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Authors

Lopez-Mattei, Juan
Yang, Eric H
Baldassarre, Lauren A
et al.

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Practice guidelines

Cardiac computed tomographic imaging in cardio-oncology: An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT). Endorsed by the International Cardio-Oncology Society (ICOS)

Juan Lopez-Mattei [a,1,*], Eric H. Yang [b,1], Lauren A. Baldassarre [c,1], Ali Agha [d,1], Ron Blankstein [e,1], Andrew D. Choi [f,1], Marcus Y. Chen [g,1], Nandini Meyersohn [h,1], Ryan Daly [i,1], Ahmad Slim [j,1], Carlos Rochitte [k,1], Michael Blaha [l,1], Seamus Whelton [l,1], Omar Dzaye [l,1], Susan Dent [m,1], Sarah Milgrom [n,1], Bonnie Ky [o,1], Cezar Iliescu [a,1], Mamas A. Mamas [p,1], Maros Ferencik [q,1]

[a] Heart and Vascular Institute, Lee Health, Fort Myers, FL, USA
[b] UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
[c] Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, CT, USA
[d] Department of Cardiology, Baylor College of Medicine, Houston, TX, USA
[e] Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[f] Division of Cardiology and Department of Radiology, The George Washington University School of Medicine, Washington, DC, USA
[g] National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[h] Division of Cardiovascular Imaging, Department of Radiology, Massachusetts General Hospital, USA
[i] Franciscan Health Indianapolis, Indianapolis, IN, USA
[j] Pulse Heart Institute, Tacoma, WA, USA
[k] InCor Heart Institute, University of São Paulo Medical School, São Paulo, Brazil
[l] Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, MD, USA
[m] Duke Cancer Institute, Department of Medicine, Duke University, Durham, NC, USA
[n] Department of Radiation Oncology, University of Colorado, Boulder, CO, USA
[o] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[p] Keele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, UK
[q] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

A B S T R A C T

Cardio-Oncology is a rapidly growing sub-specialty of medicine, however, there is very limited guidance on the use of cardiac CT (CCT) in the care of Cardio-Oncology patients. In order to fill in the existing gaps, this Expert Consensus statement comprised of a multidisciplinary collaboration of experts in Cardiology, Radiology, Cardiovascular Multimodality Imaging, Cardio-Oncology, Oncology and Radiation Oncology aims to summarize current evidence for CCT applications in Cardio-Oncology and provide practice recommendations for clinicians.

Introduction

Cardio-Oncology is a rapidly growing sub-specialty of medicine. Many cancer therapies affect the cardiovascular system and may lead to adverse cardiovascular outcomes during treatment or long-term follow-up. The field of Cardio-Oncology is focused on the cardiovascular care of cancer patients with the goal to optimize cardiovascular outcomes, minimize cardiovascular side effects of cancer treatments, and allow for uninterrupted delivery of best possible cancer care. Societal guidelines provide recommendations for the care of Cardio-Oncology patients,[1–10]

* Corresponding author. Heart and Vascular Institute, Lee Health System, HealthPark Medical Center, 9981 S HealthPark Dr, Fort Myers, FL 33908, USA.
E-mail address: juan.lopezmattei@leehealth.org (J. Lopez-Mattei).

[1] In accordance with SCCT policy, writing group members and reviewers are required to disclose relationships with industry; see Appendices 1 and 2 for detailed information.

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however, there is very limited guidance on the use of cardiac CT (CCT) in the care of Cardio-Oncology patients. In order to address this knowledge gap, the Society of Cardiovascular Computed Tomography (SCCT) convened a group of experts to develop an Expert Consensus Statement to summarize the current evidence for CCT applications in Cardio-Oncology and provide practical recommendations for clinicians.

In July 2019, SCCT formed a multidisciplinary collaboration of experts in the fields of Cardiology, Radiology, Cardiovascular Multimodality Imaging, Cardio-Oncology, Oncology and Radiation Oncology. The members of this group performed an extensive literature review using PubMed database and limiting our search up to December 2021 and included the most relevant work in our opinion supporting the role of CCT in Cardio-Oncology. Our PubMed search queries included the following terms, key concepts: "Cancer", "Cardiac CT", "Cardio-Oncology", "Cardiovascular Computed Tomography", "Oncology", "Coronary Calcium Score", "Cardiotoxicity", "CAC" and combinations of terms related to cancer and CCT. We excluded some editorials and opinion pieces not relevant to our topics of interest from our literature search and included peer-reviewed original research, consensus statements and current guidelines in Cardio-Oncology and CCT. We evaluated concordances and discordances of current guidelines and consensus statement recommendations and weighted the evidence available from original research. Due to limited evidence from randomized controlled trials or large epidemiologic studies, the current recommendations are based on expert consensus among the committee members. The recommendations are labeled with phrases such as "**is recommended**," "**should**," "**should be considered,**" "**can be considered**" and "**can be useful**", similar to previously reported American College of Cardiology/American Heart Association (ACC/AHA) consensus statements.[11] The strength of recommendation was deemed as "**strong"** if there was complete agreement among the writing group that the recommendation was appropriate. The strength of the recommendation was deemed as "**moderate"** if there was majority consensus that the recommendation was appropriate.

1. Shared risk factors and role of CCT in risk stratification of cancer patients

CVD is the leading cause of morbidity and mortality among adult cancer survivors.[12,13] In part, this is attributable to advances in cancer screening and treatment therapies that have reduced cancer related mortality and improved overall survival as well as cardiovascular consequences of cancer treatments.[14–17] In addition, there are many underlying shared risk factors between CVD and cancer including hypertension, hyperlipidemia, obesity, physical inactivity, poor diet, diabetes, and smoking.[18–20]

Patients with a coronary artery calcium (CAC) score of 0 in the general population have low CVD risk and a lower risk of cancer as compared to those with CAC score >400.[21] Incidental CAC found in non-cardiac chest CT studies in lung cancer patients is seldom acted upon and could potentially identify patients that could benefit from preventive treatment.[22] Furthermore, cancer survivors who develop CVD have a much higher total mortality rate and they are disproportionately affected with coronary artery disease (CAD), which constitutes approximately three quarters of all CVD mortality in cancer survivors.[13,23] In cancer deaths, high antecedent CAC predicts risk of having CVD as a supporting cause of death on death certificates, independently of ASCVD risk score and risk factors.[24]

Among patients treated for cancer, their risk for CVD is directly associated with their CVD risk factor burden.[23] In addition, there are certain cancer subgroups at especially high-risk including patients diagnosed with cancer at a young age and those with breast, prostate, urinary, endometrial, or melanoma cancers.[13] Therefore, as part of a comprehensive evaluation (see Fig. 1), it is essential to estimate patient's CVD risk in order to mitigate risk using primary/secondary prevention strategies, while permitting delivery of the most efficacious cancer treatment

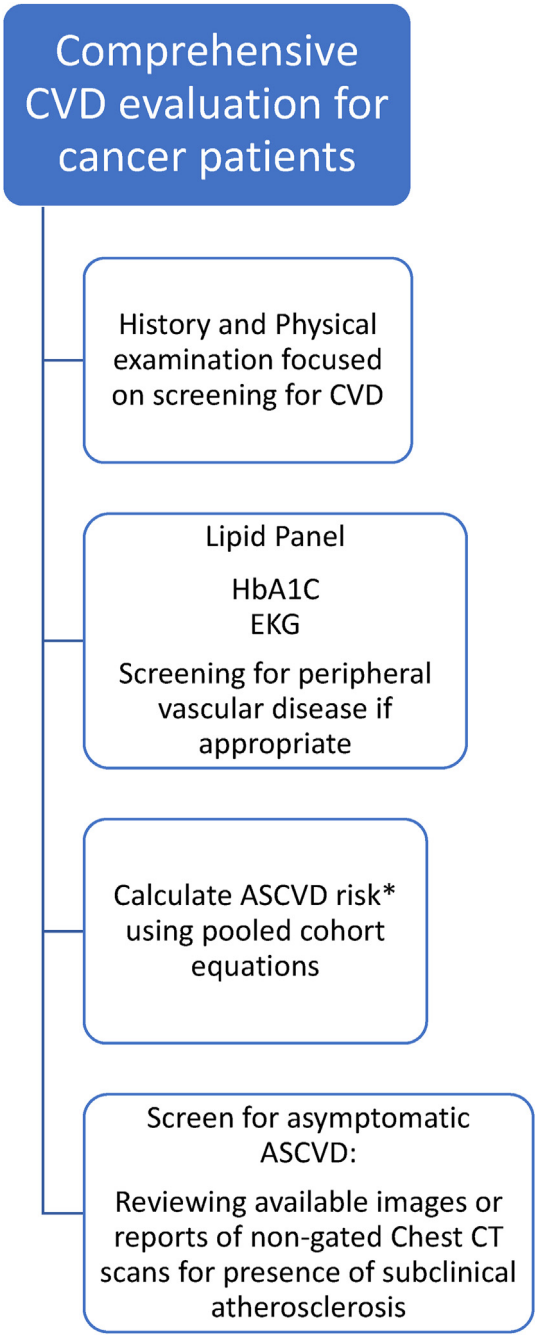

Fig. 1. Comprehensive Cardiovascular evaluation (CVD) evaluation for cancer patients and survivors.

and reducing the risk of future adverse CVD events.[25] The baseline assessment of CVD risk factors can be obtained with the use of online tools. It is important to note that these risk calculators were not derived considering cancer patients (see Table 1).

The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD endorses the use of CAC score in patients at intermediate risk and uncertain risk with regard to preventative therapies.[26] CAC may also be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects as per European Society of Cardiology (ESC) guidelines for evaluation of chronic coronary syndromes.[27] This consensus group recommends that this approach be applied to cancer patients, particularly as some of these patients may have non-traditional risk factors that have known associations with ASCVD, including clonal

Table 1
Atherosclerosis-related cardiovascular risk score calculators.

