DOI:
10.1148/ryct.230048

Document Version
Publisher's PDF, also known as Version of record

Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Echocardiography versus Cardiac MRI for Measurement of Left Ventricular Ejection Fraction in Individuals with Cancer and Suspected Cardiotoxicity

Muhummad Sohaib Nazir, MBBS, PhD • Joseph Okafor, MBBS • Theodore Murphy, MBBS • Maria Sol Andres, MD • Sivatharshini Ramalingham, MBBS • Stuart D. Rosen, MA, MD, FRCP • Amedeo Chiribiri, MD, PhD • Sven Plein, MD, PhD • Sanjay Prasad, MD • Raad Mohiaddin, MD, PhD • Dudley J. Pennell, MD • A. John Baksi, MBBS, PhD • Rajdeep Khattar, DM, FRCP • Alexander R. Lyon, BM, BCh, PhD

From the Cardio-Oncology Service (M.S.N., T.M., M.S.A., S.R., S.D.R., A.R.L.), Department of Echocardiography (J.O., R.K.), and Cardiovascular Magnetic Resonance Unit (S. Prasad, R.M., D.J.P., A.J.B.), Royal Brompton & Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; School of Biomedical Engineering and Imaging Sciences, King's College London, Guy's and St Thomas' Hospital, London SE1 7EU, United Kingdom (M.S.N., A.C., S. Plein); and National Heart & Lung Institute, Imperial College London, London, United Kingdom (S.D.R., S. Prasad, R.M., D.J.P., A.J.B., A.R.L.). Received February 20, 2023; revision requested June 13; final revision received October 9; accepted November 27. **Address correspondence to** M.S.N. (email: *sohaib.nazir@kcl.ac.uk*).

The authors acknowledge financial support from the Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust and by the NIHR MedTech Co-operative for Cardiovascular Disease at Guy's and St Thomas' NHS Foundation Trust. M.S.N. supported by a NIHR Clinical Lectureship (CL-2019-17-001). S. Plein supported by the British Heart Foundation (BHF) (grant CH/16/2/32089). A.R.L. supported by the Fondation Leducq Network of Excellence in Cardio-Oncology. The Royal Brompton Cardio-Oncology Centre of Excellence supported by the The Big Heart Foundation. The views expressed are those of the authors and not necessarily those of the BHF, NHS, or the NIHR.

Conflicts of interest are listed at the end of this article.

Radiology: Cardiothoracic Imaging 2024; 6(1):e230048 • https://doi.org/10.1148/ryct.230048 • Content codes: CA MR

Purpose: To compare left ventricular ejection fraction (LVEF) measured with echocardiography and cardiac MRI in individuals with cancer and suspected cardiotoxicity and assess the potential effect on downstream clinical decision-making.

Materials and Methods: In this prospective, single-center observational cohort study, participants underwent same-day two-dimensional (2D) echocardiography and cardiac MRI between 2011 and 2021. Participants with suboptimal image quality were excluded. A subset of 74 participants also underwent three-dimensional (3D) echocardiography. The agreement of LVEF derived from each modality was assessed using Bland-Altman analysis and at relevant thresholds for cardiotoxicity.

Results: A total of 745 participants (mean age, 60 years ± 5 [SD]; 460 [61.7%] female participants) underwent same-day echocardiography and cardiac MRI. According to Bland-Altman analysis, the mean bias was –3.7% ± 7.6 (95% limits of agreement [LOA]: –18.5% to 11.1%) for 2D echocardiography versus cardiac MRI. In 74 participants who underwent cardiac MRI, 3D echocardiography, and 2D echocardiography, the mean LVEFs were 60.0% ± 10.4, 58.4% ± 9.4, and 57.2% ± 8.9, respectively ($P < .001$). At the 50% LVEF threshold for detection of cardiotoxicity, there was disagreement for 9.3% of participants with 2D echocardiography and cardiac MRI. Agreement was better with 3D echocardiography and cardiac MRI (mean bias, –1.6% ± 6.3 [95% LOA: –13.9% to 10.7%]) compared with 2D echocardiography and cardiac MRI (mean bias, –2.8% ± 6.3 [95% LOA: –15.2% to 9.6%]; $P = .016$).

Conclusion: Two-dimensional echocardiography had variations of ±15% for LVEF measurement compared with cardiac MRI in participants with cancer and led to misclassification of approximately 10% of participants for cardiotoxicity detection. Three-dimensional echocardiography had better agreement with cardiac MRI and should be used as first-line imaging.

Supplemental material is available for this article.

An earlier incorrect version appeared online. This article was corrected on January 18, 2024.

Left ventricular ejection fraction (LVEF) is an important biomarker for the detection of cancer therapy–related cardiac dysfunction (CTRCD) in patients receiving anticancer therapies. The measurement of LVEF is recommended in guidelines for patients at risk for cardiotoxicity (1–3) and is important for clinical decision-making to initiate cardioprotective therapy. Therefore, the accurate and reproducible measurement of LVEF is of great importance in patients receiving anticancer therapies.

Cardiac MRI is the reference standard for assessment of left ventricular volumes and ejection fraction (4), but transthoracic echocardiography remains the most widely used imaging modality because of its widespread accessibility and lower cost. Various thresholds of LVEF have been used to define cardiotoxicity based on position papers and guidelines. These include a reduction in LVEF from baseline to less than 55%, less than 53%, and, most recently, less than 50% (1,3,5–8). The magnitude of reduction in LVEF in early cardiotoxicity may be relatively small, leading to measurements close to the lower limits of the normal range, typically in the region of 50%–55%. As a result, small absolute changes in LVEF may have important downstream consequences on the clinical management of patients with cancer.

Several studies have compared echocardiography-derived versus cardiac MRI–derived LVEF measurements (9). However, there is a paucity of data regarding how

Abbreviations

CTRCD = cancer therapy–related cardiac dysfunction, ICC = intraclass correlation coefficient, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, 3D = three-dimensional, 2D = two-dimensional

Summary

Two-dimensional echocardiography showed large variations compared with reference standard cardiac MRI for left ventricular ejection fraction measurement, which may lead to downstream impact on clinical decision-making for cardio-oncology patients.

