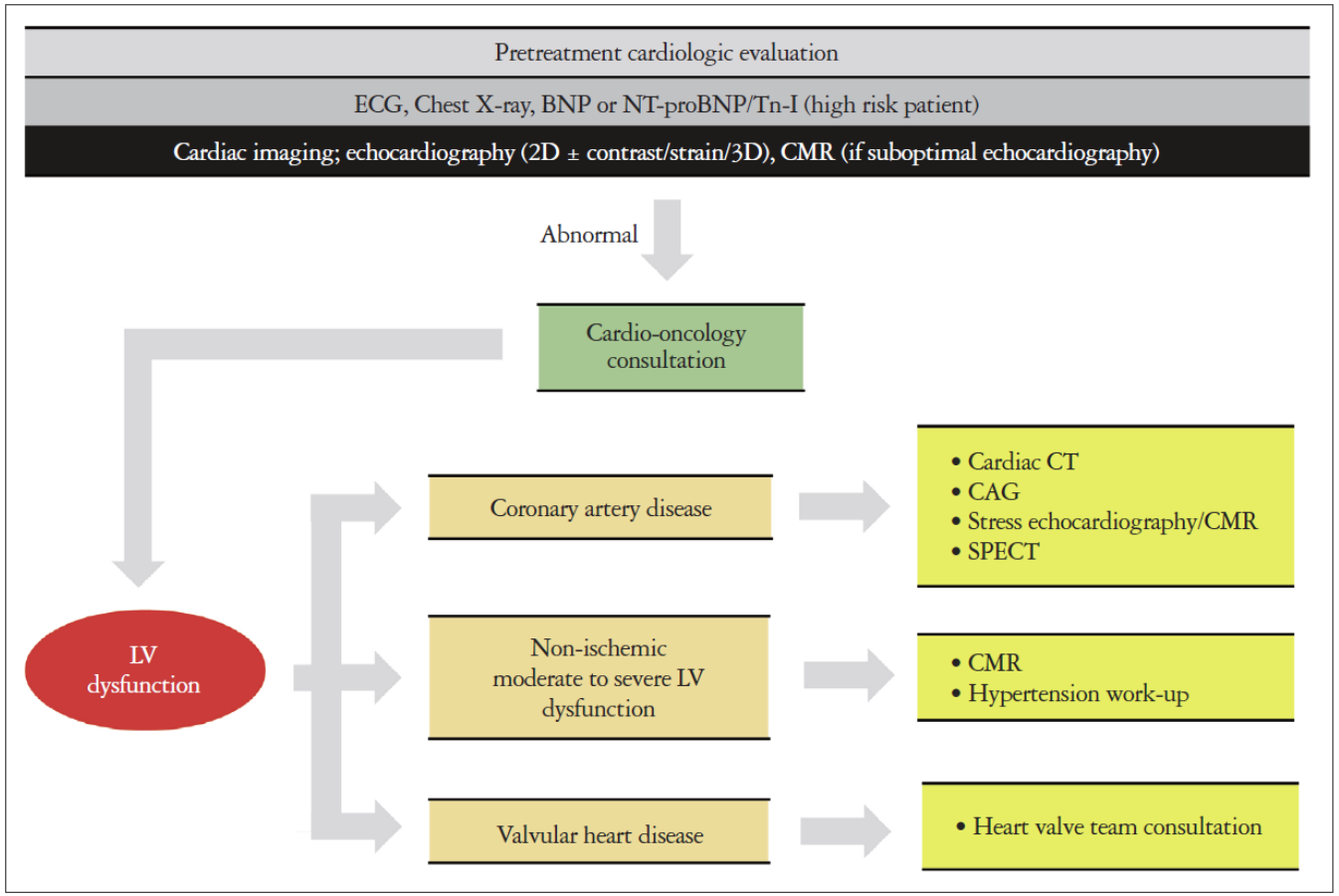


Fig. 2. Approach of LV dysfunction in diagnostic or therapeutic modalities. Baseline cardiac imaging for LV function can be performed using 2D-echocardiography (or contrast-/3D-echocardigraphy) or strain. In case of LV dysfunction, cardio-oncologic consultation is required, and the etiologies of LV dysfunction should be evaluated using appropriate imaging modalities, including CMR, CAG, SPECT, and cardiac CT. ECG: electrocardiography, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, Tn-I: troponin-I, 2D: two-dimensional, 3D: three-dimensional, CMR: cardiac magnetic resonance, LV: left ventricle, CT: computed tomography, CAG: coronary angiography, SPECT: single-photon emission computed tomography.

Quale test di II e III livello introdurre nella diagnostica della cardiotossicità durante trattamenti in oncologia?