Risk score[a]	Website
MESA CHD Risk Score	https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx
ACC/AHA pooled cohort CV risk calculator (2013)	http://www.cvriskcalculator.com
ESC HeartScore	www.heartscore.org
JBS3 risk score (2014)	http://www.jbs3risk.com

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; JBS, Joint British Societies.

[a] Risk scores may be used for guidance; however, they have not been validated in a patient population with cancer or those that have been previously treated for cancer.

hematopoiesis of indeterminate potential (CHIP),[28] history of radiation therapy,[29] traditional chemotherapy (i.e. platinum based therapies, anthracyclines and others)[30] and certain novel therapies (i.e. tyrosine kinase inhibitors,[31] immune checkpoint inhibitors[32]). CCT can provide additional information for CVD risk assessment and stratification during cancer screening, diagnosis, and surveillance. Robust evidence supports the use of preventive therapies (there is evidence for statins and potentially for aspirin) in patients with moderate to severe CAC (CAC score >100 or >75th percentile for age and gender) and is endorsed by ACC/AHA, SCCT and National Lipid Association (NLA) guidelines[26,33–36] There may be limitations in using radiation therapy (RT) treatment plan scans (see Fig. 2) and non-gated chest CT scans (see Fig. 3) for CAC evaluation due to limited spatial resolution. When indicated, CAC scan should be the preferred method for CAC evaluation and quantification.

Diagnosis of patients with cancer presents a special opportunity for the evaluation of the presence of CAC and other extra-coronary calcium, as well as quantification of cardiovascular risk. A significant proportion of Cardio-Oncology patients undergo non-cardiac non-gated CT (with or without contrast) for cancer screening, cancer diagnosis, staging, treatment planning (e.g., surgery, radiation therapy) or follow-up. The sensitivity for the detection of CAC on non-cardiac CT is high[37] and the evaluation is supported by the SCCT guidelines.[35,38] While quantification of CAC and calculation of an Agatston score may be feasible on high-quality exams, semiquantitative assessment of CAC (e.g. number of coronary arteries or segments with CAC) or visual assessment (mild, moderate, severe) is a viable alternative for the CVD risk assessment in Cardio-Oncology.[38] (see Figs. 4 and 5). Semiquantitative assessment (e.g. number of coronary arteries or segments with CAC) has been shown to have prognostic value for future CVD events.[39–41] Preventive therapies can be recommended in patients with moderate or severe CAC (2 or more vessels, 3 or more segments).[39–41] In patients with mild CAC (CAC score 1–99, 1 vessel, 1–2 segments), preventive therapies, especially statin therapy can be considered through the process of shared decision making, while also incorporating the presence of other underlying CVD risk factors.[34]

CAC scores can be readily obtained from CT imaging performed for lung cancer screening in order to provide indispensable information for CVD risk stratification,[42,43] and are predictive for CVD events,[44] therefore providing support for the synergistic use of cancer screening/surveillance modalities to improve CVD risk prediction. The presence and semi-quantitative assessment of CAC should be considered as part of the reporting templates in lung cancer screening. The findings of the cancer screening should be then implemented in the prevention of CVD as directed by existing guidelines.[26] A simple system (CAC-Data Reporting System - CAC-DRS), which includes both quantitative and qualitative visual assessment of calcified coronary plaque burden, has been developed by SCCT and can be used to estimate CVD risk.[35] It also provides preventive treatment recommendations according to risk categories. For a quantitative approach, the system uses Agatston score, which is a summed score of the calcified plaque area and the maximal density of calcium in all calcified lesions, and CVD risk categories can be determined as shown in Table 2, column *a*.[35] For visual assessment, the system uses a qualitative approach (as shown in Table 2, column *b*), and CVD risk assessment can be provided. This type of visual scoring system should be used for non-contrast non-gated studies.[35] For examples in regard to visual quantification of CAC and how to grade using CAC-DRS in non-contrast thoracic CT scans, please refer to the full document entitled "CAC-DRS: Coronary Artery Calcium Data and Reporting System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT)".[35]

Traditionally there has been a concern of radiation exposure from CT and some may tend to be more conservative towards cardiac CT. However, the magnitude of exposure has decreased significantly by advances in scanner technology and acquisition modes. In a decade, radiation doses from CCT have decreased by 78%.[45] Estimated radiation doses from CCTA with optimal radiation reduction protocols range is 2–5 mSv and low dose CAC scan range is 0.2–0.4 mSv.[46] It is important to have physician-patient discussion regarding goals of care and considering cancer prognosis balanced with the benefits of cardiovascular disease (CVD) risk assessment and treatment when utilizing clinical pathways suggested by this consensus statement document.

Recommendation 1.1. A comprehensive baseline evaluation to screen for, and subsequently optimize, any underlying atherosclerotic cardiovascular disease (ASCVD) risk factors **is recommended** for all patients with cancer and cancer survivors.

Level of Recommendation: **Strong**

Recommendation 1.1.1. Physicians reporting on non-cardiac chest CT scan for cancer imaging **should** include a statement regarding presence or absence of coronary artery calcium in the report. This includes the chest CT component of PET scans.

Level of Recommendation: **Strong**

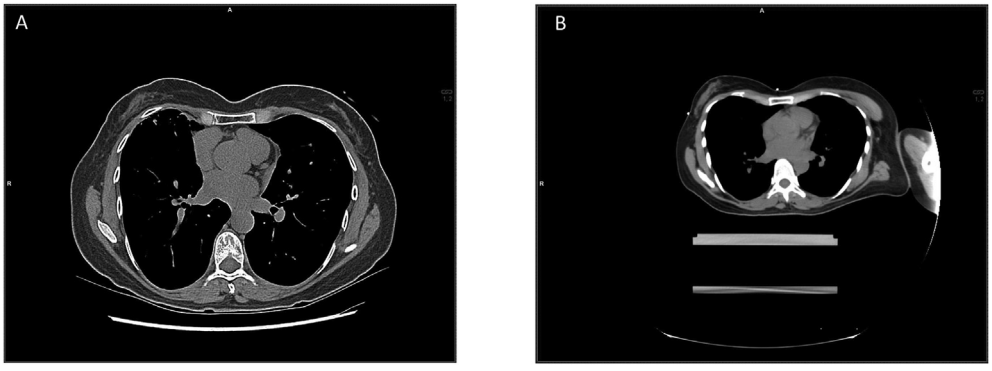

Fig. 2. Image comparison between a CAC scan (A) and radiotherapy (RT) treatment plan CT (B) in a patient with breast cancer. This figure demonstrates how gated images (A) show cardiac substructures better in comparison with a larger field of view and lower spatial resolution RT treatment plan (B).

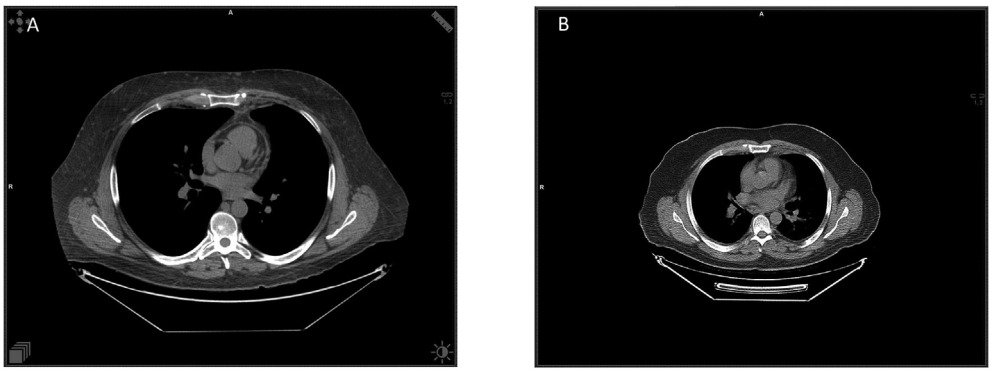

Fig. 3. Image comparison between a CAC scan (A) and non-contrast non-gated CT component of a PET study (B) in a patient with lymphoma. This figure demonstrates gated images (A) with improved identification of cardiac substructures in comparison with non-gated CT (B).

