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REVIEW

Echocardiography and Cardio-Oncology

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Owing to the ongoing increase in cancer survivors because of the remarkable and continuous progress in cancer management, a paradigm shift is occurring from cancer as a 'terminal illness' to a 'chronic condition' with cardiovascular risks. This also affects cardiology practice with increased cardiovascular morbidity and mortality rates among patients with cancer due to direct and/or indirect side effects of anticancer treatment. Thus, cardio-oncology has emerged as a new cardiology subspecialty, which focusses on risk stratification, prevention, diagnosis, treatment, and follow-up of cardiovascular disease related to cancer treatment. This review summarises echocardiographic evaluation of cardiac dysfunction and heart failure as they are the most concerning cardiovascular complications of cancer therapy and worsen its morbidity and mortality. This review covers cardiac function assessment and proposed cut-off values before/during/after cancer chemotherapy. The goal of this review is to aid clinicians to manage the patients with cancer sufficiently by connecting the existing knowledge in clinical cardiology with novel information from current advances in cardio-oncology.

Keywords Cancer therapy-related cardiac dysfunction • Cardiotoxicity • Myocardial strain • Ejection fraction • Anthracycline • Trastuzumab

Introduction

Cardio-oncology is an emerging medical discipline that focusses on the risk stratification, prevention, early identification, and treatment of cardiovascular (CV) complications related to cancer therapy [1]. There are several reasons for the increasing interest from global cardiology communities. The first is the improvement in cancer-free and overall survival due to advances in cancer management and anticancer therapies. Contemporary cancer therapy has been shown to have reduced cancer-related mortality rate by 23% in the period between 1991 and 2012 [2]. Combined with the continuous increase in the incidence of cancer, which is estimated to reach 23.6 million patients per year globally by 2030 [3], the consequence is the continuous increase in cancer survivors. In the USA, there were >15.5 million cancer survivors in 2016, and this figure is estimated to reach over 20.3 million by 2026 [2]. The critical factor for CV health care providers is that most of the cancer survivors have higher cardiovascular disease (CVD) risk than non-cancer controls [4,5]. In a population-based study of breast cancer patients, CV death was the second largest cause of death (16%) after breast cancer itself (50%) [6]. When analyses were restricted to those with prior CVD, the risk of death from CVD and breast cancer were equivalent for the first 5 years, after which CV death was more frequent [6]. Collectively, there has been a paradigm shift from cancer as a terminal illness to a chronic condition with CVD risk.

Cancer treatment can cause various types of CV complications. Different cancer therapies have different CV complications. Table 1 summarises a variety of anti-cancer therapies and their associated complications, including myocardial dysfunction, heart failure (HF), coronary artery disease, valvular heart disease, arrhythmias, hypertension, thromboembolic disease, peripheral vascular disease, stroke, and pulmonary hypertension [7]. Among these complications, this review focusses on echocardiographic evaluation of cardiac dysfunction related to cancer chemotherapy, as CV imaging, particularly echocardiography, plays a pivotal role.

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Table 1 **Cardiovascular complications of cancer therapy.**

Cardiovascular complications of cancer therapy	Anti-cancer therapy
Myocardial dysfunction and heart failure	Anthracyclines, Anti-HER2, VEGF inhibitors
Coronary artery disease	Fluoropyrimidines, Platinum compounds, VEGF inhibitors, radiotherapy
Valvular heart disease	Radiotherapy
Arrhythmias	Anthracyclines, Histone deacetylase inhibitors, tyrosine kinase inhibitors
Systemic hypertension	VEGF inhibitors
Thromboembolic disease	No specific agents. Prothrombic state due to malignancy
Peripheral vascular disease and stroke	Nilotinib, Ponatinib or BCR-ABL tyrosine kinase inhibitors
Pulmonary hypertension	Tyrosine kinase inhibitors (except for imatinib)

Abbreviations: HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor.

Who Should Be Screened?