Risonanza Magnetica: presenta una elevata risoluzione spaziale

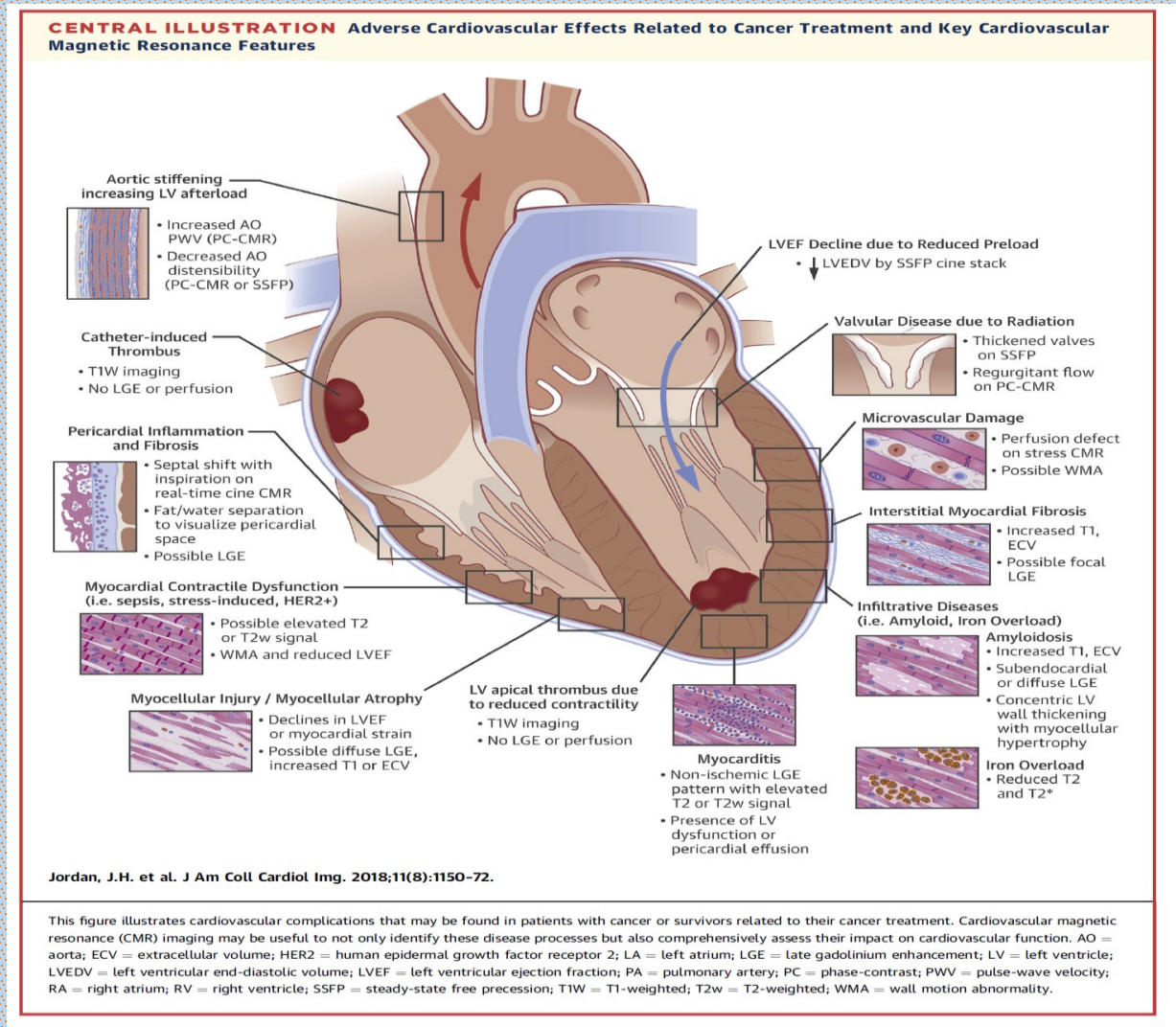
non espone a radiazioni ionizzanti “vantaggi significativi per esami ripetuti e pazienti giovani”

precocità nella determinazione del danno

presenta qualche svantaggio nei pazienti con ridotta funzionalità renale

Qualità della Risonanza Magnetica nella valutazione della HF del paziente oncologico

Caratterizzazione del tessuto cardiaco: presenta capacità di caratterizzare il danno sia nella forma acuta che subacuta della tossicità, infiammazione, edema e nel danno cronico la fibrosi e le cicatrici.



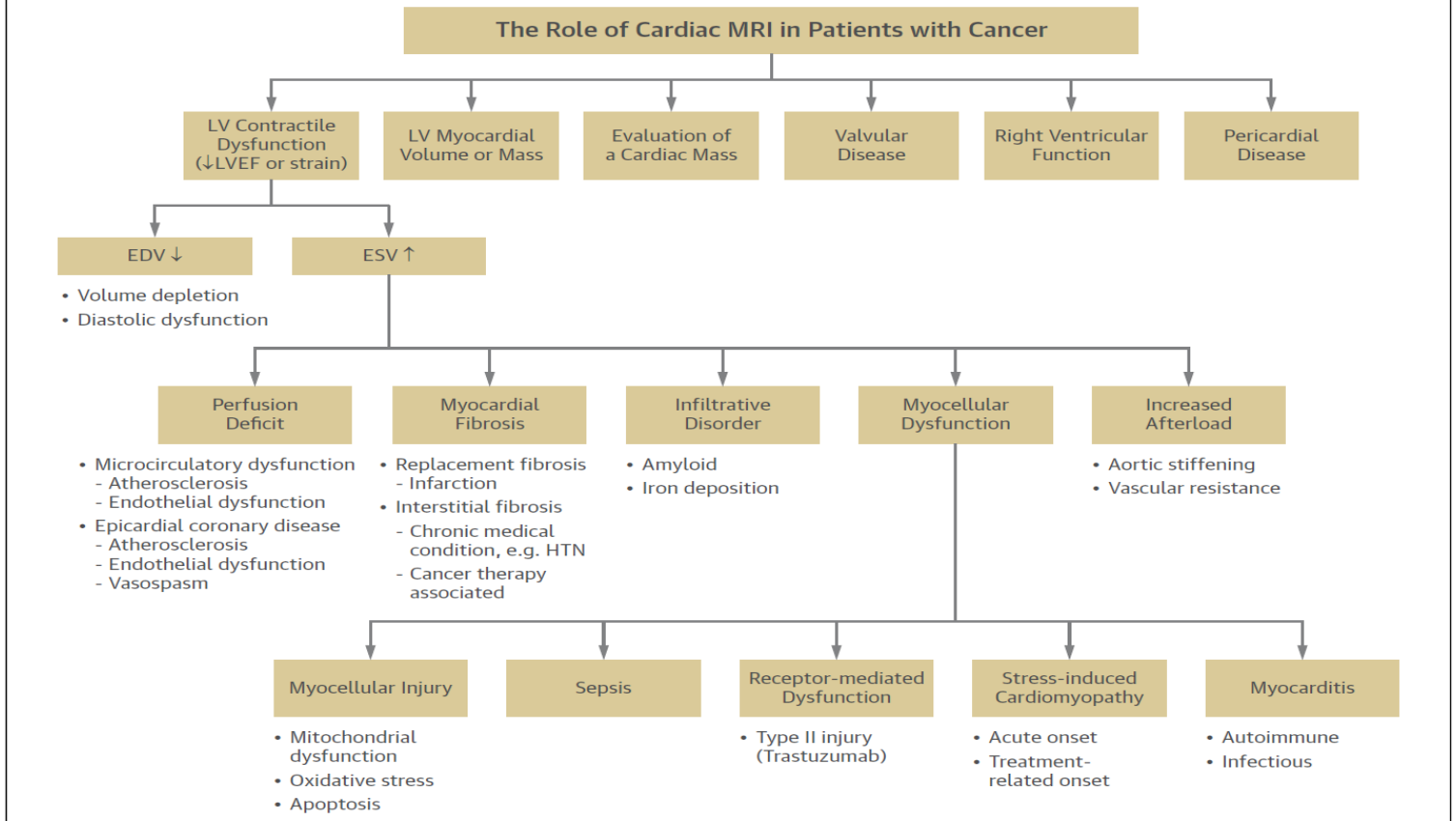
Qualità della Risonanza Magnetica nella valutazione della HF del paziente oncologico

Determinazione della funzione cardiaca: LVEF è il parametro più importante nella valutazione della tossicità, la Risonanza Magnetica nella misura di questo parametro può essere considerata una indagine Gold Standard.
Viene inoltre misurato con accuratezza il volume ventricolare e la massa ventricolare.