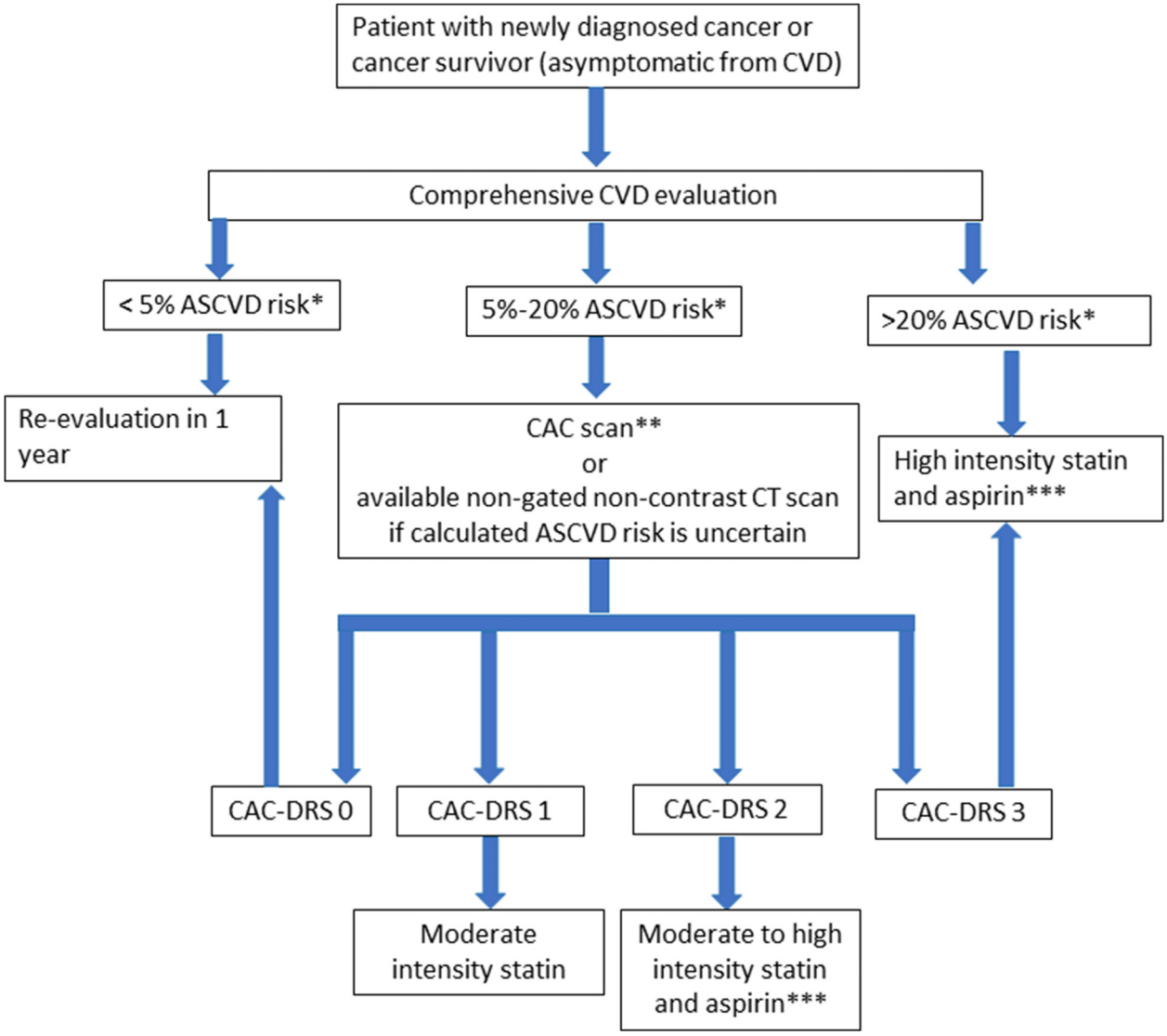

Fig. 4. CVD risk guided pathways for cancer patients and survivors. * ASCVD risk score may be used for guidance, however it has not been validated in a patient population with cancer or those that have been previously treated for cancer. **If available, CAC scan is the preferred method to evaluate CAC quantitatively using the Agatston score in patients with Intermediate ASCVD risk. Non-gated non-contrast CT scans for cancer imaging may be used for qualitative assessment of CAC-DRS risk categories and it should be part of a comprehensive CVD evaluation. *** Caution if thrombocytopenia and evaluate cancer related bleeding risk before treatment with aspirin.

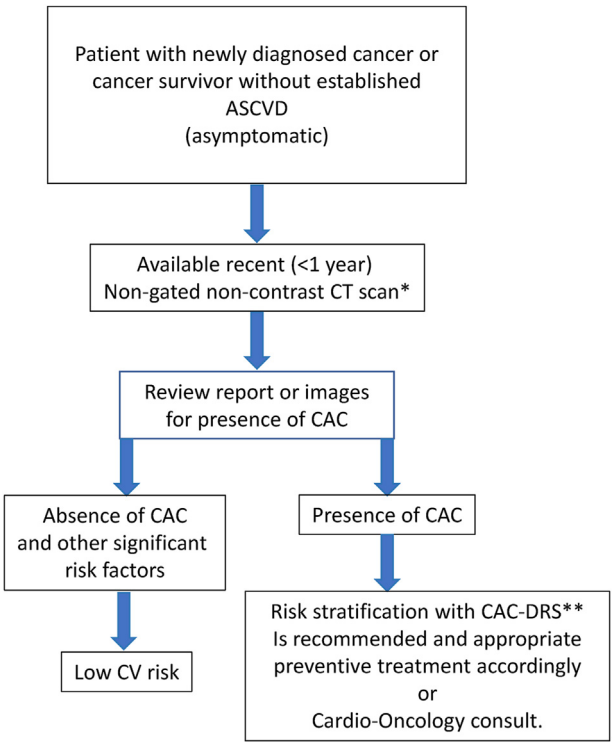

Fig. 5. Simplified clinical pathway for non-cardiologists *Non-gated non-contrast CT scans for cancer imaging may be used for qualitative assessment of CAC-DRS risk categories and it should be part of a comprehensive CVD evaluation. ** CAC-Data Reporting System (CAC-DRS).

Recommendation 1.2. In asymptomatic cancer patients, clinicians **should** review available non-cardiac chest CT reports and/or images. If there is evidence of coronary artery calcium (CAC) in a patient without history of ASCVD, measures should be taken to improve CV risk stratification and reduce ASCVD risk.

Level of Recommendation: **Strong**

Recommendation 1.2.1. Severity of CAC in available non-cardiac non-contrast chest CT images **should be** quantified qualitatively or quantitatively using the CAC-DRS scoring system.

Level of Recommendation: **Moderate**

Recommendation 1.3. If no previous recent non-cardiac chest CT is available, a CAC scan **may be considered** in all cancer patients without known ASCVD who are not on lipid lowering therapy, if they have 5–20% ASCVD risk, consistent with SCCT, ACC/AHA and ESC guidelines.

Level of Recommendation: **Moderate**

2. Multimodality imaging in cardio-oncology

Most societal guidelines and consensus statements focus on the utility of the different cardiac imaging modalities for left ventricular ejection fraction assessment before, during, and after cancer therapies. However, the application of cardiac imaging in this patient population extends far beyond that to many other clinical scenarios, as further detailed subsequently in this document.

An expert consensus document from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) in 2014 delineates the role of transthoracic echocardiography (TTE) for imaging adult patients during and after cancer therapy, and although cardiac magnetic resonance (CMR) imaging and multi-gated nuclear angiography (MUGA) are highlighted, the utility of CCT in this population is not well described.[47] Many comprehensive review documents have further brought to light the utility of CMR in the Cardio-Oncology population, demonstrating its value as a highly accurate and reproducible tool for assessment of cardiac function and its benefits of tissue characterization for identification of inflammation and fibrosis.[48,49] The multi-faceted utility of nuclear cardiac imaging for diagnosis and management in these patients is described in an American Society of Nuclear Cardiology (ASNC) information statement[50] and its role within a multi-modality approach has been described.[51] Similarly, oncology societies offer guidelines for cardiac monitoring in cancer patients, such as the American Society of Clinical Oncology (ASCO) clinical practice guideline published in 2017, which recommends clinical assessment with TTEs, and when TTE is not available or technically feasible, preference is given to CMR followed by MUGA, in light of the more anatomic information provided and no ionizing radiation exposure associated with CMR.[52,53] For cardiomyopathy surveillance assessment specifically in survivors of childhood cancer, a 2015 report from the International Late Effects of Childhood Cancer Guideline Harmonization Group demonstrates concordance in recommendations for TTE monitoring in these patients, although the utility of other cardiac imaging modalities is not well defined.[54] An expert consensus document for multi-modality imaging specifically of cardiovascular complications of radiotherapy in adults was reported from the EACVI and the ASE in 2013, which does highlight the utility of CCTA as a non-invasive technique for imaging of the coronary arteries and atherosclerotic plaque, with some additional value for pericardial and valve assessment secondary to radiation-induced pathology.[55]

In the section to follow, this Expert Consensus statement from the SCCT provides guidance on the use CCT in the field of Cardio-Oncology in the context of multi-modality imaging.

Table 2
CAC-Data Reporting System (CAC-DRS) category determined risk classifications and preventive treatment recommendations from Hecht et al. JCCT 2018;12(3):185–191.[35]

Categories	CAC score	Cardiovascular Risk	Possible Treatment Recommendation
a. Agatston Score			
CAC-DRS 0	0	Very low	Statin not recommended[a]
CAC-DRS 1	1–99	Mildly increased	Moderate intensity statin
CAC-DRS 2	100–299	Moderately increased	Moderate to high intensity statin + aspirin 81 mg[b]
CAC-DRS 3	≥300	Moderately- Severely increased	High intensity statin + aspirin 81 mg[b]
b. Visual Score			
CAC-DRS 0	0	Very low	Statin not recommended[a]
CAC-DRS 1	1	Mildly increased	Moderate intensity statin
CAC-DRS 2	2	Moderately increased	Moderate to high intensity statin + aspirin 81 mg[b]
CAC-DRS 3	3	Moderately- Severely increased	High intensity statin + aspirin 81 mg[b]

[a] Excluding familial hypercholesterolemia.
[b] Caution in thrombocytopenia and in patients at risk of bleeding from malignancy.

Table 3
Most common types of the treatment related cardiotoxicity and chemotherapy related cardiac dysfunction and role of cardiac computed tomography. CT: Computed Tomography. CAC: Coronary Artery Calcium scoring. CCTA: Coronary Computed Tomography Angiography; 5-FU: 5-Fluorouracil; CAR-T: Chimeric Antigen Receptor Therapy; ACS: Acute Coronary Syndrome; CAD: coronary artery disease.