This section discusses risk stratification by patients' characteristics to identify high-risk patients. The high-risk factors are determined by the cancer treatment, irrespective of the timing of involvement of a cardio-oncology team (Figure 1). If we consider high-risk as an early stage of heart failure (HF), those who receive cardiotoxic chemotherapy are already at risk (i.e., Stage A HF – ''at high risk for HF but without structural heart disease or symptoms of HF'') in the framework of American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) HF Guidelines' stages [8]. Thus, baseline screening is recommended to identify any Stage B HF cases — ''structural heart disease but without signs or symptoms of HF''.

The contemporary clinical practice guidelines on cardio-oncology provide greater details on risk stratification [7–11] (Table 2). These four documents reflect several perspectives in this field, as two are from cardiac societies and the other two from oncology societies; two from North America and two from European societies. Most of them share very similar concepts with some heterogeneity. The common understanding is that high risk patients can be identified by four dimensions of risk factors [7]: concomitant myocardial disease, CV risk factors, lifestyle risk factors, and previous cardiotoxic cancer treatment (Table 3). This scheme provides a general concept of the risk factors of this population, where the first three categories are nothing new for cardiovascular health care providers, as these are a part of daily practice. However, each of these are critical because a single HF risk factor could increase the risk of subsequent CV events significantly [12]. The fourth risk factor, previous cardiotoxic cancer treatment, is specific to this population of patients. In addition, there are also anti-cancer agents' specific risk factors to consider (Table 3). The unique risk factors for those treated with anthracyclines are female sex, cumulative dose, concomitant chemotherapy, and radiation therapy (Table 4). Obesity is particularly important for those who receive trastuzumab.

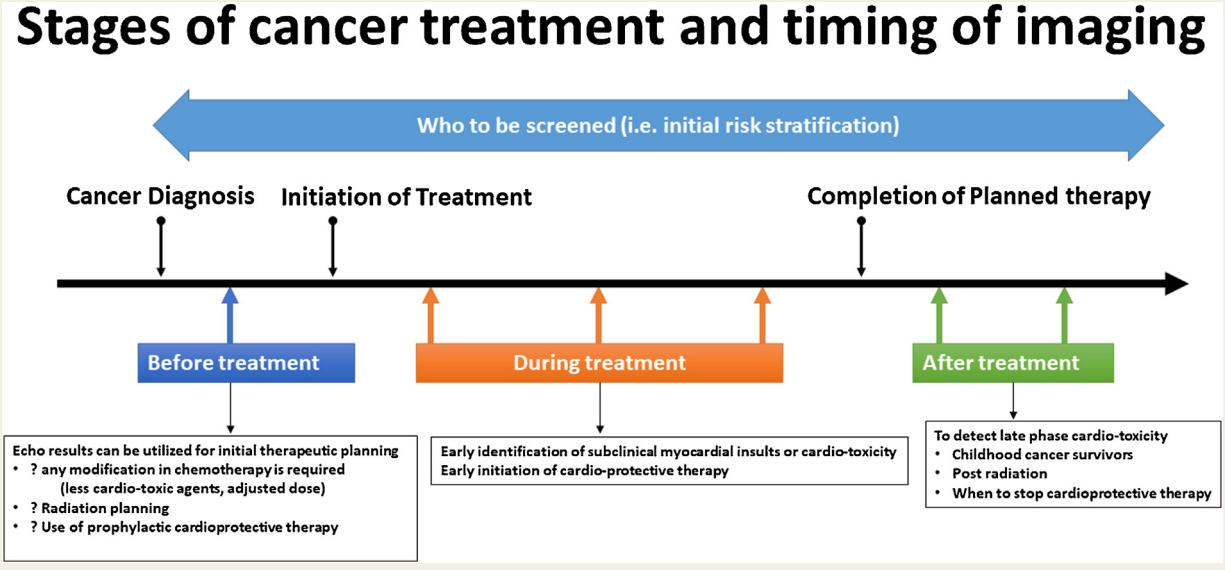

Figure 1 Stages of cancer treatment and timing of imaging.

Table 2 A List of Current Recommendation articles for cardiovascular complications of cancer therapy.