Elevata precisione
(operatore dipendente- indipendente)

Accuratezza

FIGURE 1 The Role of Cardiovascular Magnetic Resonance in Patients With Cancer



Cardiovascular magnetic resonance imaging may be used to identify a number of cancer-associated conditions or treatment-related effects. EDV = end-diastolic volume; ESV = end-systolic volume; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

TABLE 2 Cardiovascular Magnetic Resonance Imaging Methods to Assess the Left Ventricle in Cardio-Oncology

Left Ventricle
Anatomy • Single-phase white-blood imaging in 2-, 3-, and 4-chamber views • Cine white-blood imaging in short-axis orientation for assessment of LVEDV, LVESV, stroke volume, LVEF, and LV mass
Function/flow • Cine white-blood imaging in short-axis orientation for assessment of LV wall motion abnormalities • Short- and long-axis strain imaging (tagged or feature-tracking methods)
Tissue characterization • Native T1, T2, and T2* mapping • Late gadolinium enhancement imaging • Post-gadolinium contrast-enhanced T1 mapping

LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Ragionevole prevedere una equipe dedicata

TABLE 3 Left Ventricular Ejection Fraction Decreases and Reported Cardiotoxicity Are Variable in Serial Imaging Studies of Women With Breast Cancer Treated With Anthracyclines by Different Imaging Modalities

Imaging Modality First Author (Ref. #)	n, Total	% Breast Cancer	Age, yrs	Treatment	Follow-Up, months	Baseline LVEF, %	Follow-Up LVEF, %	LVEF Decline, %	CT
MUGA									
Cottin et al. (141)	60	47	50 (23–72)	Anthracycline	1	57 ± 5	55 ± 6	2	NR
Lapinska et al. (142)	71	100	53 (38–71)	Anthracycline + cyclophosphamide (n = 47)	6	62.7 ± 4.4	59.5 ± 6.1	3	NR
				Anthracycline + docetaxel (n = 24)		63.7 ± 5.2	61.7 ± 5.3	2	
Feola et al. (143)	53	100	55 (28–73)	Anthracycline	24	63.9 ± 4.8	53.1 ± 6.6	11	n = 13 (25%)
Echocardiography									
Fallah-Rad et al. (62)	42	100	47 ± 9	Anthracycline + trastuzumab	6	62 ± 5 (normal LVEF, n = 32)	64 ± 4 (normal LVEF, n = 32)	No decline	n = 10 (24%)
						64 ± 3 (CT, n = 10)	42 ± 4 (CT, n = 10)	22	
Stoodley et al. (144)	52	100	49 ± 9	Anthracycline	4–6	58.6 ± 2.6	56.0 ± 2.8	No decline	n = 0 (0%)
CMR									
Fallah-Rad et al. (62)	42	100	47 ± 9	Anthracycline + trastuzumab	12	65 ± 3 (normal LVEF, n = 32)	63 ± 5 (normal LVEF, n = 32)	No decline	n = 10 (24%)
						66 ± 5 (CT, n = 10)	47 ± 4 (CT, n = 10)	22	
Drafts et al. (27)*	53	42	50 ± 2	Anthracycline	6	58 ± 1	53 ± 1	5	n = 14 (26%)
Chaosuwannakit et al. (43)	40	48	52 ± 11	Anthracycline	4	58.6 ± 6.3	53.9 ± 6.4	5	NR
Wassmuth et al. (26)*	22	36	43 (17–66)	Anthracycline	1	67.8 ± 1.4	58.9 ± 1.9	9	n = 6 (27%)

Values are median (range) or mean ± SD unless otherwise noted. *Mean ± SE.

CMR = cardiovascular magnetic resonance; CT = cardiotoxicity; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition ventriculography; NR = not reported.

FIGURE 3 Cardiovascular Magnetic Resonance Case Examples of Left Ventricular Ejection Fraction Due to Either a Decline in Left Ventricular End-Diastolic Volume or an Increase in Left Ventricular End-Systolic Volume After Chemotherapy