Key Points

- This prospective study of 745 participants with cancer who underwent same-day two-dimensional (2D) echocardiography and cardiac MRI demonstrated a mean bias of -3.7% ± 7.6 and wide limits of agreement (-18.5% to 11.1%) between the two modalities for left ventricular ejection fraction (LVEF) measurement.
- Two-dimensional echocardiography led to misclassification of approximately 10% of participants as having cardiotoxicity according to current cardio-oncology guidelines.
- In a substudy, three-dimensional echocardiography had better agreement with cardiac MRI for LVEF measurement compared with 2D echocardiography and cardiac MRI (P = .016).

Keywords

Echocardiography, MR Functional Imaging, Cardiac

these imaging modalities compare in patients with cancer who are suspected of having cardiotoxicity and the potential effect on clinical decision-making. The aims of this study were to *(a)* determine the agreement of two-dimensional (2D) echocardiography–, three-dimensional (3D) echocardiography–, and cardiac MRI–derived LVEF in individuals with cancer who are suspected of having cardiotoxicity and *(b)* assess the effect of discordant findings on clinically relevant thresholds for cardiotoxicity, in real-world practice.

Materials and Methods

Study Participants

In this single-center study, we prospectively collected demographic and imaging biomarker data in consecutive participants referred to the Royal Brompton Hospital, part of Guy's and St Thomas' Hospital NHS Trust, London, United Kingdom, cardio-oncology service for suspected cardiotoxicity during a 10-year period between 2011 and 2021. Participants were excluded if image quality was suboptimal. To minimize the biologic temporal variation of LVEF measurements, only participants who underwent echocardiography and cardiac MRI on the same day were included in the analysis. The study was approved by the institutional review boards at Guy's and St Thomas' Hospital and the Health Research Authority.

From an initial cohort of 1290 consecutive participants, after screening and exclusions, 745 participants were included in the analysis of 2D echocardiography–derived and cardiac MRI–derived LVEF. In a subset of 74 participants, LVEF measurements were also available from 3D echocardiography.

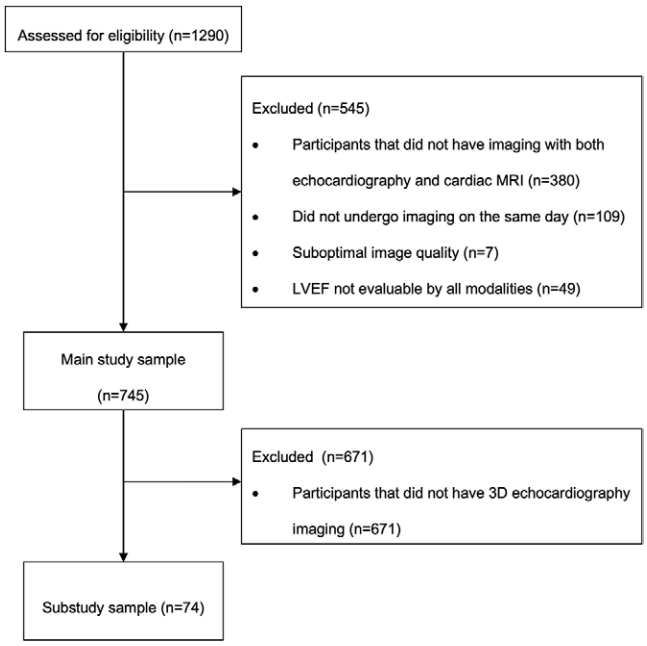

Figure 1: Flowchart summarizes participant selection. LVEF = left ventricular ejection fraction, 3D = three-dimensional.

A flowchart is provided in Figure 1, which details the reasons for exclusions.

Image Acquisition and Analysis

Echocardiography was performed by operators consisting of physiologists or cardiologists, who were accredited by the British Society of Echocardiography, according to the society guidelines for transthoracic echocardiography (10). Two-dimensional echocardiography was performed according to guidelines recommended for image acquisition, and left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF were derived using the modified Simpson biplane method (10). This involved manual tracing of the left ventricular endocardial borders from one side of the mitral valve annulus to the other side in the apical four-chamber and two-chamber views at end diastole and end systole, with inclusion of the papillary muscles as part of the blood pool. The 3D echocardiography data were acquired from multibeat full-volume data sets with an X5-1 matrix array transducer (Philips; frequency, 5–1 MHz) using the tissue harmonic mode with electrocardiography-gated acquisition. Images were acquired from apical four-chamber views with a breath hold of 6 seconds. Care was taken to maximize the frame rate and adjust depth and width for left ventricle optimization. In participants with arrhythmia, multiple acquisitions were performed until a data set with no appreciable translation artifact was obtained.

Cardiac MRI was performed at 1.5 T (Sonata or Avanto; Siemens) or 3 T (Vida; Siemens) using a steady-state free precession sequence according to recommended guidelines (11). Long-axis views were obtained along with contiguous short-axis sections from the base to apex of the heart. LVEDV and LVESV were calculated by manual contouring of the left ventricle endocardium in short axis, with exclusion of the papillary