Year	Scientific Society	First Author	Type
2012	ESMO [9]	Curigliano G.	Clinical practice Guidelines
2014	ASE/EACVI [10]	Plana JC.	Expert Consensus
2016	ESC [7]	Zamorano JL.	Position Paper
2017	ASCO [11]	Armenian SH.	Clinical practice Guidelines

Abbreviations: ASCO, American Society of Clinical Oncology; ASE, American Society of Echocardiography; EACVI, European Association of Cardiovascular Imaging; ESC, European Society of Cardiology; ESMO, European Society for Medical Oncology.

An important discrepancy among these guidelines relates to the cut-off values for cumulative dose of anthracyclines (Table 5). For instance, the cut-off for doxorubicin was 500 mg/m^2 in the 2012 European Society of Medical Oncology (ESMO) Guidelines [9]. However, the 2016 European Society of Cardiology (ESC) guidelines advised using a cut-off value of <360 mg/m^2 to reduce cardiotoxicity due to the higher incidence of left ventricular (LV) dysfunction and/or HF when the dose is greater than >400 mg/m^2. Even more recent guidelines from the American Society of Clinical Oncology (ASCO) use the cut-off of 250 mg/m^2 to classify risk as high or low. A conservative approach would be to use the lowest cut-offs, which are shown in bold font in Table 5. The important caveat here is that, although a dose-dependent association between anthracyclines and cardiotoxicity has been established [13], no safety threshold exists. In other words, even a low to moderate dose of anthracyclines can cause cardiotoxicity [14].

How to Screen

There are three settings of echocardiographic screening for patients with cancer (Figure 1):

- 1) baseline (prior to the initiation of cardiotoxic chemotherapy),
- 2) during the chemotherapy, and
- 3) after completion of chemotherapy.

The baseline imaging provides a further risk stratification beyond the baseline characteristics discussed in the previous section. The results can be utilised for cancer therapy planning or adjustment, including alternative chemo-regimens with less cardiotoxicity (less cardiotoxic agents, dose adjustment, continuous infusion, etc.), radiation planning (lower cumulative dose, avoid cardiac exposure), and/or the prophylactic administration of cardioprotective therapy. During chemotherapy, the echocardiogram results can inform whether any adjustment

Table 3 Four dimensions of risk factors.

Concomitant myocardial disease	Cardiovascular Risk Factors	Risk factors	Previous Cardiotoxic Cancer Treatment
HF (HFpEF or HFrEF)	Age <18 year-old	Smoking	Prior anthracycline use
Asymptomatic LV dysfunction (EF < 50%, High BNP)	>50 for trastuzumab >65 for anthracyclines	High Alcohol intake	Prior radiotherapy to the chest or mediastinum
Evidence of CAD (previous MI, AP, PCI/CABG, myocardial ischaemia)	Family history of premature CVD (<50 year-old)	Obesity	
Moderate or Severe VHD with LVH or Impaired LV	Arterial hypertension	Sedentary habit	
Hypertensive heart disease	Diabetes mellitus		
HCM	Hypercholesterolaemia		
DCM			
Restrictive CM			
Cardiac sarcoidosis			
Significant arrhythmias (e.g. AF, VT)			

Abbreviations: AF, atrial fibrillation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VT, ventricular tachycardia; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVH, left ventricular hypertrophy; VHD, ventricular heart disease; CM, cardiomyopathy; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; BNP, brain natriuretic peptide; AP, angina pectoris.
Modified from 2016 ESC position paper [7].

Table 4 **Risk factors by anti-cancer chemotherapy agents.**

Anti-cancer chemotherapy agents	Anthracyclines	Anti-HERs compounds	VEGF inhibitors
Examples	Doxorubicin Epirubicin	Anti-bodies: Trastuzumab TKI: Lapatinib	Anti-bodies: Bevacizumab TKI: Sunitinib
Age	Age (>65 years old) Or paediatric population (<18 years old)	Age >65 years old	–
Sex	Female sex	–	–
Hypertension	Hypertension	Hypertension	Hypertension
Diabetes mellitus	Diabetes mellitus	–	–
Obesity	–	High BMI (>30 kg/m^2)	–
Renal failure	Renal failure	–	–
Previous chemotherapy	Cumulative dose Concomitant chemotherapy (alkylating or anti-microtubules agents, Immuno- and targeted therapies)	Previous or concomitant anthracyclines use (esp. short time between anthracyclines and anti-HER2 treatment)	–
Radiation therapy	Concomitant or previous radiation therapy involving the heart	Previous radiation therapy	–
Pre-existing cardiac disease	Cardiac disease associating increased wall stress	Previous LV dysfunction	Pre-existing cardiac disease. HF, significant CAD, or left side VHD. Chronic ischaemic cardiomyopathy
Genetic factors	Genetic factors	–	–