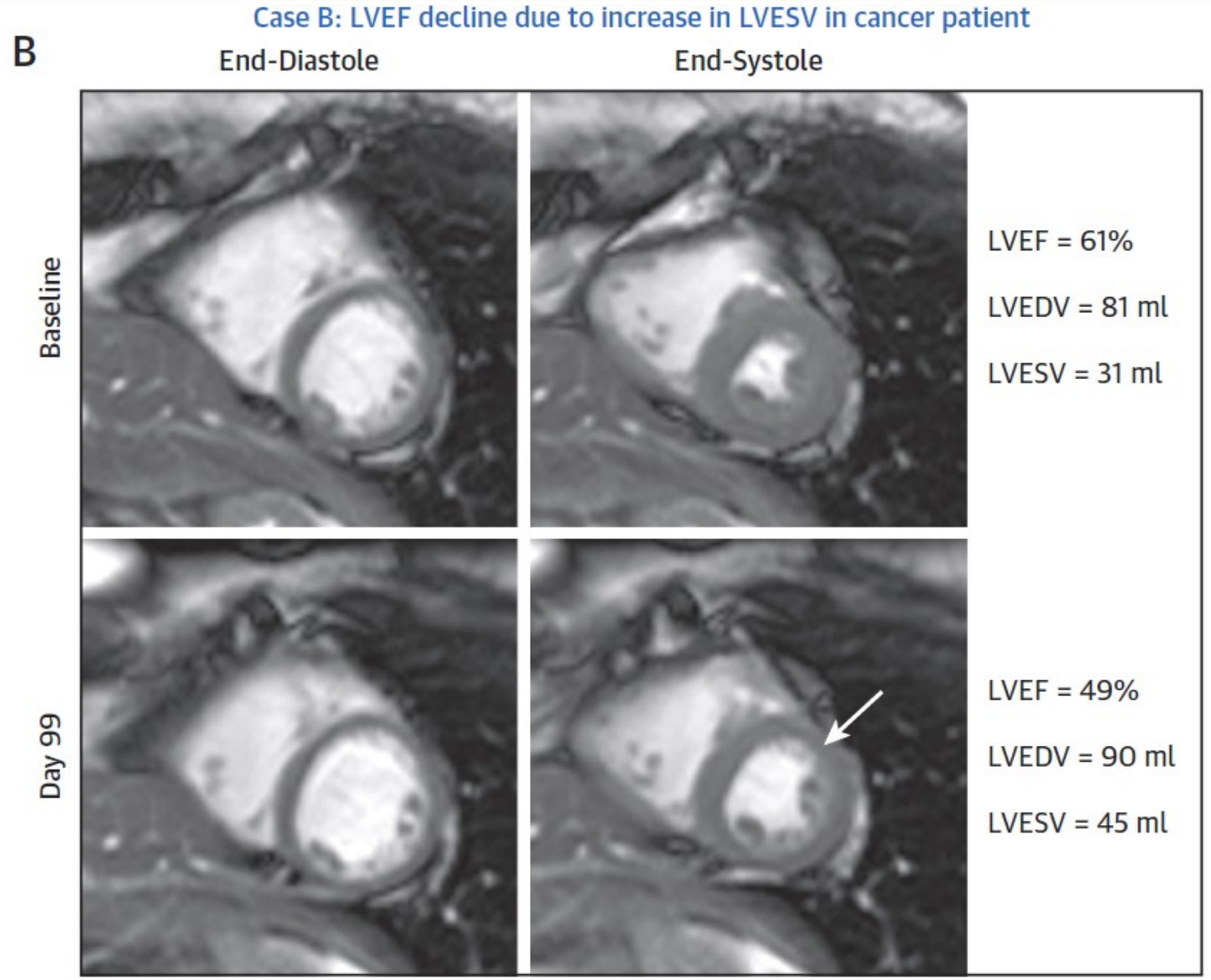
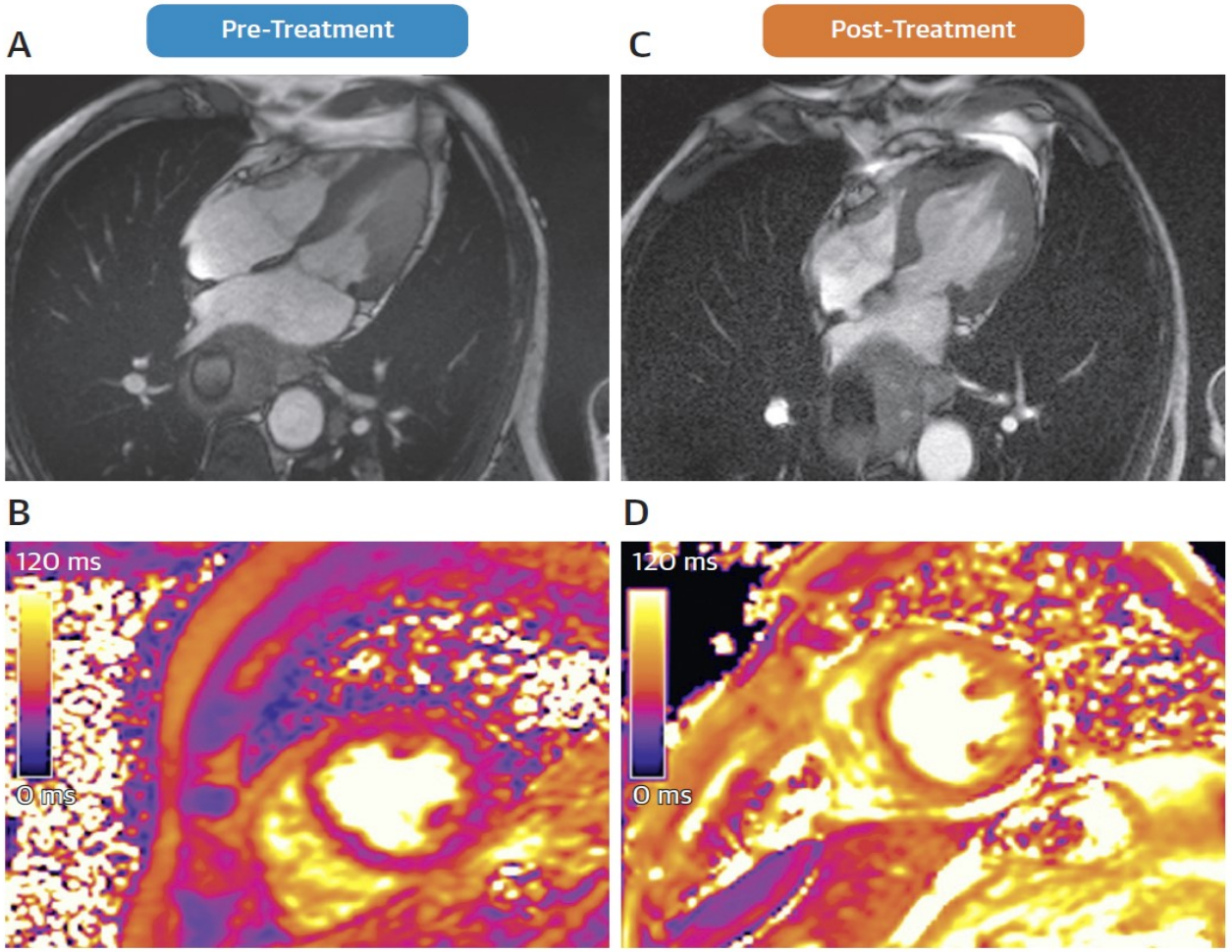
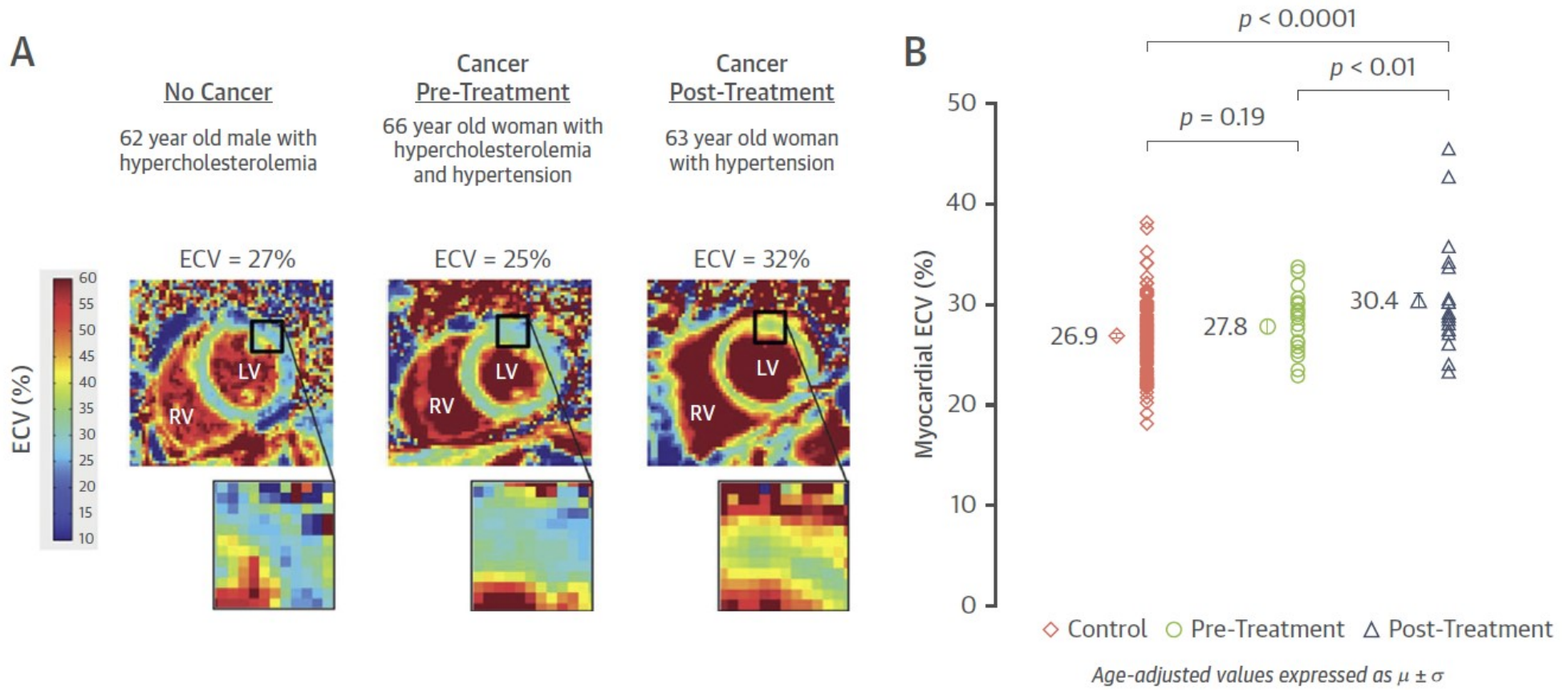