Table 1: Characteristics of Study Participants

Characteristic	Value (n = 745)
Mean age ± SD (y)	60 ± 5
Sex	
Female	460 (61.7)
Male	285 (38.3)
Cardiovascular risk factors	
Hypertension	225 (30.2)
Hyperlipidemia	195 (26.2)
Smoking history	55 (7.4)
Diabetes mellitus	26 (3.5)
History of ischemic heart disease	61 (8.2)
Medications	
β-Blocker	318 (42.7)
ACE inhibitor	288 (38.7)
Angiotensin receptor blocker	80 (10.7)
Mineralocorticoid receptor antagonist	37 (5.0)
Loop diuretic	64 (8.6)
Thiazide diuretic	45 (6.0)
Antiplatelet	109 (14.6)
Statin	162 (21.7)
Calcium channel blocker	93 (12.5)
Primary malignancy (n = 745)	
Breast	265 (35.6)
Other (unknown primary, nonspecific)	118 (15.8)
Gastrointestinal	63 (8.5)
Urinary tract	60 (8.1)
Gynecologic	50 (6.7)
Hematologic	52 (7.0)
Thyroid	43 (587)
Skin	26 (3.5)
Prostate	23 (3.1)
Bone	8 (1.1)
Pancreas	9 (1.2)
Lung	5 (0.7)
Nasopharyngeal	5 (0.7)
Hepatocellular	4 (0.5)
Testicular	2 (0.3)
Brain	1 (0.1)

Note.—Unless otherwise indicated, data are numbers of participants, with percentages in parentheses. ACE = angiotensin-converting enzyme.

muscles by use of blood pool thresholding as previously described (12). Analysis was performed by cardiologists or radiologists who were level III accredited in reporting of cardiac MRI scans using CMRtools (CMRtools; Cardiovascular Imaging Solutions), and data were reported according to recommended guidelines (11,13).

For both imaging modalities, LVEF was calculated as (LVEDV – LVESV)/(LVEDV) × 100.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 27 (IBM). All data are presented as means ± SDs unless specified. Normality of data was determined using Kolmogorov-Smirnov tests. Parametric data were compared with the Student t test for unpaired data and using paired samples t tests for paired data. Nonparametric data were compared with the Wilcoxon signed rank test for paired data and the Mann-Whitney U test for unpaired data. Agreement of LVEF was determined at Bland-Altman analysis to calculate mean bias and 95% limits of agreement (14). Agreement was also assessed using intraclass correlation coefficients (ICCs) with a two-way mixed effects for single measurements for absolute agreement (<0.50 as poor, between 0.50 and 0.75 as moderate, between 0.75 and 0.90 as good, and >0.90 as excellent) (15). Multiple groups with matched LVEF and volumes were compared using a repeated-measures analysis of variance test, with a Tukey post hoc analysis for multiple comparisons with adjusted P values, for parametric data. Agreement of categorical data based on clinically relevant thresholds for cardiotoxicity were analyzed using Cohen κ. Multiple group comparisons of unrelated groups were performed using Kruskal-Wallis H test, with multiple group comparison with Bonferroni correction applied, for nonparametric data. Two-tailed P values less than .05 were considered to indicate statistically significant differences.

Results

Participant Characteristics

Among the 745 participants included, 460 (61.7%) were female and 285 (38.3%) were male; the mean participant age was 60 years ± 5. The demographic characteristics, cardiovascular risk factors, and prevalence of primary malignancy types are provided in Table 1.

Two-dimensional Echocardiography and Cardiac MRI

The LVEF measured with 2D echocardiography was significantly lower than that measured with cardiac MRI, with a median of 60% (IQR, 54%–65%) versus 63% (IQR, 56%–69%), respectively (P < .001). Bland-Altman analysis demonstrated a mean bias of –3.7% ± 7.6 (95% limits of agreement: –18.5% to 11.1%) for 2D echocardiography–derived versus cardiac MRI–derived LVEF (Fig 2). Overall, there was moderate agreement between the two measurements, with an ICC of 0.72 (95% CI: 0.56, 0.80; P < .0001). Subgroup analysis at different mean LVEF ranges demonstrated small overall biases but consistently wide 95% limits of agreement throughout all ranges (Table 2).

Evaluation of the differences in echocardiography-derived LVEF according to sex showed that female participants had a statistically greater LVEF compared with male participants (58.8% ± 10.0 vs 56.9% ± 10.0, respectively; P = .007). A similar difference was observed for cardiac MRI–derived LVEF (63.1% ± 11.5 for female participants vs 59.5% ± 11.3 for male participants; P < .001).

We evaluated agreement between 2D echocardiography and cardiac MRI on predefined LVEF thresholds for cardiotoxicity to determine the potential clinical effect. The levels of agreement were moderate across these ranges of thresholds, as summarized in Table 3.

Further analyses of the main cohort showed a similar magnitude of difference between LVEF derived from 2D echocardiography and cardiac MRI between the different subgroups ($\chi^2(2) = 4.21$; $P = .52$) (Fig 3). Post hoc analysis with Wilcoxon signed rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at a P value less than .0083. There were no statistically significant differences between the groups.

According to the different thresholds for cardiotoxicity, there were varying levels of disagreement (Table 4). The level of disagreement for a contemporary clinical LVEF threshold of 50% was 9.3%, as illustrated in Figure 4.

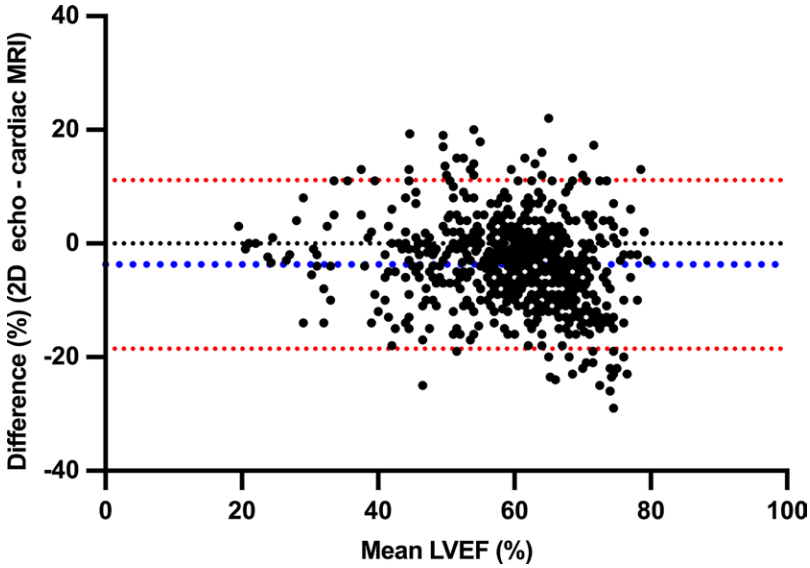

Figure 2: Bland-Altman analysis of same-day left ventricular ejection fraction (LVEF) with two-dimensional (2D) echocardiography (echo) and cardiac MRI on the whole cohort ($n = 745$). Dashed blue line represents mean bias. Dashed red lines represent 95% upper and lower limits of agreement.