Oncologic Therapy Type	Examples	Common Cardiovascular Side Effects	Possible Roles of Cardiac CT
Anthracyclines[180–183]	Doxorubicin Daunorubicin Idarubicin Mitoxantrone	Cardiomyopathy (toxicity increases in a cumulative, dose-dependent fashion) Myopericarditis Arrhythmia Pericardial effusion	• CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy • CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely • CAC assessment on non-cardiac CT scans for baseline risk assessment
Alkylating Agents[184]	Cyclophosphamide	Hemorrhagic myopericarditis	• Cardiac CT to evaluate pericardial effusion (HU measurements for characterization of the effusion if clinically relevant) • CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely (e.g., myopericarditis) • CAC assessment on non-cardiac CT scans for baseline risk assessment
Fluoropyrimidines[185, 10,186–190]	5-fluorouracil Capecitabine	Anginal chest pain (incidence up to 18%)[10,186–190] Coronary vasospasm Myocardial infarction	• CCTA to rule out obstructive CAD in patients presenting with symptoms of chest pain suspected to be coronary vasospasm to exclude other concomitant processes that could account for an acute coronary event. • Coronary CTA to evaluate coronary atherosclerosis prior to therapy • CAC assessment on non-cardiac CT scans for baseline risk assessment
HER2/neu Receptor Inhibitors[191–193]	Trastuzumab Pertuzumab	Cardiomyopathy	• Same as anthracyclines
Taxanes[10,186,194,195]	Paclitaxel Docetaxel	Myocardial ischemia[10,186] Coronary vasospasm[195] Cardiomyopathy Arrhythmias	• CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy • CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely • Coronary artery calcium assessment on non-cardiac CT scans for baseline risk assessment
Vascular Endothelial Growth Factor (VEGF) Inhibitors[196–200]	Bevacizumab Sunitinib Sorafenib Pazopanib	Arterial hypertension Acute thromboembolic events, including ACS[196–200]	• CCTA to rule out ACS • CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely
Immune Checkpoint Inhibitors[201–211]	Pembrolizumab Nivolumab Ipilimumab Atezolizumab	Myocarditis Increased risk of coronary atherosclerosis[211]	• CCTA to rule out obstructive CAD when myocarditis is suspected (e.g., elevated troponin) • CCTA to evaluate coronary atherosclerosis prior to therapy • CAC assessment on non-cardiac CT scans
CAR-T Therapy[212]		Cytokine release syndrome Elevated troponin Cardiomyopathy Arrhythmias	• CCTA to rule out obstructive CAD with elevated troponin • CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy • CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely
Hematopoietic Stem Cell Transplantation[213,214]	Autologous Allogenic	Population with an increased prevalence of CV risk factors	• Coronary artery calcium assessment on non-cardiac CT scans or CAC scan for baseline risk assessment • CCTA to rule out obstructive CAD in patients with symptoms suggestive of obstructive CAD

3. Role of cardiac CT in cancer treatment related cardiotoxicity

3.1. Basics of the treatment related cardiotoxicity and related cardiac dysfunction

The field of Cardio-Oncology has evolved from the management of cardiomyopathy in cancer patients exposed to common chemotherapeutic agents (e.g., anthracyclines) to a more proactive approach of screening, intervening, and management of cardiovascular toxicity during and following completion of cancer therapy. This evolution has led to an increasing interest in defining the optimal cardiovascular imaging strategies needed to support patients throughout their cancer treatment and into survivorship. Currently, the list of agents impacting cardiovascular health in the field of oncology is vast, including but not limited to the ones mentioned in Table 3[56,57] with varying mechanisms impacting cardiovascular health and potential roles of CCT in appropriate clinical scenarios.

3.2. Cardiac CT imaging in the evaluation of cancer therapy related cardiac dysfunction

3.2.1. systolic function assessment

There is limited data on the application of cardiac CT in patients undergoing chemotherapeutic, targeted or immune based therapies[58] (see Table 3). With respect to cardiomyopathy evaluation, TTE remains widely used for initial baseline function assessment and monitoring. There is increasing use of 3D left ventricular ejection fraction (LVEF) and global longitudinal strain by TTE for the prediction and management of cardiotoxicity with excellent correlation with cardiac MRI data.[59–62] CMR is an imaging modality commonly used for characterizing cardiomyopathies, and is considered the gold standard in the evaluation of ventricular volumes and function.[63] Retrospective multiphase electrocardiogram (ECG)-gated CCT, especially when obtained using biphasic or triphasic injection protocol may provide both volumetric and morphological information,[64] and are considered an accurate and reproducible alternative to CMR with studies showing positive correlation both for the evaluation of biventricular volumes and function.[65,66] However, CCT is not in the initial modality for cardiotoxicity screening or monitoring of cardiac function, but its role lies as part of the workup to identify the etiology of reduction in systolic function especially when coupled with rise of cardiac biomarkers where either obstructive coronary artery disease (CAD) needs to be excluded in the context of possible cardiotoxicity.

3.2.2. Obstructive and non-obstructive CAD in the context of LV dysfunction

Coronary CTA has high negative predictive value (approaching 99%) for the exclusion of obstructive CAD.[67–72] Therefore, it can reliably rule out obstructive CAD as the etiology of systolic dysfunction. However, in

patients that have moderate to extensive coronary calcifications, blooming artifact may cause difficulty in assessing the severity of coronary stenosis and may lead to overestimation of severity.[73] The initial step in the workup of heart failure is to diagnose or exclude ischemic cardiomyopathy due to its high prevalence and potential therapeutic effect with recovery of left ventricular function through coronary revascularization. A screening calcium score is a simple and cost-effective method, where a coronary calcium score of 0, has a specificity of 98.4% and a positive predictive value of 98.3% to exclude ischemic etiology for cardiomyopathy.[74] Oncologic patients may have routine chest CT evaluations and the visual assessment for coronary calcification (or its absence) correlates with dedicated ECG-gated cardiac exams.[75] The absence of coronary artery calcium significantly decreases the likelihood of significant obstructive CAD as the cause of cardiomyopathy. In cancer patients with coronary calcium or higher clinical suspicion for CAD, coronary CTA is an accurate first-line non-invasive imaging test for exclusion of significant CAD due to its high negative predictive value.[76] Coronary CTA is accepted as an alternative to invasive coronary angiography for evaluating for the presence of coronary artery disease in patients with new onset heart failure to differentiate between ischemic and non-ischemic etiologies in low to intermediate risk patients.[27,77,78] Furthermore, several cancer treatments have been implicated in the development of cardiac ischemia, coronary events or cardiac inflammation/myocarditis[10] and in select cases coronary CTA can provide risk stratification prior to administration of therapeutic drugs.

3.2.3. Acute coronary syndrome

Coronary CTA also plays a role in patients with chest pain and suspected acute coronary syndrome (ACS).[79,80] It has a growing role in the evaluation of these patients, especially in the setting of low to moderate risk ACS (e.g. transient ECG abnormalities, mildly elevated troponin, wall motion abnormalities with no other significant findings) and stable chest pain syndrome.[80–82] The advantage of coronary CTA is its ability to detect obstructive coronary artery disease (CAD) and if present, permit timely initiation of treatment according to the current ACC/AHA guidelines.[80] Cancer therapy related thrombocytopenia and anemia places cancer patients at increased risk of access site related major bleeding complications from invasive procedures such as invasive coronary angiography. The Society for Cardiovascular Angiography and Interventions (SCAI) guidelines provide recommendations for these patients, and coronary CTA can be a preferred method for evaluation.[83] Coronary CTA has a unique non-invasive capability to detect non-obstructive atherosclerosis and characterize coronary atherosclerosis.[84–87] The presence of atherosclerosis detected on CCT or non-cardiac CT obtained for other clinical indications may be used to start preventative therapies (e.g. statins and aspirin) as described in Section 1.

3.2.4. CCT derived extracellular volume fraction in cardiomyopathies

Beyond the differentiation between ischemic and non-ischemic cardiomyopathy, CCT has the ability to detect subtle attenuation changes of the myocardium from cardiotoxic damage. Initially validated in CMR, CCT utilizes the same principle using extracellular and intravascular routine contrast agents to permit measurement of extracellular volume (ECV) fraction to detect diffuse myocardial fibrosis and obviate the need for endomyocardial biopsy.[88] CT ECV has been validated against CMR using subtraction of non-contrast and contrast enhanced images,[89] or rapid kV switching dual energy,[90] dual energy from 2 x-ray tubes.[91] Furthermore, CT based ECV can be used to differentiate normal vs abnormal myocardial[92] or for the non-invasive diagnosis and quantification of cardiac amyloidosis.[93] The utility of monitoring CT derived ECV lags behind CMR; however, it is an area of active investigation.

3.2.5. Strain

The evaluation of myocardial strain in CCT is feasible using dedicated software and has shown good correlation with TTE in patients treated with transcatheter aortic valve replacement.[94] The clinical role of CT-derived strain in monitoring cancer treatment related cardiotoxicity or other clinical uses, such as evaluation of cardiomyopathies, remains investigational. If validated, this technique may represent a valuable alternative for the assessment of myocardial deformation in selected patients with poor acoustic windows and contraindication to cardiac MRI, and merits further investigation.

Recommendation 3.1. Coronary CTA **is recommended** for the exclusion of obstructive CAD as the possible etiology of cardiomyopathy in the evaluation of patients with systolic left ventricular dysfunction with low to intermediate risk for CAD in the context of cancer therapy.

Level of Recommendation: **Strong**

Recommendation 3.1.1. Coronary CTA **should be** the preferred method to evaluate for significant obstructive CAD as the cause of left ventricular dysfunction, in stable cancer patients with increased risk of bleeding due to thrombocytopenia or coagulopathies associated with cancer therapy.

Level of Recommendation: **Strong**

Recommendation 3.2. Coronary CTA **should be considered** as an alternative to invasive coronary angiography in the context of troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely, especially in those who are at high risk of bleeding complications.

Level of Recommendation: **Moderate**

Recommendation 3.3. Coronary CTA **should be considered as the initial cardiac imaging modality** in cancer patients with stable chest pain and no prior known CAD.