Abbreviations: BMI, body mass index; CAD, coronary artery disease; HER2, human epidermal growth factor receptor 2; HF, heart failure; LV, left ventricular; TKI, Tyrosine kinase inhibitors; VHD, valvular heart disease.
Modified from 2016 ESC position paper [7].

is required for the planned cancer therapy, including initiation of cardioprotective therapy during subclinical myocardial damage, modifying the planned chemotherapy and/or radiation therapy (e.g. reducing the cumulative dose, etc). The main aim of echocardiography after the completion of cancer therapy is surveillance for late cardiac toxicity (e.g. in childhood cancer survivors, and/or after radiation therapy).

Before the Initiation of Chemotherapy

Left ventricular ejection fraction (LVEF) of 50–55% is considered borderline low LVEF and considered as a high risk for potential cardiotoxic effects of chemotherapy [11]. If the baseline LVEF is less than 50%, cardio-protection therapy with an angiotensin converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) and a beta blocker can

Table 5 **Cut-off values for cumulative dose of anthracyclines.**

	2012 ESMO	2016 ESC [7]				2017 ASCO [11]
(mg/m^2)	At risk	To reduce cardiotoxicity*	LV dysfunction#		HF >5% [40]†	High or Low risk
Doxorubicin	>500	<360	>400	35%	400	**250**
Epirubicin	>720	<720	>900	0911.4%	900	**600**
Daunorubicin	–	<**800**	–	–	800	–
Idarubicin	>**90**	<150	>**90**	518%	150	–

Bold fonts denote the lowest cut-off cumulative doses.
Abbreviations: HF, heart failure; LV, left ventricular; ESMO, European Society of Medical Oncology; ESC, European Society of Cardiology; ASCO, American Society of Clinical Oncology.
*Table 13, #Table 1, †Table 5 from 2016 ESC position paper [7].

Table 6 Baseline cut-off value to predict subsequent cardiac dysfunction and heart failure.

Year	First Author	Anthracycline dose mg/m2	Malignancy type	Sample size	Outcome	Outcome type	Ultrasound system	Strain SW	GLS cut-off	Findings
2015	Mousavi [15]	207 ± 99	Breast/Blood/etc (LVEF 50-59%)	158	12	Symptomatic HF	Vivid 7, E9 or iE33	TomTec	16%	HR 4.7 (1.50-15.96)
2016	Ali [16]	247(8-670)	Leukaemia and Lymphoma	450	28	Symptomatic HF or cardiac death	Vivid 7 or E9	TomTec	17.5%	r = 0.89
2018	Hatazawa [17]	265 ± 107	Lymphoma	73	10	HF hospitalisation	iE33	QLAB 10	19%	AUC 0.77 Sensitivity 60% Specificity 87%

Abbreviations: AUC, area under the curve; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; r correlation coefficient.

improve the LVEF. If LVEF-recovered, the patients even may be able to tolerate a chemotherapy regimen with potential cardiotoxic effect. Several studies have reported baseline global longitudinal strain (GLS) cut-off values for those treated with anthracycline-based regimens [15–17] (Table 6). Two studies reported similar values of 16% and 17.5%, the other reported 19%. Given healthy controls never show a GLS value of <16% [18], asymptomatic patients with that level of GLS should be considered as having subclinical LV dysfunction and high baseline risk.