Two-dimensional Echocardiography, 3D Echocardiography, and Cardiac MRI Substudy

A subset of 74 participants underwent cardiac MRI, 3D echocardiography, and 2D echocardiography, with mean LVEF measurements of 60.0% ± 10.4, 58.4% ± 9.4, and 57.2% ± 8.9, respectively (Fig 5). A repeated-measures analysis of variance with a Greenhouse-Geisser correction showed that LVEF significantly differed between modalities ($F(1.67, 121.928) = 8.907$; $P < .001$). Post hoc analysis with a Bonferroni adjustment revealed that LVEF was significantly lower with 2D echocardiography than with cardiac MRI (–2.8% [95% CI: –4.6, –1.0]; $P < .001$) and with 2D echocardiography compared with 3D echocardiography (–1.2% [95% CI: –2.4, –0.1]; $P = .047$), but not between 3D echocardiography and cardiac MRI (–1.6% [95% CI: –3.4 to 0.2]; $P = .11$).

There was good agreement between 3D echocardiography–derived and cardiac MRI–derived LVEF (ICC, 0.79 [95% CI: 0.69, 0.87]; $P < .001$) and between 2D echocardiography–derived and cardiac MRI–derived LVEF (ICC, 0.76 [95% CI: 0.60, 0.85]; $P < .001$). There was very good agreement between 2D echocardiography and 3D echocardiography (ICC, 0.89 [95% CI: 0.82, 0.93]).

Bland-Altman analysis demonstrated an absolute mean bias of –1.6% ± 6.3 (95% limits of agreement: –13.9% to 10.7%) for 3D echocardiography–derived versus cardiac MRI–derived LVEF (Fig 6A). There was a mean bias of –2.8% ± 6.3 (95% limits of agreement: –15.2% to 9.6%) for 2D echocardiography–derived versus cardiac MRI–derived LVEF (Fig 6B). The LVEF difference between 3D echocardiography and cardiac MRI was –1.6% ± 6.3 compared with a difference between 2D echocardiography and cardiac MRI of –2.8% ± 6.3, which was statistically significant ($P = .016$).

A breakdown of the differences in left ventricular volumes between the different modalities is provided in Appendix S1.

Table 2: Two-dimensional Echocardiography– versus Cardiac MRI–derived LVEF

LVEF Range	Bias ± SD (%)
≥55%	–3.4 ± 7.7 (–18.4 to 11.65)
≥53 and <55%	–4.4 ± 7.8 (–19.8 to 10.1)
≥50 and <53%	–3.6 ± 6.7 (–16.8 to 9.6)
>40 and <50%	–4.5 ± 6.7 (–17.5 to 8.6)
>35 and ≤40%	–4.8 ± 8.3 (–21.1 to 11.6)
≤35%	–5.7 ± 7.7 (–20.1 to 9.3)

Note.—Table shows bias and 95% limits of agreements at clinically relevant ranges for cardiotoxicity and heart failure. Numbers in parentheses are the 95% limits of agreement. LVEF = left ventricular ejection fraction.

Table 3: Agreement of LVEF Derived from 2D Echocardiography and Cardiac MRI according to Clinically Relevant Thresholds to Define Cardiotoxicity

Threshold for LVEF	Cohen κ	*P* Value
<55%	0.64	<.001
<53%	0.69	<.001
<50%	0.63	<.001
<40%	0.64	<.001
<35%	0.69	<.001

Note.—LVEF = left ventricular ejection fraction, 2D = two-dimensional.

Discussion

Cardiovascular imaging remains the cornerstone for the assessment of CTRCD secondary to cancer therapies such as anthracyclines and anti-human epidermal growth factor re-

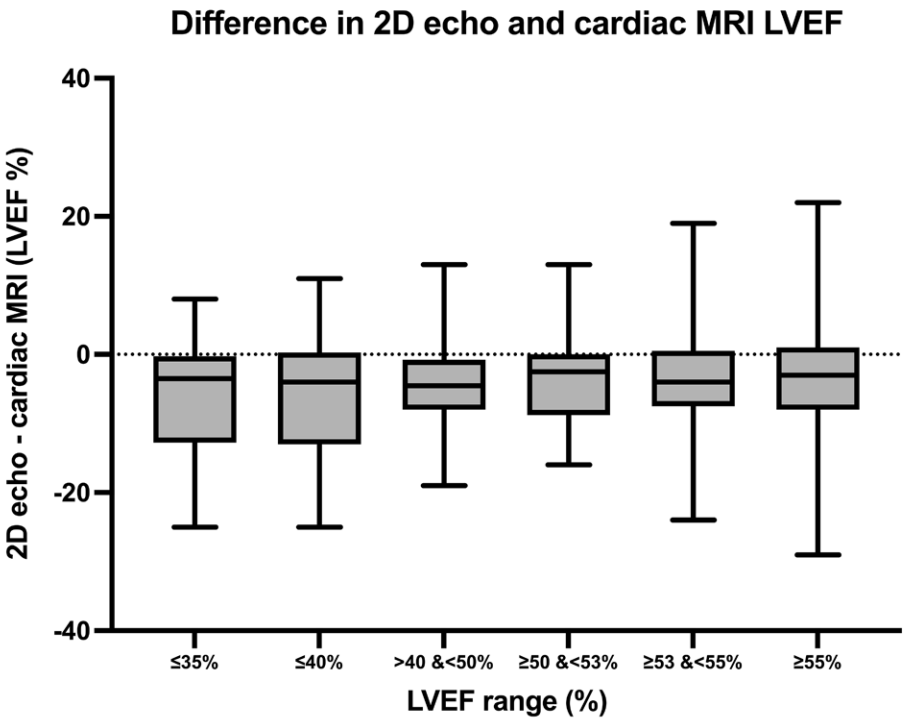

Figure 3: Box plot (median and IQR) and whiskers (minimum and maximum) for the difference in left ventricular ejection fraction (LVEF) between two-dimensional (2D) echocardiography (echo) and cardiac MRI at the clinically relevant thresholds for cardio-oncology and heart failure.