FIGURE 4 Cardiovascular Magnetic Resonance Case Example of Transient Left Ventricular Dysfunction Syndrome in Patient With Cancer



Case presentation of a 77-year-old man with esophageal melanoma admitted for acute heart failure with "inverted" transient left ventricular dysfunction syndrome (TLVDS) pattern of basal and mid-left ventricular (LV) akinesia presenting 65 days after treatment with perfusions of ipilimumab and ipilimumab-nivolumab immunotherapy. Pre-treatment cardiovascular magnetic resonance demonstrated normal systolic function (**A,** Online Video 5) and normal T2 signal (36 ms), demonstrating no myocardial edema **(B)**. At 65 days after treatment, his LV ejection fraction (LVEF) was 40% (**C,** Online Video 6), with evidence of myocardial edema by increased T2 signal (mean 60 ms) **(D)**. After treatment with steroids, angiotensin-converting enzyme inhibitors, and beta-blockers, the patient's LVEF returned to 60% within 28 days of initial presentation. Reprinted with permissions from Ederhy et al. (56).

FIGURE 6 **Myocardial Fibrosis Imaging in Anthracycline-Treated Cancer Survivors Using Extracellular Volume Mapping**



Case examples demonstrating elevated myocardial fibrosis measured with extracellular volume (ECV) mapping in a cancer survivor **(A)** and aggregated elevations in group data showing mean ECV of 30.4% in anthracycline-treated patients with cancer 3 years after treatment **(B)**. Reprinted with permission from Jordan et al. (100).

Quale test di II e III livello introdurre nella diagnostica della cardiotossicità durante trattamenti in oncologia?

Medicina Nucleare:

MUGA (marcatura in vivo degli eritrociti con misura estremamente precisa della Frazione di Eiezione del Ventricolo Sinistro)

SPECT Miocardica di Perfusione (misura precisa della frazione di Eiezione, dei volumi ventricolari, accorciamento ed ispessimento ventricolare, ricerca di ipoperfusione inducibile)

PET-ammonia, Gold Standard nella misura della riserva coronarica

Per quel che riguarda il dato dosimetrico:

MUGA 5-7 mSievert
SPECT di perfusione circa 3-4 mSievert per singolo esame (totale nella ricerca di ischemia 7-8 mSievert)
PET ammonia 2mSievert

ES: paziente oncologico sottoposto a TC whole body di stadiazione con MDC 15-20 mSievert

Scintigraphic Techniques for Early Detection of Cancer Treatment–Induced Cardiotoxicity*

Lioe-Fee de Geus-Oei[1], Annelies M.C. Mavinkurve-Groothuis[2], Louise Bellersen[3], Martin Gotthardt[1], Wim J.G. Oyen[1], Livia Kapusta[4,5], and Hanneke W.M. van Laarhoven[6]

[1]Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Pediatric Hematology and Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [3]Department of Cardiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [4]Children's Heart Centre, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [5]Heart Institute, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel; and [6]Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

New antitumor agents have resulted in significant survival benefits for cancer patients. However, several agents may have serious cardiovascular side effects. Left ventricular ejection fraction measurement by ^{99m}Tc multigated radionuclide angiography is regarded as the gold standard to measure cardiotoxic

targeting to the myocardium. To define the prognostic importance and clinical value of each of these functional imaging techniques, prospective clinical trials are warranted.