Level of Recommendation: **Strong**

4. Role of cardiac CT in the evaluation of the effects of radiation therapy

4.1. Radiation therapy induced coronary atherosclerosis and potential applications of calcium scoring and CCT in treatment planning, and monitoring

Radiation therapy (RT) is an essential component in the treatment of malignancies involving the thoracic region. However, following RT there is an increased risk of development and progression of CAD and subsequent CV mortality[29,95–98] and radiation-associated ischemic heart disease is an important competing cause of death in survivors.[29,95,99–101]

Historically, the heart has been considered one uniform structure during RT planning, and mean heart dose has been used to predict toxicity risk. However, mean heart dose is not a reliable surrogate for dose to cardiac substructures. In one study, the risk of coronary artery stenosis was significantly associated with the median coronary artery dose, but not with mean heart dose.[102] Thus, calculating and constraining the radiation dose to specific cardiac substructures is necessary. However, accurate delineation of the coronary arteries on RT planning CT scans is complicated by limited spatial resolution, non-gated acquisition and breath hold difficulties. The left anterior descending coronary artery (LAD) may be visualized reliably in just one-third of patients, even with the use of iodinated contrast,[103] suggesting that advanced imaging is necessary. Preliminary data demonstrate that ECG-gated cardiac CT scans allow precise delineation of the coronary arteries throughout the cardiac cycle on RT planning scans.[104–107] Thus, an avoidance structure can be created that encompasses each coronary artery's position, taking motion into consideration. In the current 3- and 4-dimensional RT planning era, it is possible to shape the radiation dose precisely. Accurate delineation of coronary artery avoidance structures is necessary in order to minimize dose to these regions. Furthermore, uniform, accurate contouring of the coronary arteries across patients and studies would improve the consistency of dose reporting and contribute to our understanding of thresholds for the development of toxicity.

CCT may play a role in pre-treatment risk stratification and post-treatment evaluation for toxicity. The assessment of CAC may be used to assess for coronary atherosclerosis prior to RT to establish baseline risk. Pre-treatment CAC detected on RT planning CT scans are associated with the cumulative incidence of acute coronary events after RT, even after correcting for confounders such as radiation dose to the heart.[108] Baseline detection of CAC could be implemented to identify high-risk patients[37] that may benefit from preventive measures. In addition, CAC may play a role in monitoring for coronary atherosclerosis after RT.[109,110] (Fig. 6). Preliminary data suggest that higher radiation exposure of individual coronary arteries is significantly associated with the presence and extent of calcification on post-RT CT scans.[111]

Coronary CTA may be a useful tool to screen for coronary artery disease, as well as other radiation-related cardiotoxicities after RT.[109,112] Smaller studies have found that coronary CTA is an appropriate diagnostic test and the most suitable screening modality for early detection of radiation-related CAD in asymptomatic survivors of Hodgkin's lymphoma who were treated with chest radiation.[109,112–114] Prior guidelines have recommended functional non-invasive stress testing for CAD detection 5–10 years after exposure in asymptomatic high-risk patients, followed by reassessment every 5 years,[55,115] based on smaller studies showing that functional stress testing identified CV disease in patients with no symptoms and no abnormalities on cardiac testing at rest.[116,117] Coronary CTA is an alternative test for patients who have clinically suspected CAD with its high negative predictive value for exclusion of obstructive CAD.[67–72] Coronary CTA has the added advantage of identifying atherosclerotic plaque that may not be detected by functional stress testing approaches. In one study of HL survivors treated with chest RT, 36% of patients with a negative stress echocardiogram and 78% of patients with a negative nuclear perfusion test had >50% stenosis on invasive coronary angiography.[117] In addition, the presence of non-obstructive CAD detected on coronary CTA can be used to start preventive therapies (e.g. statins and aspirin) as described in Section 1 that have been shown to improve outcomes in patients with stable chest pain on randomized trials.[118,119] A recent consensus statement from the International Cardio-Oncology Society in regard to CV manifestations from therapeutic RT recommends reviewing available CT chest imaging for the presence of coronary and aortic calcifications, to improve CV risk stratification and mitigation of future atherosclerotic cardiovascular events.[120]

Recommendation 4.1. In asymptomatic cancer patients being evaluated prior to chest irradiation, clinicians **should** review available non-cardiac chest CT reports and/or images and if there is evidence of CAC presence in a patient without history of ASCVD, measures should be taken to improve CV risk stratification and reduce ASCVD risk.

Level of Recommendation: **Strong**

Recommendation 4.2. In asymptomatic cancer patients with history of prior chest irradiation and no history of ASCVD, a CAC scan **should be considered** 5–10 years after last RT for evaluation of radiation induced CAD. If no evidence of ASCVD, it **should be considered** repeating at 5–10-year intervals thereafter. Acquired images should be carefully evaluated for valvular and pericardial calcifications.

Level of Recommendation: **Strong**

Recommendation 4.3. In patients with history of prior chest irradiation and stable clinical symptoms, coronary CTA **should be considered as the initial cardiac imaging modality** for evaluation of radiation induced CAD.

Level of Recommendation: **Strong**

4.2. Radiation therapy induced valvular heart disease and potential applications of cardiac CT

Valvular heart disease develops in a subgroup of patients who received chest radiation, for example lymphoma and breast cancer. Clinically significant radiation-induced valvular disease typically develops 10–20 years or more after radiation exposure. The reported prevalence of radiation-induced valvular disease has varied widely across studies with the range of 2–37% for patients treated for Hodgkin's lymphoma and 0.5–4.2% for patients treated for breast cancer as reported in a systematic review.[121] In a retrospective single institution study of 415 patients treated with RT from 1962 to 1998 it was demonstrated that amongst other sequelae, 6.2% developed clinically significant valvular dysfunction at a median of 22 years.[123] With improvements in modern radiation techniques, it is anticipated that the incidence of radiation induced heart disease will decrease compared to historical techniques. Nonetheless, survivors who have received radiation dose to the valves remain at risk of developing valvular disease.

Radiation valvular disease can manifest as a spectrum of anatomic abnormalities along with associated coronary lesions, myocardial

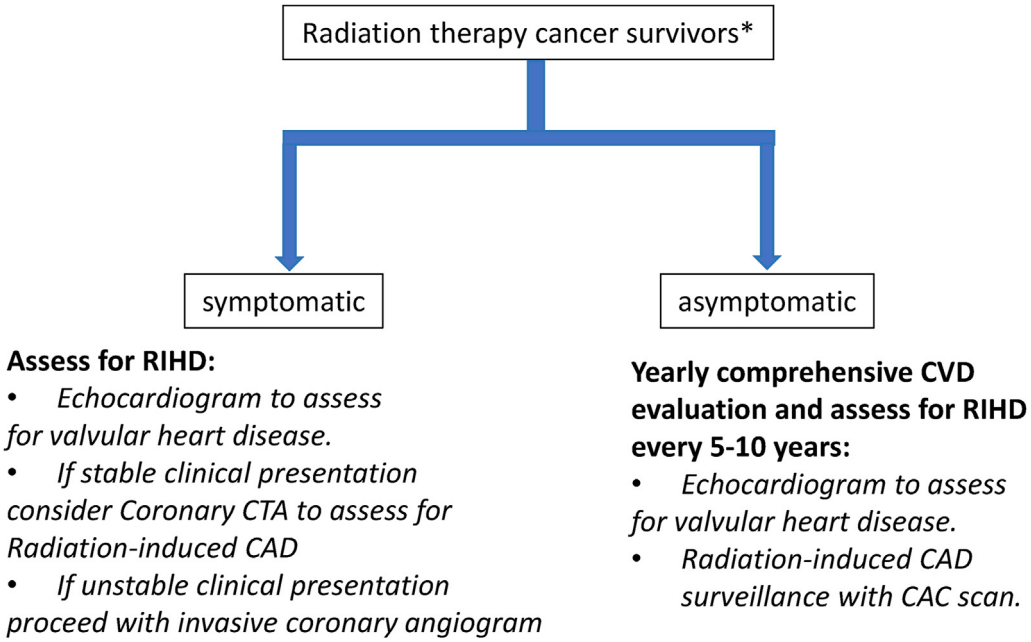

Fig. 6. Radiation-induced heart disease surveillance.

disease, and extracardiac disease. The histopathology and mechanisms of radiation induced valvular disease continue to be investigated and can have varying manifestations; possible risk factors include radiation dose and techniques, and the age of the patient at time of treatment. Older necropsy studies of young patients with a history of lymphoma found that diffuse fibrosis and calcification were seen in all cardiac valves, with some surgically removed specimens being severely fibrotic and stenotic[124] Fibrosis appears to be a major late finding after radiation treatments, that follows an initial phase of inflammation based on animal model studies.[125,126] A recent histopathological study compared surgically removed aortic valves of 28 patients who underwent RT for breast cancer or lymphoma to 15 control patients. It was seen that high-dose radiation at a young age (e.g., for lymphoma) resulted in cell loss and premature fibrotic aortic valve stenosis, whereas breast cancer patients had degenerative calcific stenosis noted with more collagen deposits than controls. Markers of inflammation were low in the cancer survivors, suggesting that inflammation was an acute manifestation observed immediately after treatment, rather than a late effect.[127]

The imaging techniques used to evaluate radiation-induced valvular disease should detect anatomical valve abnormalities, valve dysfunction and should assess the functional consequences of valve dysfunction on the ventricles. TTE provides comprehensive evaluation for the majority of patients with prior exposure. Transesophageal echocardiography (TEE) may provide additional information in patients with radiation-induced valve disease for a more detailed characterization of valvular abnormalities and planning of interventions. CMR imaging can complement echocardiography in selected patients for the assessment of valvular disease. CCT has a supplementary role in valve imaging, especially for detailed assessment of valvular calcification. The role of cardiac CT in valvular disease is in pre-procedural planning of transcatheter valvular interventions (transcatheter aortic, mitral and tricuspid valve replacement - TAVR, TMVR, TTVR).