Table 4: Disagreement in Classification of Cardiotoxicity according to Different LVEF Thresholds

		Breakdown	
LVEF Threshold	Disagreement	2D Echocardiography LVEF < Threshold and Cardiac MRI LVEF ≥ Threshold	2D Echocardiography LVEF ≥ Threshold and Cardiac MRI LVEF < Threshold
<55%	99 (13.3)	67 (9)	32 (4.3)
<53%	74 (9.9)	48 (6.4)	26 (3.5)
<50%	69 (9.3)	44 (5.9)	25 (3.4)
<40%	25 (3.4)	15 (2.0)	10 (1.3)
<35%	14 (1.9)	9 (1.2)	5 (0.7)

Note.—Data are numbers of disagreements, with percentages in parentheses. LVEF = left ventricular ejection fraction.

ceptor 2 therapy (16–18). Current guidelines recommend echocardiography or cardiac MRI to derive LVEF; therefore, the accurate measurement of LVEF is of paramount importance to detect cardiotoxicity and guide subsequent management (3). In this prospective study, we performed same-day echocardiography and cardiac MRI in the largest reported oncologic cohort suspected of having cardiotoxicity to determine the absolute bias and variation in measurements of LVEF. We found that 2D echocardiography underestimated LVEF compared with cardiac MRI by approximately 3% and, more important, that measurements varied widely between cardiac MRI and 2D echocardiography (by ±15%).

The implications of the variability in measurements of LVEF are highly relevant for clinical practice and design of clinical trials, given classification of CTRCD at thresholds based on LVEF (3). Although we found moderate agreement in LVEF measurements, there was also significant discordance at the relevant clinical thresholds. Using cardiac MRI as the reference standard, there was a disagreement in the diagnosis of cardiotoxicity in approximately 10% of participants with 2D echocardiography when LVEF thresholds of 50% were used for cardiotoxicity. Nevertheless, this is lower than the degree of misclassification reported between radionuclide multiple-gated acquisition scanning and cardiac MRI, ranging between 20% and 35% depending on the LVEF threshold used to define cardiotoxicity (19).

Previous studies have demonstrated that 3D echocardiography is a better imaging technique to assess LVEF given the reduced temporal variability of around 6% compared with 10% for 2D echocardiography (20). In our substudy, 3D echocardiography showed better agreement with cardiac MRI compared with 2D echocardiography for quantification of LVEF in patients with cancer. Thus, our study supports the recent guidelines that LVEF should be measured with 3D echocardiography as first line where feasible and available in cardio-oncology patients (1,3).

The measurement of LVEF has proven prognostic value in patients with heart failure (21). Several previous studies have compared different imaging modalities for the assessment of LVEF. In a prospective study of participants with chronic stable heart failure (n = 52), there was a mean bias of −2%, with large limits of agreement (−24% to 20%) between cardiac MRI and 2D echocardiography (9). In a substudy of the multicenter study of the Surgical Treatment for Ischemic Heart Failure (STICH) trial (n = 204), the mean bias was 2.5%, with wide limits of agreement (20% to −15%) (22). In another study (n = 55), 2D echocardiography underestimated LVEF compared with cardiac

MRI, again with a broader range of LVEF and wide limits of agreement (–21.6% to 20.1%) (23). In a meta-analysis comparing 2D echocardiography and cardiac MRI, there was a small overall underestimation of LVEF by 2D echocardiography versus cardiac MRI (24). The findings of our main study are in keeping with these previous studies; although there has been small overall bias, as reported in previous studies, the limits of agreement are substantial. Our study adds to the literature because the effect of this variation must be carefully considered in the assessment of cardio-oncology patients, which may trigger an alteration in clinical management depending on LVEF thresholds for cardiotoxicity.

Our findings have important implications for clinical practice because the definition of CTRCD is heavily dependent on the accurate measurement of LVEF at baseline and during surveillance in asymptomatic patients with cancer. This may affect the downstream management of patients with cancer if 2D echocardiography alone is used. For instance, an incorrect diagnosis of cardiotoxicity in a patient with a true normal LVEF may lead to a delay in the use of highly effective cancer therapies or the deferral to other agents that are considered less cardiotoxic but are also less effective cancer treatments (25). In addition, such a situation may lead to the inappropriate initiation of cardiac medications, such as angiotensin-converting enzyme inhibitors, which require additional blood tests and clinic visits (26). Furthermore, incorrect assignment of CTRCD may lead to unnecessary long-term surveillance, with additional hospital visits and diagnostic investigations. On the other hand, the misclassification of a patient with true underlying cardiotoxicity and an apparently normal LVEF may provide false reassurance and miss the opportunity to initiate cardioprotective therapy and minimize the risk of symptomatic heart failure and adverse outcomes (27). These effects are likely to be associated with unnecessary, increased health care costs and adverse clinical outcomes.

