Review Article

Imaging modalities to detect and track cancer treatment-related cardiovascular dysfunction

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Abstract: Advances in cancer treatments have led to an increase in the number of cancer survivors, but also high rates of short- and long-term cardiovascular (CV) toxicities. The number of new cancer drugs is constantly increasing, and the increasing incidence of toxicities of these drugs make long-term care and monitoring difficult. Moreover, traditional type I and type II cardiotoxicities may not be applicable to all of these agents. Multidisciplinary care with expertise in oncology, cardiology and other related specialties is required to mitigate cancer therapeutics-related cardiovascular dysfunction (CTRCD). Accordingly, CTRCD should include all kinds of toxic/side effects affecting the CV system, including hypertension, endothelial and vascular dysfunction, accelerated atherosclerosis, thrombosis and bleeding, pulmonary hypertension, pericardial disease, QT prolongation, conduction disease/arrhythmias, as well as radiation-induced CV disease (CVD). This study reviews the currently recommended imaging modalities including advanced echocardiographic parameters including global longitudinal strain (GLS), left atrial strain (LAS), fast strain encoded cardiac magnetic resonance (CMR) imaging (fast-SENC) and T1 and T2 mapping, myocardial ^{18}F-fluorodeoxyglucose (FDG) uptake in heart positron emission tomography (PET) and computed tomography coronary angiography for risk assessment, detection and early diagnosis of CTRCD. Experts in cardiology, oncology, hematology, and radio-oncology must work together closely to foster patient awareness and further research in this field.

Keywords: Cardio-oncology; cancer therapeutics-related cardiovascular dysfunction (CTRCD); chemotherapy; radiotherapy; imaging

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Introduction

Cardio-oncology is a new research field which focuses on cardiovascular (CV) disease associated with patients undergoing chemotherapy or radiation and cancer survivors. Cardio-oncology is also an important health issue in Taiwan, as the two leading causes of death are cancer and CV disease (CVD) (1). Cancer treatment has advanced rapidly from cytotoxic chemotherapy, radiation therapy (RT)

and surgery to include targeted and immune-based therapies over the past decades (2). These advances in therapy have led to an increase in the number of cancer survivors (3), however an emerging issue associated with these new cancer therapies is side effects on the CV system, which cause different spectrums of morbidity and mortality (4). Cardiotoxicity refers to the direct harmful effects of cancer treatments on the CV system and/or the acceleration of CVD in addition to traditional CV risk factors (4,5). In order to detect cancer therapeutics-related cardiovascular dysfunction (CTRCD) as early as possible and mitigate the progression of CTRCD, it is important to be aware of the current guideline-recommended and promising imaging modalities. Therefore, in this study, we review these imaging modalities.

Evolving concepts of cardiotoxicity

Previous studies on cardiotoxicity have focused on anthracyclines and trastuzumab (6,7). Type I irreversible CTRCD, doxorubicin is the most well-known characteristic agent, is cumulative, dose-dependent and progressive while type II reversible CTRCD trastuzumab is the characteristic agent, is not cumulative, dose-dependent or progressive (8). However, recent arguments have arisen owing to doxorubicin-induced cardiotoxicity is not always irreversible (9,10) and trastuzumab-induced cardiotoxicity is not always reversible (11). Indeed, in addition to myocardial dysfunction, CTRCD should include all kinds of toxic/side effects affecting the CV system, including hypertension, endothelial and vascular dysfunction, accelerated atherosclerosis, thrombosis and bleeding, pulmonary hypertension, pericardial disease, QT prolongation, conduction disease/arrhythmias, as well as radiation-induced CVD (5,12-17). In addition, RT may cause damage to every component of the heart, which can present in the acute (<6 months) or late (3–30 years) phase (18,19). Breast cancer patients with RT have been reported to have greater risk of coronary heart disease and cardiac death compared to those without RT (20). The risk of CV events is higher in patients receiving RT concomitantly with anthracyclines (21,22). Patients with left-sided breast cancer have a 1.4-fold higher risk of heart injury than those with right-sided breast cancer (23). The rate of major adverse cardiac events (MACEs) has been shown to increase linearly by 7.4% per Gray (Gy) increase in mean heart dose (24). Therefore, it is important to consider which imaging modalities can be used to detect, diagnose and differentially diagnosis the increasingly varied types of CTRCD.