During the Cancer Therapy

Guidelines from cardiac societies [7,10] define cardiotoxicity when the LVEF falls below the lower limit of normal (e.g. 53% in American Society of Echocardiography [ASE] guidelines) with more than a 10 percentage point reduction. ESMO Guidelines used EF 50% as the cut-off [9], at which point cardio-protection should be considered [19]. Even though withholding a certain cancer therapy is a last resort in cardio-oncology, it has been suggested to withhold chemotherapy when the LVEF becomes <45% during anthracyclines use or LVEF becomes <40% with trastuzumab [19]. Although LVEF has been used for cardio-oncology decision making, growing evidence has revealed that LVEF is an imperfect marker because it is insensitive to early changes in cardiac function during a potentially cardiotoxic treatment [20,21]. Detailed reasons for this can be found elsewhere [22]. Briefly, the main evidence which supports the early detection of cardiotoxicity is a study of 201 patients with anthracycline-induced cardiomyopathy [23]. Even when all patients were treated with cardioprotective medications (enalapril ± carvedilol), 1) only responders who recovered their LVEF to >50% showed an excellent event-free survival (85%) over 2-year follow-up, whereas non-responders or those with partial response had dismal outcomes; and, 2) the longer it took to initiate cardio-protective medicine, the less responders were detected. No responders were found when the medication was started >6 months after the detection of cardiotoxicity. Effective cardio-protective medicines exist in our armamentarium, hence many studies have sought to identify how to detect patients who may benefit from their use early during treatment.

Many parameters have been reported as sensitive markers of the early subclinical changes. Among these indices, the change in GLS had the most accurate prediction of subsequent cardiotoxicity [24] with the cut-off value of an 11 percentage-point decrease in ΔGLS [95% CI 8.3, 14.6]. Current guidelines adapted the upper confidence interval (i.e., 15%) as a conservative cut-off to suggest subclinical LV dysfunction [7,10]. Our retrospective analysis demonstrated the possibility that ΔGLS could be utilised to guide an early initiation of cardio-protective intervention [25]. In addition, absolute GLS value may predict reversibility. Those with GLS < 15.8 % at the time of cardiotoxicity diagnosis are less likely to recover from LV dysfunction [26]. A prospective international, multicentre, randomised controlled trial using

Table 7 Recommended frequency of cardiac function surveillance.

Age at Treatment	Chest Radiation	Total anthracycline dose	Recommended frequency of echocardiography or MUGA
< 1 year	Yes	Any	Every year
	No	< 200 mg/m^2	Every 2 years
		≥ 200 mg/m^2	Every year
1 to 4 years old	Yes	Any	Every year
	No	< 100 mg/m^2	Every 5 years
		≥ 100 to < 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
≥ 5 years old	Yes	< 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year
	No	< 200 mg/m^2	Every 5 years
		≥ 200 to < 300 mg/m^2	Every 2 years
		≥ 300 mg/m^2	Every year

Abbreviation: MUGA, multigated acquisition.

GLS as guidance for the initiation of cardio-protective therapy has completed the enrolment phase This trial is testing the hypotheses that information from strain imaging leads to the use of adjunctive cardioprotective therapy that will limit: a) the development of LV dysfunction; b) interruptions of planned chemotherapy; and c) development of heart failure during the follow-up (Strain sUrveillance during Chemotherapy for improving Cardiovascular Outcomes: SUCCOUR study, ANZCTR [Australian New Zealand Clinical Trials Registry] number ACTRN12614000341628) [27]. The core laboratory of the SUCCOUR study has been monitoring the concordance of echocardiographic measurements between the core laboratory and participating sites. Up to 12 months, the absolute difference observed in two-dimensional LVEF was 4.5%, whereas GLS and three-dimensional LVEF had better concordance with 1.1.5% and 3.3.5%, respectively [28] Like other echocardiographic measurements, experience is required in accurately measuring GLS, although the precision of GLS is still reasonably high for the novice reader [29]. Concordance for GLS measurements was significantly greater than that for LVEF, regardless of image quality. Experience with strain measurement affected the concordance in strain values among the readers; the group with the highest level of experience showed significantly better precision than those with no experience [29]. One study reported that, after 50 cases of strain measurements, the concordance reached plateau [30].