Annual clinical evaluation with history and physical exam is recommended for patients after the completion of radiation therapy. TTE remains the first-line, most accessible imaging modality to screen for radiation-induced valvular disease. However, there is limited evidence to guide as to when and how frequently to perform imaging. The recommendations for screening are based on expert consensus.[121,128,129] The onset of clinically significant valvular disease typically at 10 years or more after radiation exposure.[123,130] Based on these observations, the expert consensus from the American Society of Echocardiography recommends TTE as the screening test for patient 10 years after the completion of radiation exposure, with screening starting earlier at 5 years in patient with additional risk factors (e.g. younger age at exposure, concomitant cardio-toxic chemotherapy, underlying structural heart disease, and traditional cardiac risk factors of diabetes, hypertension, obesity, and smoking).[129] In the absence of significant valvular abnormalities, patients should be evaluated subsequently every 5 years with TTE. In patients diagnosed with radiation-induced valvular heart disease with valvular dysfunction, the follow-up echocardiographic imaging is dictated by appropriate societal guidelines.[131] CCT usually does not play important role in screening and routine follow-up.

CCT plays a cornerstone role in the evaluation of patients diagnosed with significant radiation-induced valvular disease who are considered for interventions. There is data supporting that presence of aortic valve calcifications in CAC scans strongly predicts outcomes.[132] CCT is indicated for transcatheter aortic valve replacement (TAVR) pre-planning for aortic annulus and peripheral vascular measurements,[133,134] as well as defining coronary anatomy in relation to the valve and the presence of co-existent CAD. Another important role of cardiac CT in the setting of suspected low-flow, low gradient severe aortic stenosis is to measure the aortic valve calcium score to further define severity as a class 2a recommendation endorsed by ACC/AHA valvular heart disease guidelines.[131] Cancer survivors, particularly those with prior mediastinal RT exposure with older techniques, may be at elevated risk of complications with surgical replacement due to comorbidities, which can be also assessed by CCT. These findings, potentially more common in the cancer population with a history of RT, include radiation induced aortic/coronary artery/myocardial/pericardial disease, calcification of the aortic valve, pulmonary fibrosis and/or peripheral vascular disease. In some institutions, cancer patients are often preferentially treated with transcatheter valvular interventions.[135]

Transcatheter techniques for mitral and tricuspid valve replacement (TMVR, TTVR) are still being developed and investigated. Nevertheless, CCT can provide anatomic assessment of mitral or tricuspid annular and leaflet dimensions, and prediction of left ventricular outflow tract outflow tract obstruction post TMVR deployment and it has become an integral part of pre-interventional imaging.[136–141] In addition of providing detailed anatomical information for vascular access planning CCT also help with the evaluation of alternative approaches for minimally invasive valve repair or transcatheter valvular replacement techniques in complex patients.

Primary mitral valve disease can develop from cancer treatments such as RT associated to malignancies as non-bacterial thrombotic endocarditis (NBTE)[142] or functional causes from cardiomyopathic states from chemoradiation treatments. CCT also has an important role in the evaluation of infective endocarditis, especially to exclude valvular abscesses,[143] which may be important to exclude in immunocompromised patients.

In summary, CCT, has applications for assessing cardiac function and aiding planning for percutaneous structural and surgical approaches, it can yield important anatomic information regarding not just the cardiac sequalae of cancer treatment associated valvular disease, but also other cardiac and extracardiac late radiation injury that can help determine a patient's suitability for either surgical or percutaneous approaches.

Recommendation 5.1. CCT **is recommended** prior to planned valvular interventions (TAVR, TMVR and TTVR) in patients with radiation-induced valve disease.

Level of Recommendation**: Strong**

5. Role of cardiac CT in patients with neuroendocrine tumors

Neuroendocrine tumors (NET) may lead to carcinoid heart disease as a result of significant serotonin secretion.[144] Right sided valves tend to be more affected than left sided valves given there are enzymes in the lungs that degrade serotonin. However, if there is presence of high burden of disease, metastatic disease in lungs or presence of cardiac shunt, the left sided valves may be affected.[144] Typically carcinoid heart disease manifest as significant fibrosis of tricuspid and pulmonic valve resulting in valve immobility and significant regurgitation more than stenosis.[144] When patients have carcinoid heart disease, their survival is better when they undergo surgical valve replacement.[145,146] As stated by Davar et al.,[147] a Consensus Statement in managing carcinoid heart disease, CCT has an important role for evaluation of valvular pathology, especially of the pulmonic valve, right ventricular dimensions, systolic function, and the pre-operative non-invasive assessment of coronary arteries, as well as relations of coronary arteries and potential cardiac metastasis.[147] CCT has been used in identifying prosthetic pulmonic valve thrombus and to evaluate prosthetic tricuspid valve function.[148]

6. Role of cardiac CT in the evaluation of cardiac masses

CMR and CCT are complementary imaging technologies that can provide accurate tissue characterization, high spatial-resolution images and wide field-of-view allowing additional information on the cardiac masses, beyond the ones that can be provided by echocardiography.[149–151] CMR is considered to have the best tissue characterization capabilities and is often the imaging test of choice after TTE to identify cardiac mass. T1 and T2 relaxation times and parametric maps, cine-MR, first-pass perfusion, and late gadolinium enhancement (LGE) images provide most of the needed information to characterize morphology and tissue.[152]

Table 4
Multimodality evaluation of cardiac masses. Salient features of cardiac masses by modality.

Cardiac Masses	Echocardiography	Cardiac Magnetic Resonance	Cardiac CT	Morphology
Benign tumors				
Cardiac myxoma	Hyperechoic	T1: hypo/isointense; T2: hyperintense; LGE: peripheral, vascular pedicle, heterogeneous	Hypodense; calcifications; high iodine concentration on DECT	Irregular borders; pedunculated and usually arises from the interatrial septum, near the fossa ovalis; intracavitary, LA (75%), RA (20%), ventricles (5%)
Lipoma	Hyperechoic	T1/T2: hyperintense; fat saturation: hypointense	Hypodense; fat attenuation	Smooth, broad base; interatrial septum, intramural, intracavitary
Papillary fibroelastoma	Heterogeneous	T1/T2: hyperintense, homogeneous; LGE: high, homogeneous delayed	Hypodense	Frond, pedicle; valvular, small in sized; developed "head" or with elongated strand-like projections
Rhabdomyoma	Hyperechoic	T1: isointense; T2: iso/hyperintense; T2: iso/hyperintense;	Hypodense	Smooth, broad base; intramural
Fibroma	Hyperechoic	T1: isointense; T2: hypointense; LGE: hyperenhancement	Hypodense; punctate calcification enhancement	Smooth, broad base; intramural
Hemangioma	Enhancement with echo-contrast	T1: isointense, heterogeneous; T2: hyperintense; first-pass: high contrast intensity.	Hypodense; heterogenous; calcifications intense enhancement	Intracavitary
Malignant tumors				
Sarcomas	Isoechoic to hyperechoic	T1: iso (rhabdo-, undiff.)/ heterogeneous (angio); T2: heterogeneous (angio)/hyperintense (rhabdo-, undiff.); LGE: heterogeneous (angio-), homogeneous (rhabdo-)	Isodense	Lobular; broad base; LA (undifferentiated, osteo-, fibro-, leiomyosarcoma), RA (angiosarcoma)
Lymphoma	Homogeneous echogenicity, thickened wall	T1: isointense, homogeneous; T2: isointense; LGE: variable	Hypo/isodense	Lobular; RA, RV, mediastinum
Metastatic tumor	Iso/hyperechoic	T1: hypo/isointense; T2: iso/ hyperintense; LGE: heterogeneous, strong	Isodense; ± calcifications	Multiple locations
Thrombus				
Thrombus	Hyperechoic	T1: homogenous, high (low if chronic); T2: iso/high (low if chronic); fat saturation: isointense; first-pass perfusion and LGE: hypointense at long inversion times	Low attenuation, non-enhancing; crescentic shape (chronic)	LAA, apical thrombus with severe LV systolic dysfunction, associated with indwelling catheters
Paracardiac lesions				
Pericardial cyst	Echolucent borders	low intensity on T1-weighted and high intensity on T2-weighted images, no post-contrast-enhancing	thin-walled, sharply defined, oval homogeneous, attenuation is slightly higher than water at 30 to 40 HU, no post-contrast-enhancing	Smooth and regular limits adjoining the cardiac border
Tumor-like				
Lipomatous hypertrophy of interatrial septum	Echo-dense	T1/T2: hyperintense; fat saturation: hypointense	non-enhancing,	smooth, well-marginated expansion of the interatrial septum >1.5 cm in transverse diameter; dumbbell-shaped; metabolic activity of brown adipose tissue (BAT) on PET/CT)
Caseous calcification of mitral annulus	Echolucent center and the more echogenic periphery	T1/T2 hypointense, SSSP hypointense, no first-pass perfusion, Enhanced border non-enhanced core	calcific rim and central homogeneous liquefied calcium, less hyperattenuating	round, ovoid shape, typically located in the posterior mitral annulus

However, CCT is also an efficient imaging technique for cardiac mass evaluation and follow-up with the advantage of high spatial resolution and 3D volumetric acquisition that provides unrestricted reconstruction of imaging planes. CCT also has an extremely fast image acquisition time allowing for a significantly more comfortable exam for the patient. CCT can provide very effective tissue characterization by the acquisition of non-contrast images (calcium score), which allow for detection of calcium and fat in entities such as caseous mitral annular calcification or lipoma. Despite a lower contrast-to-noise ratio compared to CMR, delayed images properly acquired (ideal time after contrast, lower kVp, kernel reconstruction and other technical adjustments) can allow for accurate differentiation of thrombus versus neoplastic masses. Patterns of post-contrast enhancement can also be identified such as heterogenous versus homogenous, peripheral versus central, etc. The use of new and very fast scanners allows for dynamic first-pass, late enhanced, and dual-energy CT (DECT) images which can help differentiate thrombus versus neoplastic masses and allow tissue characterization of cardiac tumors based on iodine concentration.[150] CCT is useful in the evaluation of cardiac masses/tumors proximity or invasion to native coronary arteries or bypass grafts. Adding positron emission tomography (PET) evaluation to CCT enhances the ability to differentiate malignant from benign cardiac tumors in patients that cannot undergo a CMR.[153,154] CCT is able to provide detailed information in the evaluation of cardiac mass. The basic characteristics of CCT compared to echocardiography and CMR for cardiac masses are depicted in Table 4.[150,155–157] Cardiac CT has high accuracy when protocolled for detection of left atrial appendage thrombus,[158] which may be considered prior to cardioversion in cancer patients with atrial arrhythmias that may not be able to get a TEE due esophageal obstruction from tumors or esophagitis or are at high procedural risk for sedation.