Imaging modalities for detecting cancer treatment-related cardiovascular dysfunction

Cancer therapy-related systolic myocardial dysfunction

For patients with symptoms or signs of current cardiac dysfunction, the guidelines recommend further assessing the risk using biomarkers such as troponins, natriuretic peptides, and evaluations of left ventricular (LV) ejection fraction (EF) (4). In addition to biomarkers, echocardiography-based strain imaging may be particularly useful, and is recommended in guidelines as a baseline screening and follow-up imaging tool (25,26). A relative reduction in global longitudinal strain (GLS) of >15% from baseline is generally considered to be abnormal and an early sign of LV subclinical dysfunction (4) and an early indicator of heart failure. Cardiotoxicity of the right ventricle (RV) as identified by RV GLS follows a similar pattern to LV GLS (27). The left atrium (LA) acts as a reservoir for returning blood from pulmonary veins, and then releases blood to the LV during early diastole and contracts as a pump in late diastole. Therefore, left atrial strain (LAS) may be better able to evaluate diastolic function (28), and it has been strongly correlated with invasive measurements of LV end-diastolic pressure (wedge pressure) (29). Although trans-thoracic echocardiography (TTE) usually serves as the first-line imaging modalities in the evaluation of cardiac disease owing to its low cost, portability, widespread availability, lack of ionizing radiation, and ability to evaluate both anatomy and function of the heart, there are some conditions affecting measurements and accuracies causing limitations including patient's position, patient's condition (for example, lung hyperinflation, cutaneous emphysema, trauma, wound), effects of mechanical ventilation, suboptimal ultrasound windows (poor image quality), Heart plane motion during measurements, Doppler angle error (poor angle alignment) and arrhythmias (30). Dyspnea, often due to elevated LV filling pressure (LVFP), is a presenting symptom for patients with heart failure, and TEE provides a good algorithm for assessments of increasing LVFP with following parameters—peak tricuspid regurgitation velocity >2.8 m/s, E/e' >14 and left atrial maximal volume index >34 mL/m^2 (31,32). Aside from strain in echocardiography, cardiac magnetic resonance (CMR) imaging with T1 and T2 mapping may be particularly useful to evaluate CTRCD (26). The novel fast

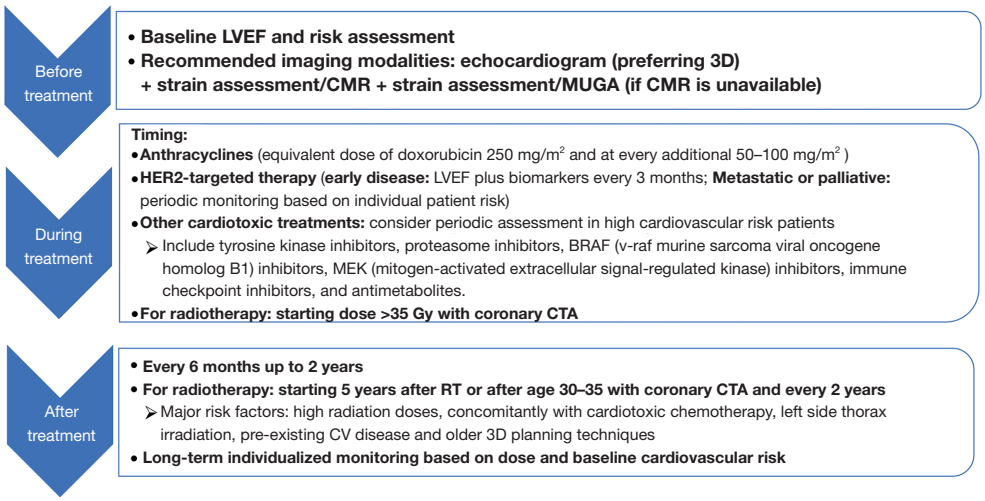

Figure 1 Recommended imaging evaluation for cancer therapy-related systolic myocardial dysfunction. LV, left ventricular; EF, ejection fraction; CMR, cardiac magnetic resonance; CTA, computed tomography angiography; CV, cardiovascular; MUGA, multigated acquisition.

strain encoded CMR imaging (fast-SENC) also provides a highly reproducible method for assessing LV functional performance which is not dependent of the echogenic windows (33) and the ability of CMR strain has also been validated for the detection of cardiotoxicity and for the guidance of cardioprotective therapies (34). Low myocardial ^{18}F-fluorodeoxyglucose (FDG) uptake before doxorubicin chemotherapy in heart positron emission tomography (PET) in patients with Hodgkin disease has been shown to predict the development of CTRCD (35). In addition, doxorubicin was associated with a dose-dependent increase in LV metabolic rate of glucose, particularly in the presence of low baseline FDG uptake in a mice model (35). This increase in myocardial FDG uptake has also been reported in patients following irradiation therapy (36). In addition, the presence or increase in mean standardized uptake value (SUV) of FDG uptake in the RV after anthracycline or trastuzumab treatment has been associated with cardiotoxicity in breast cancer patients (37). *Figure 1* shows the summary of recommended imaging evaluations for cancer therapy-related systolic myocardial dysfunction.