After Completion of Chemotherapy

Cancer survivors should be informed of their increased risk of CVD at the outset of their chemotherapy and should be advised and supported to make appropriate lifestyle modifications [7]. Both paediatric and adults survivors of anthracycline-based chemotherapy have a lifelong risk for development of LV dysfunction and HF [31,32]. The time lapse between treatment and the development of HF can be very long (>10 years) [33]. Thus, periodic surveillance is recommended. ASCO Guidelines recommend an echocardiogram between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk [11]. If asymptomatic cardiac dysfunction is identified during the routine surveillance, cardiology referral is recommended. However, no recommendation has been made regarding the frequency and duration of surveillance. For childhood cancer survivors, Children's Oncology Group (A US National Cancer Institute supported international Clinical Trials Group) suggests the frequency be based on the age at treatment, total anthracycline does, and radiation (Table 7) [34].

Radiation

Patients with radiation-associated cardiac disease (RACD) typically present years or even decades after radiation exposure to malignancies, with delayed-onset cardiac insults. RACD has a broad spectrum of deleterious effects: myocardial disease, valvular heart disease (regurgitation and/or stenosis), vasculopathy including coronary artery disease, pericardial disease, and conduction system dysfunction [35]. Cardiomyocytes are resistant to radiation due to limited cell division. However, cardiac radiation exposure can cause coronary microvascular endothelial inflammation, resulting in HF with reduced (HFrEF) or preserved EF (HFpEF) [36]. Mean cardiac radiation dose was an independent risk factor for any HF, HFpEF, or HFrEF. Mediastinal radiation therapy is also associated with significant valvular abnormalities ranging from 7% to 39% at 10 years and 12% to 60% at 20 years, with mitral and aortic valves most affected [37]. Although acute pericarditis is rare with modern radiation protocols, chronic pericarditis may manifest many years after radiation, with an estimated prevalence of 8% to 30% [38], where high radiation dose is a risk factor. Up to 75% of long-term survivors who received mediastinal radiation have

conduction abnormality on electrocardiography (ECG) [39], which can be related to direct irradiation or be secondary to myocardial inflammation, ischaemia or fibrosis. In ASCO Guidelines, the cut-off is the cumulative dose of 30 (Gray) Gy where the heart is in the treatment field [11].

Conclusion

Cardio-oncology is at the intersection of cancer and CVD. The goal of this emerging subspecialty is to enable patients to complete their planned cancer treatments and to eliminate CV complications as a barrier to, or consequence of, cancer therapy. A close collaboration among members of the cardio-oncology team is essential. As cardiac imaging, especially echocardiography, plays a pivotal role in the cardio-oncology field, further research into risk stratification, early diagnosis, prevention, and treatment, as well as quality control, monitoring, and management is essential.

Conflict of Interest

All authors declare that they have no conflict of interest.