Table 5
Consensus Statement Recommendations for the use of CCT in Cardio-Oncology patients.

Number	Recommendation
1.1	A comprehensive baseline evaluation to screen for, and subsequently optimize, any underlying CVD risk factors is recommended for all patients with cancer and cancer survivors. Level of Recommendation: **Strong**
1.1.1	Physicians reporting on non-cardiac chest CT scan for cancer imaging should include presence or absence of coronary calcifications in the report. This includes chest CT component of PET scans. Level of Recommendation: **Strong**
1.2	In asymptomatic cancer patients, clinicians **should** review available non-cardiac chest CT reports and/or images. If there is evidence of coronary artery calcium (CAC) in a patient without history of ASCVD, measures should be taken to improve CV risk stratification and reduce ASCVD risk. Level of Recommendation: **Strong**
1.2.1	Severity of CAC in available non-cardiac non-contrast chest CT images **should be** quantified qualitatively or quantitatively using the CAC-DRS scoring system. Level of Recommendation: **Moderate**
1.3	If no previous recent non-cardiac non-contrast chest CT is available, a CAC scan **is recommended** in all cancer patients without known ASCVD who are not on lipid lowering therapy, if they have 5–20% ASCVD risk, consistent with SCCT, ACC/AHA and ESC guidelines. Level of Recommendation: **Strong**
3.1	Coronary CTA **is recommended** for the exclusion of obstructive CAD as the possible etiology of cardiomyopathy in the evaluation of patients with systolic left ventricular dysfunction with low to intermediate risk for CAD in the context of cancer therapy. Level of Recommendation: **Strong**
3.1.1	Coronary CTA **should be** the preferred method to evaluate for obstructive CAD, in the context of left ventricular dysfunction, in stable cancer patients with increased risk of bleeding due to thrombocytopenia or coagulopathies associated with cancer therapy. Level of Recommendation: **Strong**
3.2	Coronary CTA **should be considered** as an alternative to invasive coronary angiography in the context of troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely, especially in those who are at high risk of bleeding complications. Level of Recommendation: **Strong**
3.3	Coronary CTA **should be considered as the initial cardiac imaging modality** in cancer patients with stable chest pain and no prior known CAD. Level of Recommendation: **Strong**
4.1	In asymptomatic cancer patients being evaluated prior to chest irradiation, clinicians **should** review available non-cardiac chest CT reports and/or images and if there is evidence of CAC presence in a patient without history of ASCVD, to improve CV risk stratification and reduce ASCVD risk. Level of Recommendation: **Strong**
4.2	In asymptomatic cancer patients with history of prior chest irradiation and no history of ASCVD, a CAC scan **should be considered** 5–10 years after last RT for evaluation of radiation induced CAD. If no evidence of ASCVD, it **should be considered** repeating at 5–10-year intervals thereafter. Acquired images should be carefully evaluated for valvular and pericardial calcifications. Level of Recommendation: **Strong**
4.3	In patients with history of prior chest irradiation and stable clinical symptoms, coronary CTA **should be considered as the initial cardiac imaging modality** for evaluation of radiation induced CAD. Level of Recommendation: **Strong**
5.1	CCT **is recommended** prior to planned valvular interventions (TAVR, TMVR and TTVR) in patients with radiation-induced valve disease. Level of Recommendation: **Strong**
6.1	CCT **can be used as an adjunct imaging modality** in the evaluation of cardiac masses, often as a complimentary technique to other imaging modalities. Level of Recommendation: **Strong**
6.1.1	CCT **should be considered** in patients undergoing cardiac tumor resection to evaluate for anatomical relationships between tumor and coronary arteries for surgical planning, and to exclude obstructive CAD. Level of Recommendation: **Strong**
7.1	CCT **can be useful** to evaluate pericardial fluid and to characterize it by measuring the CT attenuation value in Hounsfield Units. It **can be useful** for evaluating pericardial thickness and pericardial calcification in cancer patients with suspected pericardial disease. Level of Recommendation: **Moderate**

An additional application of CCT to the management of primary cardiac tumors is the utilization of three dimensional (3D) models for surgical planning.[159] 3D printing creates models from images by laying down repeated layers of plastic material to create a three dimensional object.[160] This type of model can be very helpful in surgical planning in order to better understand the relationship of a primary cardiac tumor to adjacent structures and plan surgical approach in order to achieve complete resection with clear specimen margins. Presurgical CT can be acquired with retrospective ECG gating so that the appearance of the mass in both systole and diastole can be evaluated. Optimal acquisition technique should include thin slices (<1mm) to minimize stairstep artifact when the model is created.[161] Images from CCT, CMR, or 3D TTE are then manually segmented to demarcate tissue boundaries by an experienced operator and entered into a variety of vendor specific software platforms to plan the 3D model construction. This technique can also be useful in pediatric patients, for whom understanding the relationship of a cardiac mass to small and crucial adjacent anatomic structures such as the coronary arteries is especially important.[162]

Recommendation 6.1. CCT **can be used as an adjunct imaging modality** in the evaluation of cardiac masses, often as a complimentary technique to other imaging modalities.

Level of Recommendation**: Strong**

Recommendation 6.1.1. CCT **should be considered** in patients undergoing cardiac tumor resection to evaluate for anatomical relationships between tumor and coronary arteries for surgical planning, and to exclude obstructive CAD.

Level of Recommendation**: Strong**

7. Role of cardiac CT in diseases of the pericardium

The pericardial space is a fibrous sac comprised of the fibrosa rich in fibrous tissue while the serosa is a layer of mesothelial cells with a virtual space in-between containing 30–50 mL of serous fluid.[163] The pericardium can be adversely affected by therapeutic radiation and can occur acutely, but more commonly years to decades after treatment at contemporary radiation doses, particularly in patients receiving therapy for mediastinal tumors or breast malignancy.[163] Radiation-dose volume effects of 30–50 Gy have been associated with significant pericarditis.[98,164] The estimated prevalence of 8%–30% was reported for patients that received high-dose mantle radiation for Hodgkin's lymphoma, but is most likely lower in modern era. Similarly, high incidence of pericardial effusion (36%) was reported with high-dose radiation.[165] Several classes of chemotherapeutic agents have been associated with pericardial disease including anthracyclines, alkylating agents (e.g., cyclophosphamide), cytarabine and tyrosine kinase inhibitors.[166,167] In addition, direct tumor burden (e.g., metastasis) are commonly associated with pericardial involvement. Cardiac monitoring at regular intervals is important in the early detection of pericardial disease.

CCT may identify the presence of acute pericarditis through iodinated contrast enhancement of the visceral and parietal surfaces. On CCT, the pericardium will appear thickened (>4mm) and may demonstrate the presence of a pericardial effusion.[163,168] CCT may enable differentiation of pericardial fluid types by using Hounsfield Unit (HU)[169]:

- Transudative effusion (similar CT attenuation <10 HU)
- Exudative effusion with high protein content (>10 HU)