Key Words: cardiotoxicity; cancer treatment; early detection

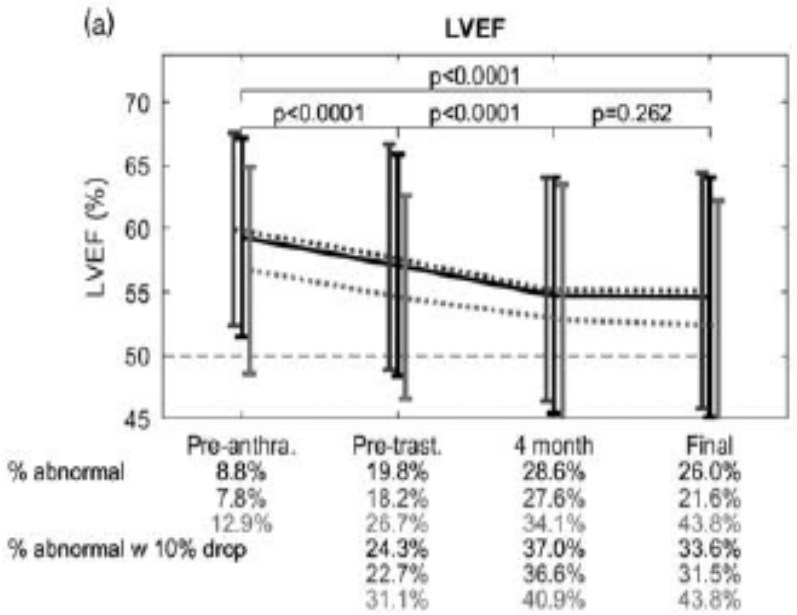
J Nucl Med Technol 2013; 41:170–181

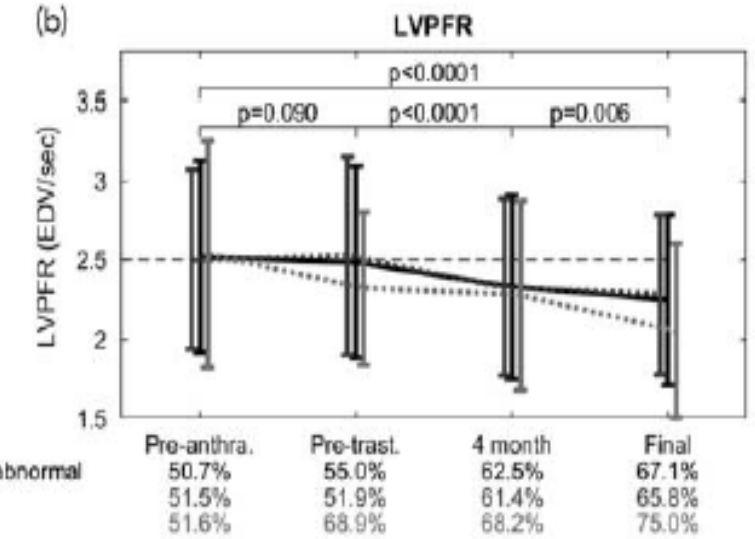
Qualità della Medicina Nucleare nella valutazione della HF del paziente oncologico

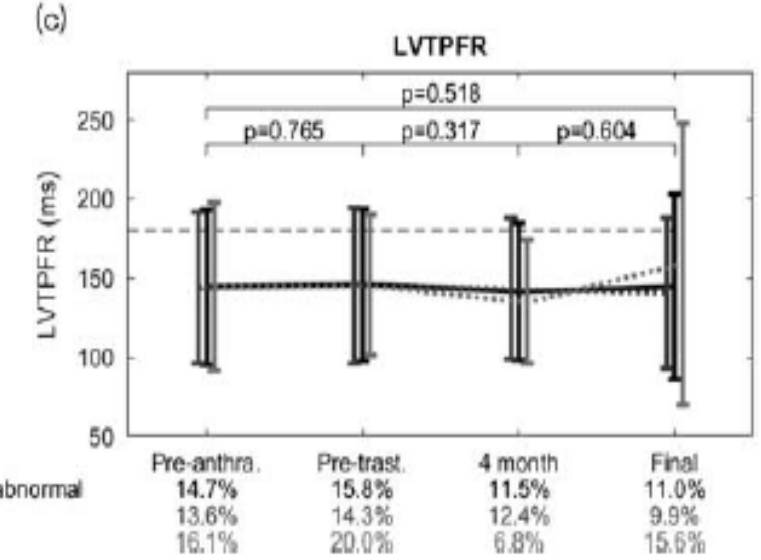
Single-Photon Techniques for Early Detection of Cardiotoxicity

Technique	Tracer
Mechanical (pump) function	^{99m}Tc MUGA (radionuclide ventriculography or equilibrium radionuclide angiocardiography) ^{99m}Tc gated blood-pool SPECT
Neuronal imaging	^{123}I-MIBG See Table 3 for neuronal imaging PET tracers
Imaging necrosis/cell death	^{111}In-antimyosin
Imaging cell death/apoptosis	^{99m}Tc-annexin V
Fatty acid use	^{123}I-BMIPP ^{123}I-paraphenyl pentadecanoic acid
Therapeutic target imaging	^{111}In-trastuzumab

MUGA







Legend and sample sizes

Group name	Pre-anthra.	Pre-trast.	4 month	Final
All patients	136	202	192	146
Early stage breast cancer	103	154	145	111
Metastatic breast cancer	31	45	44	32

Average (a) ejection fraction, (b) peak filling rate, and (c) time to peak filling rate values by time-point for all patients (black) and those with early (dark grey) and metastatic (light grey) disease at baseline. The error bars indicate one standard deviation. *P* values correspond to changes in the mean values for all patients using a paired *t*-test. LVEF, left ventricular ejection fraction.