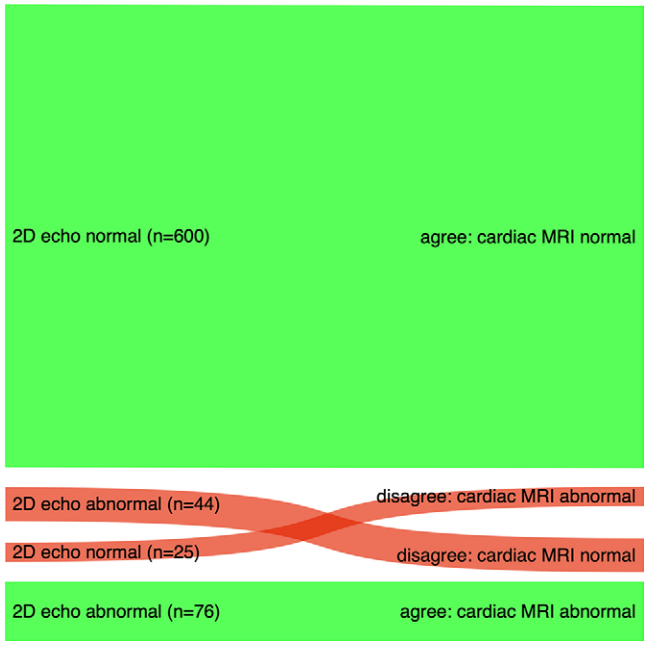

Figure 4: Diagram shows the disagreement in classification of cardiotoxicity using two-dimensional (2D) echocardiography (echo)–derived versus cardiac MRI–derived left ventricular ejection fraction (LVEF) ($n = 745$) at the 50% LVEF threshold for cardiotoxicity.

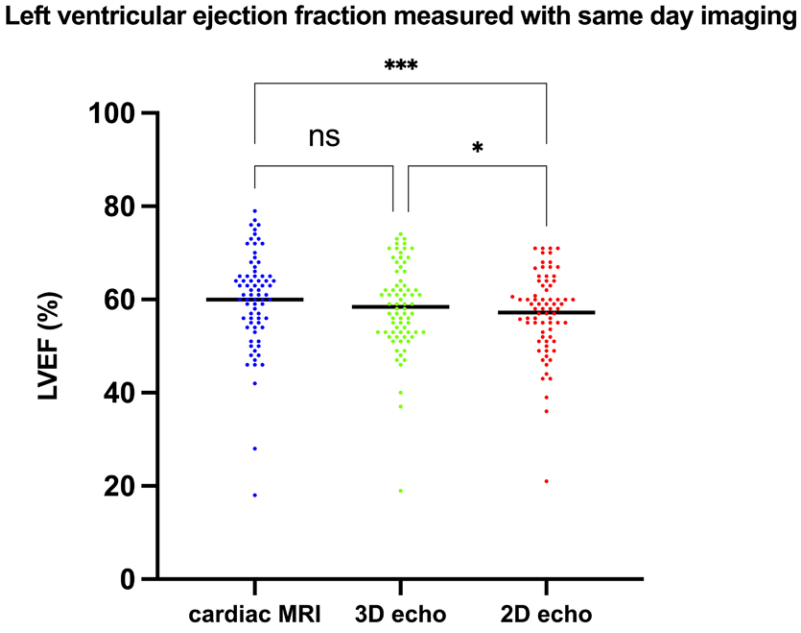

Figure 5: Left ventricular ejection fraction (LVEF) measurements for cardiac MRI, three-dimensional (3D) echocardiography (echo), and two-dimensional (2D) echocardiography in the predefined substudy ($n = 74$). ns = not significant, * = $P < .05$, *** = $P < .001$.

Pertinent clinical evidence for prognostic heart failure drug therapies and device therapies has relied on data derived from LVEF thresholds obtained from echocardiography (28,29). Such prospective studies are unlikely to be repeated again in these cohorts of patients given the well-established prognostic data. However, given the greater accuracy and precision of cardiac MRI–derived LVEF, future studies using cardiac MRI end points, which may include other features of cardiac MRI (eg, multiparametric mapping and late gadolinium enhancement), could be considered in prospective cardio-oncology studies.

Several reasons could explain the discrepancies in measurements shown in this study. An echocardiography-derived modified Simpson biplane LVEF is based on two orthogonal 2D images of the heart. The major limitations of this approach are as follows: *(a)* A mathematical model is used, which assumes that the left ventricular geometry is elliptical in shape; *(b)* the true apex may not be adequately visualized because of foreshortening; and *(c)* myocardial trabeculations may be included in the tracing of endocardial contours because the true blood pool may not be properly visualized. The latter limitation can be overcome by the use of US contrast agents, but these are not used in routine transthoracic echocardiography unless the endocardium is inadequately visualized. The use of 3D echocardiography has overcome the limitation of apical foreshortening and use of

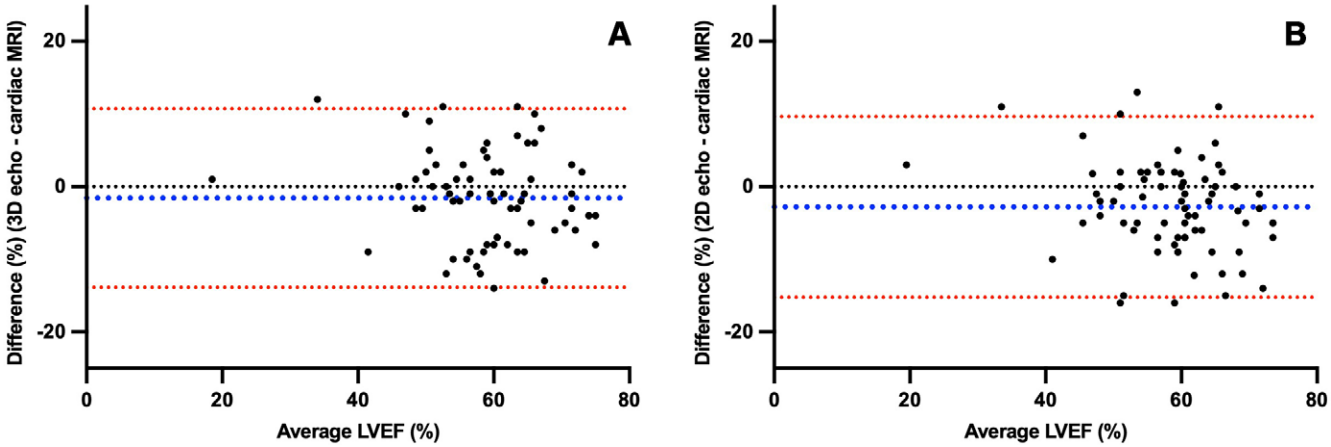

Figure 6: Bland-Altman plots demonstrate the mean bias (blue lines) and 95% limits of agreement (red lines) for **(A)** three-dimensional (3D) echocardiography–derived (echo) versus cardiac MRI–derived left ventricular ejection fraction (LVEF) and **(B)** two-dimensional (2D) echocardiography–derived versus cardiac MRI–derived LVEF.