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References

[1] Yeh ET, Chang HM. Oncocardiology-past, present, and future: a review. JAMA Cardiol 2016;1:1066–72.
[2] Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.
[3] Thun MJ, DeLancey JO, Center MM, Jemal A, Ward EM. The global burden of cancer: priorities for prevention. Carcinogenesis 2010;31:100–10.
[4] Thavendiranathan P, Abdel-Qadir H, Fischer HD, Camacho X, Amir E, Austin PC, et al. Breast cancer therapy-related cardiac dysfunction in adult women treated in routine clinical practice: a population-based cohort study. J Clin Oncol 2016;34:2239–46.
[5] Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. J Clin Oncol 2016;34:1122–30.
[6] Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA Cardiol 2017;2:88–93.
[7] Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, 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;37:2768–801.
[8] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.
[9] Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(Suppl. 7):vii155–66.
[10] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27:911–39.
[11] Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893–911.
[12] Thavendiranathan P, Abdel-Qadir H, Fischer HD, Liu Y, Camacho X, Amir E, et al. Risk-imaging mismatch in cardiac imaging practices for women receiving systemic therapy for early-stage breast cancer: a population-based cohort study. J Clin Oncol 2018. JCO2018779736.
[13] Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med 1977;62:200–8.
[14] Drafts BC, Twomley KM, D'Agostino Jr R, Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging 2013;6:877–85.
[15] Mousavi N, Tan TC, Ali M, Halpern EF, Wang L, Scherrer-Crosbie M. Echocardiographic parameters of left ventricular size and function as predictors of symptomatic heart failure in patients with a left ventricular ejection fraction of 50-59% treated with anthracyclines. Eur Heart J Cardiovasc Imaging 2015;16:977–84.
[16] Ali MT, Yucel E, Bouras S, Wang L, Fei HW, Halpern EF, et al. Myocardial strain is associated with adverse clinical cardiac events in patients treated with anthracyclines. J Am Soc Echocardiogr 2016;29:522–7. e3.
[17] Hatazawa K, Tanaka H, Nonaka A, Takada H, Soga F, Hatani Y, et al. Baseline global longitudinal strain as a predictor of left ventricular dysfunction and hospitalization for heart failure of patients with malignant lymphoma after anthracycline therapy. Circ J 2018;82:2566–74.
[18] Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013;26:185–91.
[19] 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;70:2536–51.
[20] Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. Ann Oncol 2002;13:699–709.
[21] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79.
[22] Negishi T, Negishi K. Echocardiographic evaluation of cardiac function after cancer chemotherapy. J Echocardiogr 2018;16(1):20–7.
[23] Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213–20.
[24] Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr 2013;26:493–8.
[25] Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging 2014;15:324–31.
[26] Fei HW, Ali MT, Tan TC, Cheng KH, Salama L, Hua L, et al. left ventricular global longitudinal strain in HER-2 + breast cancer patients treated with anthracyclines and trastuzumab who develop cardiotoxicity is associated with subsequent recovery of left ventricular ejection fraction. Echocardiography 2016;33:519–26.
[27] Negishi T, Thavendiranathan P, Negishi K, Marwick TH, investigators S. Rationale and design of the strain surveillance of chemotherapy for improving cardiovascular outcomes: The SUCCOUR Trial. JACC Cardiovasc Imaging 2018;11:1098–105.
[28] Negishi T, Thavendiranathan P, Penicka M, Deblois J, Aakhus S, Miyazaki S, et al. Precision and stability of parameters for assessment of left ventricular systolic function in clinical trials: lessons from the succour trial. J Am Coll Cardiol 2019;73(9):1514. http://dx.doi.org/10.1016/S0735-1097(19)32120-5, http://www.onlinejacc.org/content/73/9_Supplement_1/1514.

[29] Negishi T, Negishi K, Thavendiranathan P, Cho GY, Popescu BA, Vinereanu D, et al. Effect of experience and training on the concordance and precision of strain measurements. JACC Cardiovasc Imaging 2017;10:518–22.
[30] Chan J, Shiino K, Obonyo NG, Hanna J, Chamberlain R, Small A, et al. Left ventricular global strain analysis by two-dimensional speckle-tracking echocardiography: the learning curve. J Am Soc Echocardiogr 2017;30:1081–90.
[31] Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266:1672–7.
[32] Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol 2004;22:1864–71.
[33] de Azambuja E, Ameye L, Diaz M, Vandenbossche S, Aftimos P, Bejarano Hernandez S, et al. Cardiac assessment of early breast cancer patients 18 years after treatment with cyclophosphamide-, methotrexate-, fluorouracil- or epirubicin-based chemotherapy. Eur J Cancer 2015;51:2517–24.
[34] Children's Oncology Group. Monitoring for heart problems;[Accessed 28 May 2019]https://www.childrensoncologygroup.org/index.php/organs/heartproblems.
[35] Desai MY, Jellis CL, Kotecha R, Johnston DR, Griffin BP. Radiation-associated cardiac disease: a practical approach to diagnosis and management. JACC Cardiovasc Imaging 2018;11:1132–49.
[36] Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation 2017;135:1388–96.
[37] Veeragandham RS, Goldin MD. Surgical management of radiation-induced heart disease. Ann Thorac Surg 1998;65:1014–9.
[38] Piovaccari G, Ferretti RM, Prati F, Traini AM, Gobbi M, Caravita L, et al. Cardiac disease after chest irradiation for Hodgkin's disease: incidence in 108 patients with long follow-up. Int J Cardiol 1995;49:39–43.
[39] Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004;22:3139–48.
[40] Ewer M. Anthracycline cardiotoxicity: clinical aspects, recognition, monitoring, treatment, and prevention. In: Ewer M, Yeh E, editors. Cancer and the heart. Shelton, CT, USA: People's Medical Publishing House; 2013. p. 11–41.