Huang et al. Journal of Cardiovascular Magnetic Resonance (2017) 19:34
DOI 10.1186/s12968-017-0348-4

Journal of Cardiovascular Magnetic Resonance

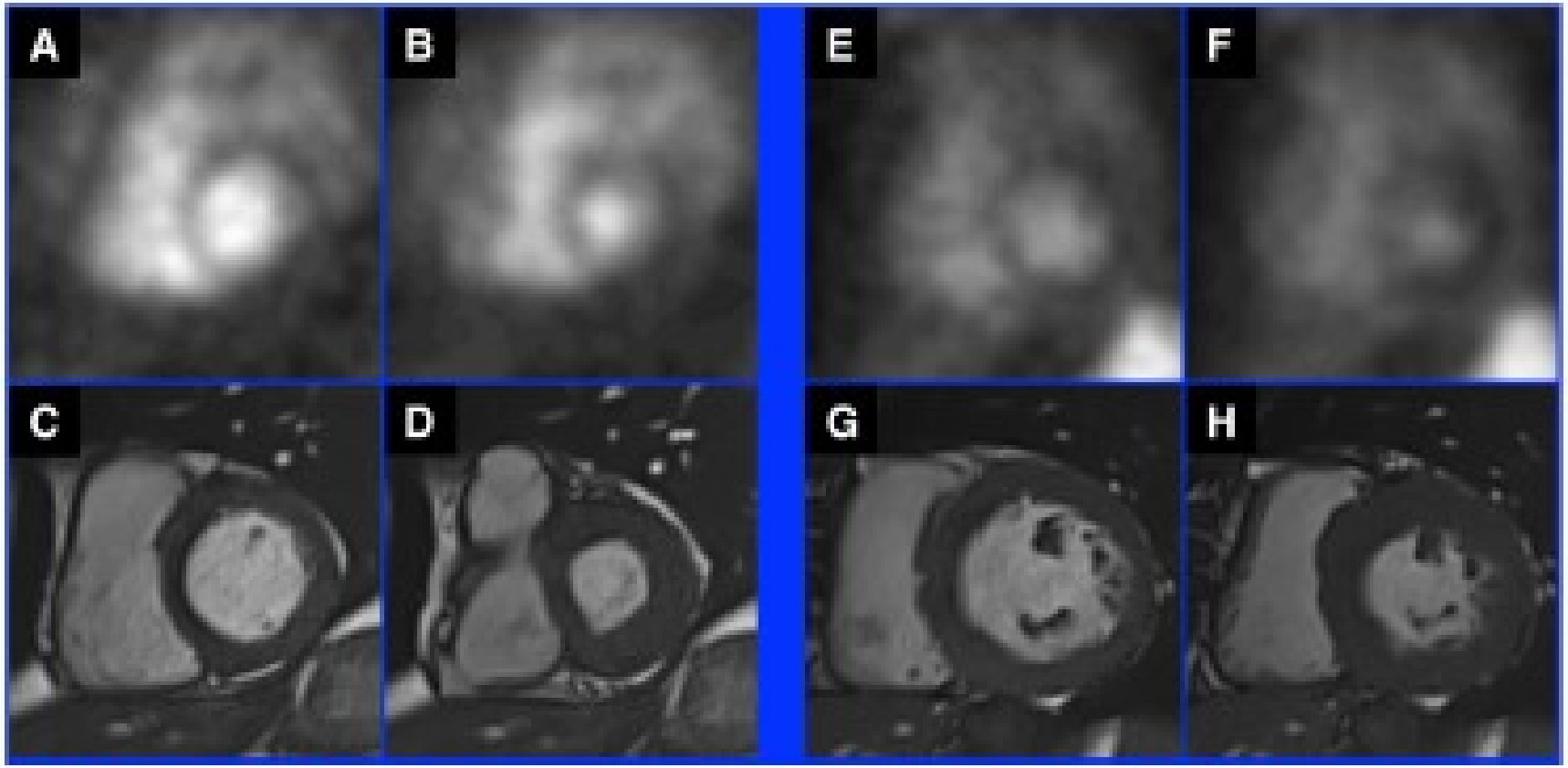


Fig. 3 MUGA and CMR images from example study patients with misclassification of MUGA LVEFs. **a** and **b** are end-diastolic and end-systolic MUGA images respectively from a patient whose LVEF was analyzed at 47.0%, **c** and **d** are end-diastolic and end-systolic CMR images respectively from the same patient acquired 4 days later, with LVEF analyzed at 55.2%. **e** and **f** are end-diastolic and end-systolic MUGA images respectively from a patient whose LVEF was analyzed at 69.2%, **g** and **h** are end-diastolic and end-systolic CMR images respectively from the same patient acquired 7 days later, with LVEF analyzed at 44.0%

MIBG

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Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure

Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study

Arnold F. Jacobson, MD, PHD,* Roxy Senior, MD,† Manuel D. Cerqueira, MD,‡ Nathan D. Wong, PHD,§ Gregory S. Thomas, MD, MPH,§ Victor A. Lopez, BS,§ Denis Agostini, MD, PHD,‖ Fred Weiland, MD,¶ Harish Chandna, MD,# Jagat Narula, MD, PHD,§ on behalf of the ADMIRE-HF Investigators

Princeton, New Jersey; London, United Kingdom; Cleveland, Ohio; Irvine, California; Caen, France; Roseville, California; and Victoria, Texas

MIBG

Objectives The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study prospectively evaluated iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) imaging for identifying symptomatic heart failure (HF) patients most likely to experience cardiac events.

Background Single-center studies have demonstrated the poorer prognosis of HF patients with reduced ^{123}I-*m*IBG myocardial uptake, but these observations have not been validated in large multicenter trials.

Methods A total of 961 subjects with New York Heart Association (NYHA) functional class II/III HF and left ventricular ejection fraction (LVEF) ≤35% were studied. Subjects underwent ^{123}I-*m*IBG myocardial imaging (sympathetic neuronal integrity quantified as the heart/mediastinum uptake ratio [H/M] on 4-h delayed planar images) and myocardial perfusion imaging and were then followed up for up to 2 years. Time to first occurrence of NYHA functional class progression, potentially life-threatening arrhythmic event, or cardiac death was compared with H/M (either in relation to estimated lower limit of normal [1.60] or as a continuous variable) using Cox proportional hazards regression. Multivariable analyses using clinical, laboratory, and imaging data were also performed.

Results A total of 237 subjects (25%) experienced events (median follow-up 17 months). The hazard ratio for H/M ≥1.60 was 0.40 ($p < 0.001$); the hazard ratio for continuous H/M was 0.22 ($p < 0.001$). Two-year event rate was 15% for H/M ≥1.60 and 37% for H/M <1.60; hazard ratios for individual event categories were as follows: HF progression, 0.49 ($p = 0.002$); arrhythmic events, 0.37 ($p = 0.02$); and cardiac death, 0.14 ($p = 0.006$). Significant contributors to the multivariable model were H/M, LVEF, B-type natriuretic peptide, and NYHA functional class. ^{123}I-*m*IBG imaging also provided additional discrimination in analyses of interactions between B-type natriuretic peptide, LVEF, and H/M.