geometric assumptions but is not yet established in conjunction with contrast agents for full visualization of the true blood pool in the left ventricle cavity, where myocardial trabeculations are present. Cardiac MRI avoids apical foreshortening, visualizes the true blood pool, and derives LVEF based on the summation of volumes of short-axis discs; therefore, it allows a better representation of the left ventricular geometric and morphologic features than does 2D echocardiography. One other potential explanation for the differences observed is that in this study, the cardiac MRI–derived left ventricular volumes were derived with exclusion of the papillary muscles, whereas in echocardiography, the papillary muscles are included as part of the left ventricular volumes. However, the effect of this may be small because the difference would affect the LVEDV and LVESV, with subsequent small overall effect to the LVEF. Finally, although the scans were obtained on the same day, there may be potential for biologic variation in measurements because it is impossible to undertake echocardiography and cardiac MRI simultaneously.

The findings of a higher LVEF measured in female participants compared with male participants in our study is in keeping with previous findings from the Dallas Heart Study (30). In addition, the findings of greater left ventricular volumes in diastole and systole with cardiac MRI compared with echocardiography are also consistent with previous published work in this area (31).

In clinical practice, LVEF is not the sole indicator of cardiotoxicity; the assessment of patient symptoms and the measurement of global longitudinal strain and serum biomarkers, such as troponin and brain natriuretic peptide, are also important (32). However, LVEF remains the most commonly used imaging measurement for the assessment of CTRCD, and our study supports the recent guidelines that recommend 3D echocardiography as first line in cardio-oncology patients (3). The routine use of more advanced echocardiographic techniques, such as contrast echocardiography and myocardial strain imaging, may enhance the assessment of cardiotoxicity in the future. Measurement of global longitudinal strain using echocardiography has been shown to be a more sensitive marker of early subclinical myocardial dysfunction in patients with cancer receiving potentially cardiotoxic therapies (33). The use of global longitudinal strain–guided care has been shown to result in better-preserved LVEF in patients who receive cardioprotective therapy and less CTRCD at follow-up (34). More recently, in a serial comparison of echocardiography- and cardiac MRI–derived LVEF and strain in individuals with breast cancer, the use of 2D echocardiography–derived global longitudinal strain provided higher incremental value for the detection of CTRCD (35). The use of these techniques in the cardio-oncology setting requires further investigation.

This study had some important limitations. First, this was an observational study of standard clinical practice without specific research protocols for undertaking image acquisition; thus, it reflects real-world practice. Echocardiography was performed and the findings interpreted by several different operators in a physiologist-led service typical of standard U.K. practice, and this could have affected the increased variability of LVEF measurements with echocardiography. Second, this was a single-center study, although this had the benefit of standardized in-house protocols for imaging. Third, the evaluation of LVEF was not blinded to the operator undertaking the analysis and thus is more representative of real-world practice. In addition, we included only patients referred to our cardio-oncology service rather than all patients with cancer, which may have introduced referral bias. Nevertheless, by evaluating many patients over a wide range of oncologic diseases, we anticipate that the findings apply to the wider scientific and clinical community. We did not undertake repeatability studies in this current study to determine interstudy reproducibility because this value has been reported as 2.5%–4.8% for cardiac MRI (36), 6% for 3D echocardiography, and 10% for 2D echocardiography (20).

In this prospective observational study of standard clinical practice, 2D echocardiography–derived LVEF measurements were lower than cardiac MRI–derived LVEF as the reference standard, and measurements varied widely. There was a discordance of approximately 10% between 2D echocardiography–derived and cardiac MRI–derived LVEF when cardiotoxicity was defined on the basis of different thresholds of LVEF. In a subset of patients who underwent

3D echocardiography, there was better agreement between 3D echocardiography–derived and cardiac MRI–derived LVEF than between 2D echocardiography and cardiac MRI, supporting recent guidelines recommending the use of 3D echocardiography in patients with cancer. These findings have important clinical implications in patients receiving anticancer therapies because an accurate assessment of LVEF is crucial in defining presence or absence of cardiotoxicity and thus guiding clinical decision-making and management for patients with cancer. Future work must be performed to evaluate strain with different imaging modalities as an early marker of CTRCD.

Author contributions: Guarantor of integrity of entire study, **M.S.N.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **M.S.N., T.M., M.S.A., A.C.**; clinical studies, **M.S.N., J.O., T.M., S.D.R., A.C., A.J.B.**; statistical analysis**, M.S.N., M.S.A., A.C.**; and manuscript editing, **M.S.N., T.M., M.S.A., S.R., S.D.R., A.C., S. Plein, S. Prasad, R.M., D.J.P., A.R.L.**

Disclosures of conflicts of interest: M.S.N. No relevant relationships. **J.O.** No relevant relationships. **T.M.** No relevant relationships. **M.S.A.** No relevant relationships. **S.R.** No relevant relationships. **S.D.R.** Participation in Orion 4 trial (Oxford University/Novartis); lecture fees from AstraZeneca and Boehringer. **A.C.** No relevant relationships. **S. Plein** No relevant relationships. **S. Prasad** No relevant relationships. **R.M.** No relevant relationships. **D.J.P.** Grant from the British Heart Foundation; deputy editor of *JACC: Cardiovascular Imaging*. **A.J.B.** No relevant relationships. **R.K.** No relevant relationships. **A.R.L.** Speaker, advisory board or consultancy fees and/or research grants from Janssens-Cilag, Astellas Pharma, Pfizer, Novartis, Servier, AstraZeneca, Bristol Myers Squibb, GSK, Amgen, Takeda, Roche, Clinigen Group, Eli Lily, Eisai, Ferring Pharmaceuticals, Boehringer Ingelheim, Akcea Therapeutics, Myocardial Solutions, iOWNA Health, and Heartfelt Technologies.