Cancer therapy-related atherosclerotic coronary and peripheral artery disease (PAD)

In addition to traditional CV risk factors, atherosclerotic processes can be accelerated by chemotherapy, RT and immune checkpoint inhibitor (ICI) in patients with cancer (38). Aside from traditional treadmill and vasodilator stress single photon emission tomography (SPECT) (39), stress echocardiography (38), stress CMR (40), computed tomography angiography (CTA) (41) and PET (39) are alternative evaluation tools for ischemia in patients receiving therapies that may cause vasospasms or accelerate atherosclerosis (26).

The time and frequency of follow-up depends on cancer treatment, cumulative dose of anthracyclines, dosing schedule and duration, and personal baseline CV risk (4). However, assessing myocardial viability is important for coronary interventionists to consider which vessels to treat to improve LV function, and stress echocardiography, SPECT (which uses perfusion tracers, thallium-201 or technetium-99m-sestamibi or -tetrofosmin, to assess both perfusion and cellular integrity, which in turn reflects tissue viability), PET (active glucose utilization as measured by PET with FDG) as well as CMR can be used for this purpose (42-44). In addition to RT (45), well-known chemotherapeutic agents that influence vascular function including vascular endothelial growth factor inhibitors (VEGFIs), tyrosine kinase inhibitors (TKIs), cisplatin, 5-fluorouracil, proteasome inhibitors (bortezomib and carfilzomib), immunomodulatory agents (thalidomide, lenalidomide and pomalidomide) (46) and even anthracyclines (47) have been reported to increase arterial stiffness, rate of PAD and stroke. Peripheral CTA can be used to quickly and accurately diagnose PAD after vascular claudication symptoms are reported in history taking with a positive and borderline ankle-brachial index (ABI) (41).

However, 70% to 90% of people with an ABI value less than 0.90 either report no exertional leg symptoms (i.e., asymptomatic) or leg symptoms with walking that are not consistent with classic claudication (48). Although arterial duplex ultrasonography is a complementary modality that can help confirm the diagnosis, evaluate the extent of disease, monitor progression, and identify complications, the performer needs a sufficient understanding of the normal anatomy and caliber of arterial vessels, pathophysiology of arterial disease, and the hemodynamics of normal and abnormal flow as well as a baseline knowledge of the various ultrasonographic modalities and appropriate settings and techniques (49). Therefore, periodically surveying ABI is suggested in patients with RT and some chemotherapeutic agents.

Immunotherapy-related myocarditis

With the rapid advances in immunotherapies, more immunotherapy-related cardiotoxicities have been reported, with the current focus being on chimeric antigen receptor T cell (CAR-T) therapy-associated cytokine release syndrome (50) and ICI-associated myocarditis. Although the reported incidence of ICI-related myocarditis is low (0.04–1.14%), it is associated with a high mortality rate (25–50%) and has been reported to occur early after the initiation of therapy (12,51-54). Although the diagnosis of myocarditis is challenging, elevated troponin and abnormal ECG findings are common (12,55). In addition, the prolonged use of ICIs has recently been linked to early progression of atherosclerosis, myocardial infarction and stroke (56,57).

In patients with myocardial edema, CMR with late gadolinium enhancement (LGE; which is often used to identify fibrosis) may be useful for an early diagnosis, however it has been reported to be present in <50% of those with ICI-associated myocarditis (55,58). In addition, Zhang *et al.* (58) reported that elevated T2-weighted short tau inversion recovery (STIR), which often represents edema, was present in <30% overall. In their study, the presence of LGE, an LGE pattern, or elevated T2-weighted STIR were not associated with MACEs, however their study only included 103 subjects. Therefore, a larger, double-blinded, prospective study is needed to explore the causal relationship between LGE and/or elevated T2-weighted STIR and MACEs. Endomyocardial biopsy is the gold standard to diagnose ICI-associated myocarditis, but it is often underused due to its invasive nature, risk of complications, and a lack of expertise in many hospitals (55,59). Therefore, CMR is an alternative approach to survey ICI-related myopathy.