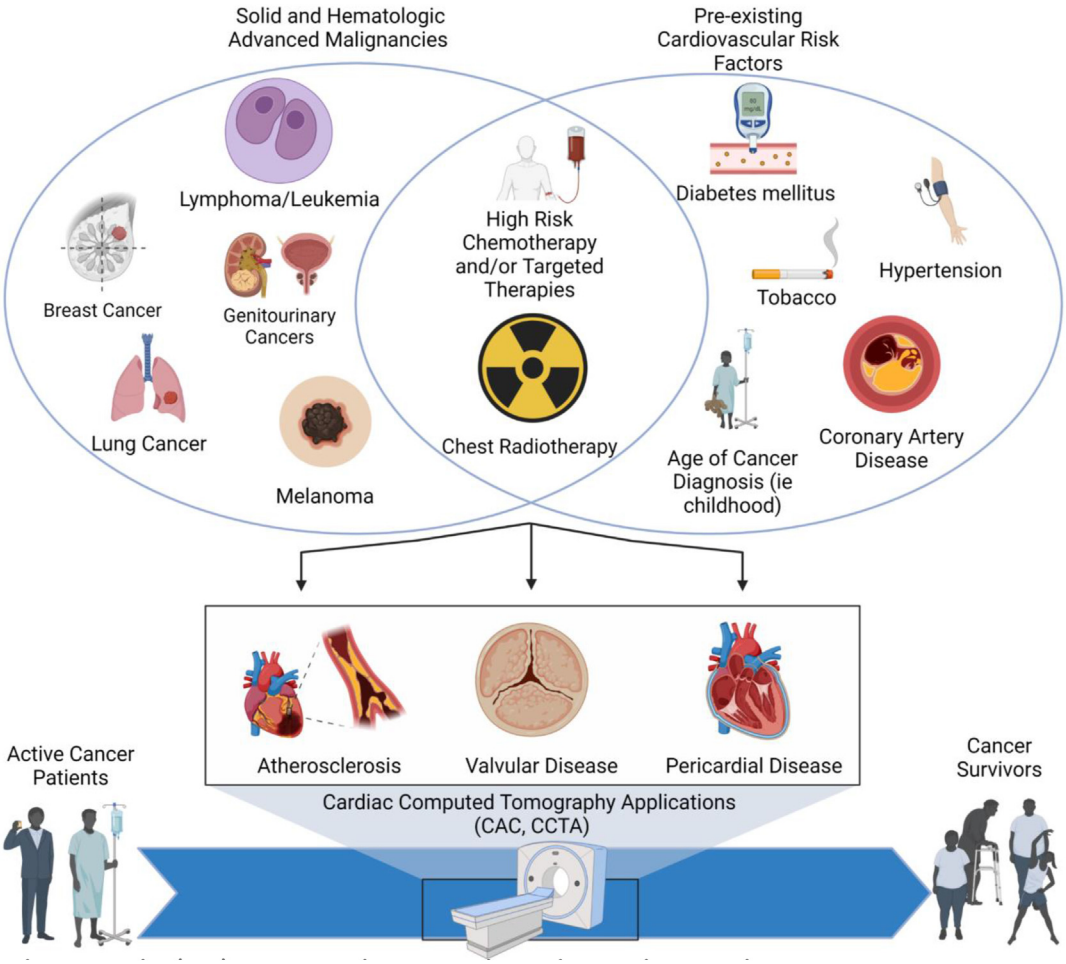

Fig. 7. Cardiac Computed Tomographic (CCT) Imaging Applications in the Cardio-Oncology population. The spectrum of cardiovascular disease (CVD) in the cancer population may stem from preexisting cardiovascular risk factors. In addition, CVD may be acquired and/or worsened from certain hematologic/oncologic disease states which involve potentially high risk cardiotoxic treatments (see Table 3). Such treatments can promote, and/or exacerbate preexisting atherosclerotic disease in which CCT imaging can help visualize and assist in cardiovascular risk modification and treatment before, during, and after cancer treatment. Examples include radiation therapy in fields involving the heart and/or major vascular structures, certain chemotherapies (ie platinum-based therapies for lung, testicular cancer) targeted therapies and immunotherapies (i.e. advanced renal cell carcinoma, lung cancer and melanoma) which may have short/long term effects on CVD which warrant further study with CCT. CAC: Coronary artery Calcium, CCTA: Coronary Computed Tomography Angiography. Created by http://biorender.com.

- Purulent, malignant or myxedematous exudative effusion (20–60 HU)
- Hemorrhagic effusion (>60 HU)

CCT may enable complementary information to other imaging modalities (e.g. echocardiography or cardiac magnetic resonance) in the diagnosis of constrictive pericarditis through thickened and heavily calcified pericardium.[169] While CCT is generally not a first line approach for the hemodynamic assessment of pericardial constriction, CCT may demonstrate signs of ventricular interdependence through septal flattening, retrograde hepatic flow of contrast into the inferior vena cava, and bi-atrial enlargement aided by the use of multiphase ECG-gated imaging.[170] Additionally, CCT is very sensitive for the detection of pericardial calcification—an important adjunctive sign of constrictive pericarditis.[169] CCT may enable planning for surgical pericardiectomy.[166] CCT is not recommended for the evaluation of pericardial tamponade.

With regard to future directions, modern advancements in CT scanner technology have enabled comprehensive whole heart assessment including that of the pericardium at increasingly negligible to low radiation doses.[171] While CCT is currently only rarely utilized to diagnose or guide therapy when managing inflammatory pericardial conditions, the validation and potential application of novel approaches such as CT-strain imaging or photon-counting CT imaging may enable enhanced diagnosis of pericardial disease and CCT guided therapy.[166,172,173]

Recommendation 7.1. CCT **can be useful** to evaluate pericardial fluid and to characterize it by measuring the CT attenuation value in Hounsfield Units. It **can be useful** for evaluating pericardial thickness and pericardial calcification in cancer patients with suspected pericardial disease.

Level of Recommendation: **Moderate**

8. Future directions for cardiac CT in cardio-oncology

In order to advance the field of Cardio-Oncology a national database registry for CAD and valvular heart disease that include CCT examinations in patients with specific cancer types associated with increased CVD risk and who have undergone cancer treatments associated with adverse CVD outcomes is recommended. This initiative may allow for better phenotyping of ASCVD toxicities of respective cancers and anti-cancer therapy. Collecting data from CAC, FFR_{CT}, plaque morphology/characteristics, aortic valve calcification burden and others, may permit a better understanding of the relationship between CCT findings and CV outcomes in these diverse populations. The role of vasodilator stress CCT in

this population is yet to be defined, but likely useful given the vascular toxicities of many cancer therapies.

For example, in a study of lymphoma patients, CAC scores of routine post-chemotherapy PET/CT scans were extracted revealing a significant increase in average CAC score from baseline to last treatment of 35%.[174] Indeed, a well-developed prospective cohort study of cancer patients followed with routine CAC scores to assess both atherosclerosis progression as well as documenting the competing risk of future CVD and cancer outcome would provide much needed information on the progression of atherosclerosis.

Future avenues to investigate our understanding of radiation induced valvular disease could involve evaluating RT techniques in the modern era with serial imaging combined with ECG gated protocols–either for radiation treatment or for cancer staging/surveillance purposes. Further areas include the evaluation of valvular remodeling and better understanding of the impact of cancer treatments, radiation techniques and doses on the natural history of valvular disease in cancer patients.

One additional area of CVD and cancer overlap that deserves attention regarding a future role of CAC is how genetic alterations predispose individuals to cancer as well as cardiovascular disease. Clonal hematopoiesis of indeterminate potential (CHIP), is defined as a somatic mutation causing an expansion of hematopoietic clones. While it is not a hematological malignancy, it is often considered to be a precursor of such, and there may be a link between CHIP and CVD events.[175,176] As the mutations related to CHIP are generally age-related and more frequently occur after chemoradiotherapy, there may be a contribution from overlapping risk factor profiles of both diseases.[177–179] Thus, a patient's atherosclerotic burden as measured by CAC could represent an association between cardiovascular disease and CHIP that may be useful in determining cardiovascular risk of patients with CHIP mutations.

9. Summary

CCT has a promising role in the evaluation of cancer patients (see Fig. 7). While we acknowledged the limited evidence for the application of CCT in this specific population, this Expert Consensus Statement provides clinicians with guidance on applications of CCT in cardio-oncology.

Conflict of interest

The authors declare that they don't have conflicts of interest related to the contents of this document to declare. Please refer to Appendix 1 for disclosures about relationships with industry for each author.

Appendix 1. Author relationships with industry—Cardiac computed tomographic imaging in cardio-oncology

Writing Group Member	Employent	Consultant/Honoraria	Speakers Bureau	Stock and stock options	Grants and research support	Royalties
Maros Ferencik (co-chair)	Oregon Health and Science University	Biograph	None	None	None	None
Juan Lopez Mattei (co-chair)	Lee Health System	None	None	None	None	None
Ali Agha	Baylor College of Medicine	None	None	None	None	None
Lauren Baldassarre	Yale School of Medicine	None	None	None	None	None
Michael Blaha	Johns Hopkins Ciccarone Center	89Bio, Amgen, Bayer, Kowa, Novartis, Novo Nordisk	None	None	89Bio, Amgen, Bayer, Novo Nordisk	None
Ron Blankstein	Brigham and Women's Hospital, Harvard Medical School	Caristo, Novartis, Silence Therapeutics	None	None	Amgen	None
Marcus Chen	National Institutes of Health	None	None	None	None	None
Andrew D. Choi	The George Washington University School of Medicine	None	None	Cleerly	None	
Ryan Daly	Franciscan Health	None	Astra Zeneca	None	None	None
Susan Dent	Duke Cancer Institute	None	None	None	None	None
Omar Dzaye	Johns Hopkins Ciccarone Center for Prevention of Cardiovascular Disease	None	None	None	None	None
Cezar Iliescu	University of Texas MD Anderson Cancer Center	None	None	None	None	None
Bonnie Ky	Perelman School of Medicine at the University of Pennsylvania	Cytokinetics, Roche Diagnostics; UpToDate	None	None	None	None
Mamas A. Mamas	Keele University	Pfizer, Terumo	Daiichi Sankyo, Terumo		Abbott Vascular, Medtronic, Terumo	
Nandini Meyersohn	Massachusetts General Hospital	None	None	None	None	None
Sarah Milgrom	University of Colorado	None	None	None	None	None
Ahmad Slim	Pulse Heart Institute	None	None	None	None	None
Seamus Whelton	Johns Hopkins School of Medicine	None	None	None	None	None
Carlos Rochitte	Heart Institute, InCor, University of São Paulo Medical School	None	None	None	None	None

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(*continued*)

Writing Group Member	Employent	Consultant/Honoraria	Speakers Bureau	Stock and stock options	Grants and research support	Royalties
Eric H Yang	University of California at Los Angeles	Pfizer	None	None	CSL Behring, Boehringer Ingelheim and Eli and Lilly	None

Appendix 2. Reviewer relationships with industry—Cardiac computed tomographic imaging in cardio-oncology

Reviewer	Employent	Consultant/Honoraria	Speakers Bureau	Stock and stock options	Grants and research support	Royalties
Daniel J. Lenihan	International Cardio-Oncology Society	None	None	None	None	None
Srilakshmi Vallabhaneni	UT Southwestern Medical Center	None	None	None	None	None
Thomas Marwick	Hobart Heart Center, Tasmania	None	None	None	None	None
Tochukwu Okwuosa	Rush University	None	None	None	None	None

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