References

1. Dobson R, Ghosh AK, Ky B, et al. British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. Echo Res Pract 2021;8(1):G1–G18.
2. Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail 2020;22(9):1504–1524. [Published correction appears in Eur J Heart Fail 2021;23(2):345.]
3. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J Cardiovasc Imaging 2022;23(10):e333–e465.
4. American College of Cardiology Foundation Task Force on Expert Consensus Documents; Hundley WG, Bluemke DA, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55(23):2614–2662.
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37(36):2768–2801.
6. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(Suppl 7):vii155–vii166.
7. 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(10):1063–1093.
8. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J 2022;43(4):280–299.
9. Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000;21(16):1387–1396.
10. Robinson S, Rana B, Oxborough D, et al. A practical guideline for performing a comprehensive transthoracic echocardiogram in adults: the British Society of Echocardiography minimum dataset. Echo Res Pract 2020;7(4):G59–G93.
11. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson 2020;22(1):17.
12. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2006;8(3):417–426.
13. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson 2020;22(1):19.
14. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307–310.
15. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15(2):155–163. [Published correction appears in J Chiropr Med 2017;16(4):346.]
16. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97(11):2869–2879.
17. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 2012;60(24):2504–2512.
18. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. J Am Coll Cardiol 2017;70(20):2536–2551. [Published correction appears in J Am Coll Cardiol 2018;71(5):587.]
19. Huang H, Nijjar PS, Misialek JR, et al. Accuracy of left ventricular ejection fraction by contemporary multiple gated acquisition scanning in patients with cancer: comparison with cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19(1):34.
20. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. 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(1):77–84.
21. Cohn JN, Johnson GR, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87(6 Suppl):VI5–VI16.
22. Pellikka PA, She L, Holly TA, et al. Variability in ejection fraction measured by echocardiography, gated single-photon emission computed tomography, and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. JAMA Netw Open 2018;1(4):e181456.
23. Hoffmann R, von Bardeleben S, ten Cate F, et al. Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. Eur Heart J 2005;26(6):607–616.
24. Rigolli M, Anandabaskaran S, Christiansen JP, Whalley GA. Bias associated with left ventricular quantification by multimodality imaging: a systematic review and meta-analysis. Open Heart 2016;3(1):e000388.
25. Gelmon KA, Boyle FM, Kaufman B, et al. Lapatinib or trastuzumab plus taxane therapy for human epidermal growth factor receptor 2-positive advanced breast cancer: final results of NCIC CTG MA.31. J Clin Oncol 2015;33(14):1574–1583.
26. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129–2200.
27. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131(22):1981–1988.

28. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 1997;337(22):1569–1575.
29. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110(17):2618–2626.
30. Chung AK, Das SR, Leonard D, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: the Dallas Heart Study. Circulation 2006;113(12):1597–1604.
31. Gardner BI, Bingham SE, Allen MR, Blatter DD, Anderson JL. Cardiac magnetic resonance versus transthoracic echocardiography for the assessment of cardiac volumes and regional function after myocardial infarction: an intrasubject comparison using simultaneous intrasubject recordings. Cardiovasc Ultrasound 2009;7(1):38.
32. Pudil R, Mueller C, Čelutkienė J, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. Eur J Heart Fail 2020;22(11):1966–1983.
33. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63(25 Pt A):2751–2768.
34. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. J Am Coll Cardiol 2021;77(4):392–401.
35. Houbois CP, Nolan M, Somerset E, et al. Serial cardiovascular magnetic resonance strain measurements to identify cardiotoxicity in breast cancer: comparison with echocardiography. JACC Cardiovasc Imaging 2021;14(5):962–974.
36. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2(4):271–278.

Radiology: Cardiothoracic Imaging

Erratum for: Echocardiography versus Cardiac MRI for Measurement of Left Ventricular Ejection Fraction in Individuals with Cancer and Suspected Cardiotoxicity

Originally published in:

Radiology: Cardiothoracic Imaging 2024;6(1)

https://doi.org/10.1148/ryct.230048

Echocardiography versus Cardiac MRI for Measurement of Left Ventricular Ejection Fraction in Individuals with Cancer and Suspected Cardiotoxicity

Muhummad Sohaib Nazir, Joseph Okafor, Theodore Murphy, Maria Sol Andres, Sivatharshini Ramalingham, Stuart D. Rosen, Amedeo Chiribiri, Sven Plein, Sanjay Prasad, Raad Mohiaddin, Dudley J. Pennell, A. John Baksi, Rajdeep Khattar, Alexander R. Lyon

Erratum in:

Radiology: Cardiothoracic Imaging 2024;6(1)

DOI:10.1148/ryct.249003

Royal Brompton Cardio-Oncology Centre of Excellence supported by the The Big Heart Foundation was moved from the disclosures of conflicts of interest section to the funding section.

In the Study Participants section, **at Guy's and St Thomas' Hospital** was added to the sentence "The study was approved by the institutional review boards at Guy's and St Thomas' Hospital and the Health Research Authority."

The first sentence under the Discussion section was changed to "Cardiovascular imaging remains the cornerstone for the assessment of CTRCD secondary to cancer therapies **such** as anthracyclines and anti-human…"