Venous thromboembolism (VTE)

Patients with cancer are at a 4- to 7-fold higher risk of initial VTE, a 3-fold higher risk of recurrent VTE, a 2-fold higher risk of anticoagulation-associated bleeding, and a 10-fold higher risk of VTE-related death compared to patients without cancer (60). Similar to PAD, RT and chemotherapeutic agents including VEGFIs, TKIs, cisplatin, 5-fluorouracil, proteasome inhibitors, immunomodulatory agents (46) and even anthracyclines (47) have also been reported to increase the rate of VTE. In addition to treatment-related risk factors for VTE, cancer-related factors (e.g., primary site, histology and initial period after diagnosis), patient-related factors (e.g., age, ethnicity and comorbidities) and some biomarkers (e.g., platelet count, white count, hemoglobin, tissue factor, D-dimer, P-selectin and thrombin generation potential) should also be taken into consideration (61). Clinically suspected VTE [including pulmonary embolism (PE) and deep vein thrombosis (DVT)] have become the most common indications for CTA in emergency departments (62). However, CTA can diagnose PE of major vessels but is not sufficiently sensitive to exclude PE due to its poor sensitivity for subsegmental pulmonary vessels, and ventilation/perfusion (V/Q) lung scans are better for subsegmental pulmonary vessels (63). Compression ultrasonography is also a good alternative to detect DVT in emergency departments (63). *Figure 2* shows the summary of recommended risk assessments and imaging evaluations for cancer-related VTE.

Pericardial disease and utility of cardiac imaging

Pericardial disease from effusion, tamponade to constrictive pericarditis can be occurred owing to cancer *per se* (primary or through metastasis) or cancer treatment (chemotherapy and radiotherapy) (64). Echocardiography is the first and often the only necessary imaging test in patients with acute pericarditis and is essential to identify complications, such as tamponade or constrictive pericarditis, and could be useful for monitoring the evolution of pericardial effusion over time and the response to medical therapy (65). While CMR is usually applied for tissue characterisation, CT scan image tumour invasion of adjacent structures which guides

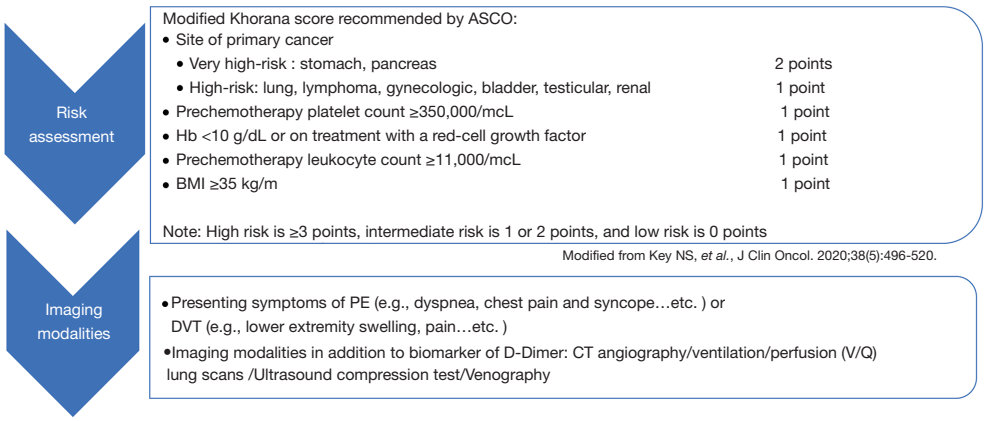

Figure 2 Recommended risk assessment and imaging evaluation for cancer related VTE. PE, pulmonary embolism; DVT, deep vein thrombosis; V/Q, ventilation/perfusion; VTE, venous thromboembolism; ASCO, American Society of Clinical Oncology.

the surgeon for tumor operative removal. PET scanning can be very helpful in determining an active or remitted lesion (64).

Conclusions

Since CTRCD should include all kinds of toxic/side effects affecting the whole CV system, multiple imaging modalities are needed to make a differential diagnosis. Proper imaging monitoring protocols at baseline, subsequent follow-up, and suggested management in patients with suspected CTRCD are important to detect as early as possible and prevent the deterioration of CTRCD with proper management in cancer patients receiving cancer therapies.

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