Conclusions ADMIRE-HF provides prospective validation of the independent prognostic value of ^{123}I-*m*IBG scintigraphy in assessment of patients with HF. (Meta-Iodobenzylguanidine Scintigraphy Imaging in Patients With Heart Failure and Control Subjects Without Cardiovascular Disease, NCT00126425; Meta-Iodobenzylguanidine [123I-mIBG] Scintigraphy Imaging in Patients With Heart Failure and Control Subjects Without Cardiovascular Disease, NCT00126438) (J Am Coll Cardiol 2010;55:2212–21) © 2010 by the American College of Cardiology Foundation

MIBG

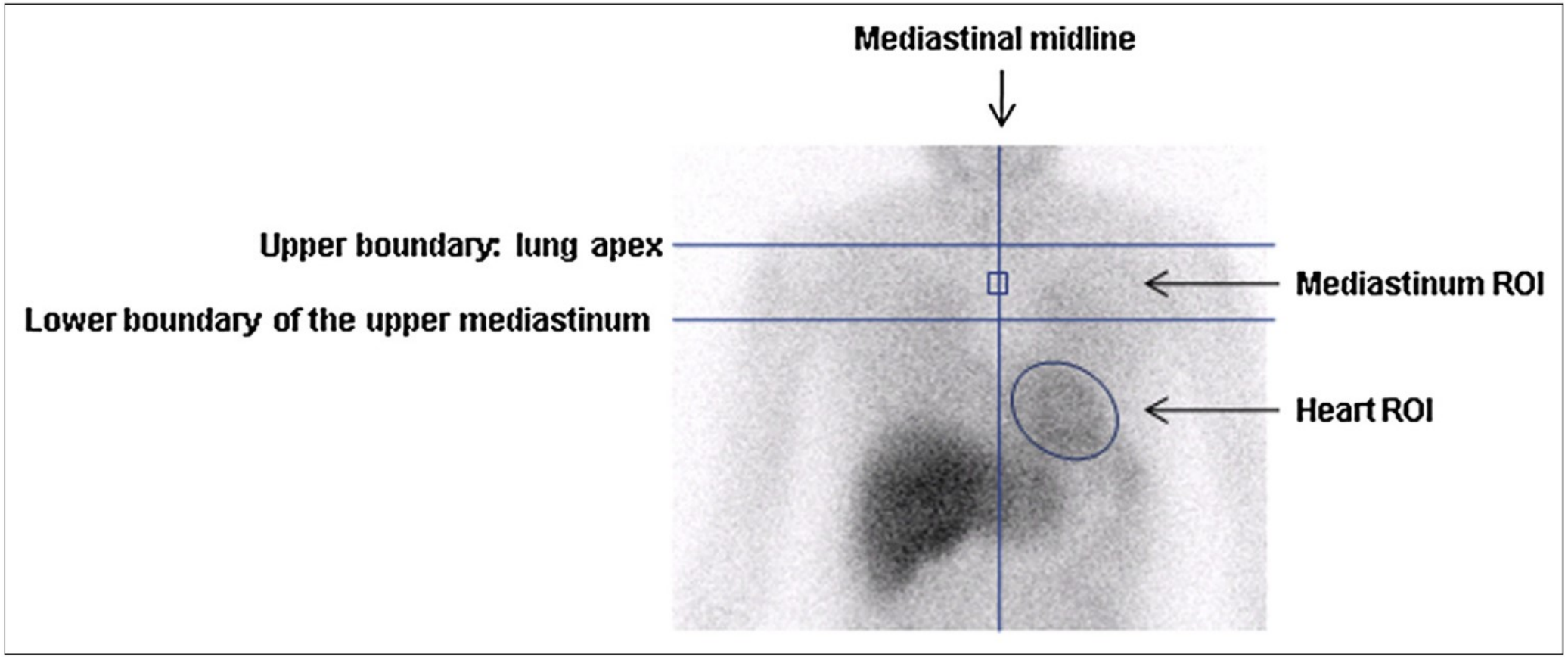

FIGURE 1. Calculation of heart-to-mediastinum count ratio of ^{123}I-MIBG. Region of interest (ROI) is drawn around left ventricle and in mediastinum. Mediastinal position of ROI is standardized in relation to lung apex, lower boundary of upper mediastinum, and mediastinal midline. Same ROIs are applied for early 15-min postinjection and late 4-h postinjection images, to calculate 4-h washout rates.

$$\text{Washout rate} = \frac{\text{image 15 min after injection (H} - \text{M)} - \text{4 h after injection (H} - \text{M)}}{\text{image 15 min after injection (H} - \text{M)}} \times 100\%,$$

where H is decay-corrected average counts of heart ROI, and M is decay-corrected average counts of mediastinum ROI.

European Heart Journal – Cardiovascular Imaging (2014) **15**, 1063–1093

Key points

- The calculation of LVEF by MUGA is highly reproducible. The main limitations are radiation exposure and the lack of ability to report on pericardial and valvular heart disease and RV function.
- The newer and most commonly used dual-head gamma cameras were not used in the initial reproducibility studies, and their inter-study reproducibility is not well known.
- CMR is the reference standard in the evaluation of LV and RV volumes and LVEF. Its main limitation is its limited availability. It may be particularly useful in situations in which discontinuation of chemotherapy is being entertained and/or when there is concern regarding echocardiographical or equilibrium radionuclide angiographic calculation of LVEF.
- Standard precautions for CMR safety need to be followed, including consideration of electromagnetic interference. This may be particularly relevant in patients with breast cancer, in whom tissue expanders placed for breast reconstruction may represent a hazard.
- It is important to realize that the different techniques use different normal reference values. Thus, the same technique should be performed for baseline assessment and follow-up studies during and after cancer treatment.

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At *iJACC*, we try consistently to select the best new discovery science, and we are proud of this issue's examples. However, we are keen to see the next steps: well-done clinical trials and economic analysis that translate the excellent discoveries of the imaging community to appropriate, evidence-based clinical practice.