REVIEW

Radiation-induced cardiac dysfunction: Practical implications

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ABSTRACT

Radiation-induced cardiac dysfunction is a critical healthcare concern facing survivors of thoracic cancers treated with radiation therapy. Despite cardiac-sparing advances in radiation therapy delivery, many patients with thoracic cancers receiving modern radiation therapy will still have incidental radiation exposure to the heart. Therefore, it is imperative that cardiovascular healthcare providers take appropriate measures to prevent, screen, and manage radiation-induced cardiac dysfunction in patients with a history of thoracic radiation therapy. In this review, we aim to provide healthcare providers with foundational information about radiation-induced cardiac pathophysiology and a chronology of advances in radiation technology. Subsequently, we provide an up-to-date review of treatment- and host-related factors that can influence a patient's risk for radiation-induced cardiac dysfunction. Finally, we culminate our discussion by detailing current screening and management guidelines to aid healthcare providers in caring for their patients with a history of thoracic radiation therapy.

Key words: cancer, cardiovascular disease, cardio-oncology, radiation, radiation-induced cardiac dysfunction

INTRODUCTION

Survival rates for patients with thoracic cancers have dramatically improved in recent decades due to advances in early detection and therapeutics. The expanding population of cancer survivors possesses a unique set of healthcare needs; integral among them is cancer treatment-induced cardiotoxicity. A number of cancer survivors treated with radiation therapy (RT) to the abdomen, chest, or neck (e.g. lymphomas, breast cancers, lung cancers, esophageal cancers) develop long-term radiation-induced cardiac dysfunction (RICD), as RT frequently results in incidental dose to the heart and/or vascular structures. Over the last 50 years, radiation oncologists have made great progress in reducing heart exposure from radiation treatments. However, up to one-third of thoracic cancer survivors receiving modern RT will present with one or more forms of RICD within 10 years of treatment [1]. Radiation-induced cardiac disorders observed in these patients range from coronary artery disease and valvular heart disease to pericarditis, arrhythmia, myocardial fibrosis, and cardiomyopathy (Figure 1). This review is intended to provide cardiovascular (CV) healthcare providers (e.g. cardiologists, cardio-oncologists, internists, etc.) with an overview of RICD pathophysiology, as well as current concepts in modern thoracic RT delivery. Furthermore, this review aims to provide CV healthcare providers with the most up-to-date guidelines for RICD screening and management in their patients.

MECHANISMS OF RADIATION--INDUCED CARDIAC DYSFUNCTION

Current evidence suggests that the cardiotoxic effects of radiation are imparted through both direct and indirect means (Figure 1) [2]. Radiation deposition directly damages nuclear DNA, which manifests as base damage, cross-linking, and single- and double-strand-

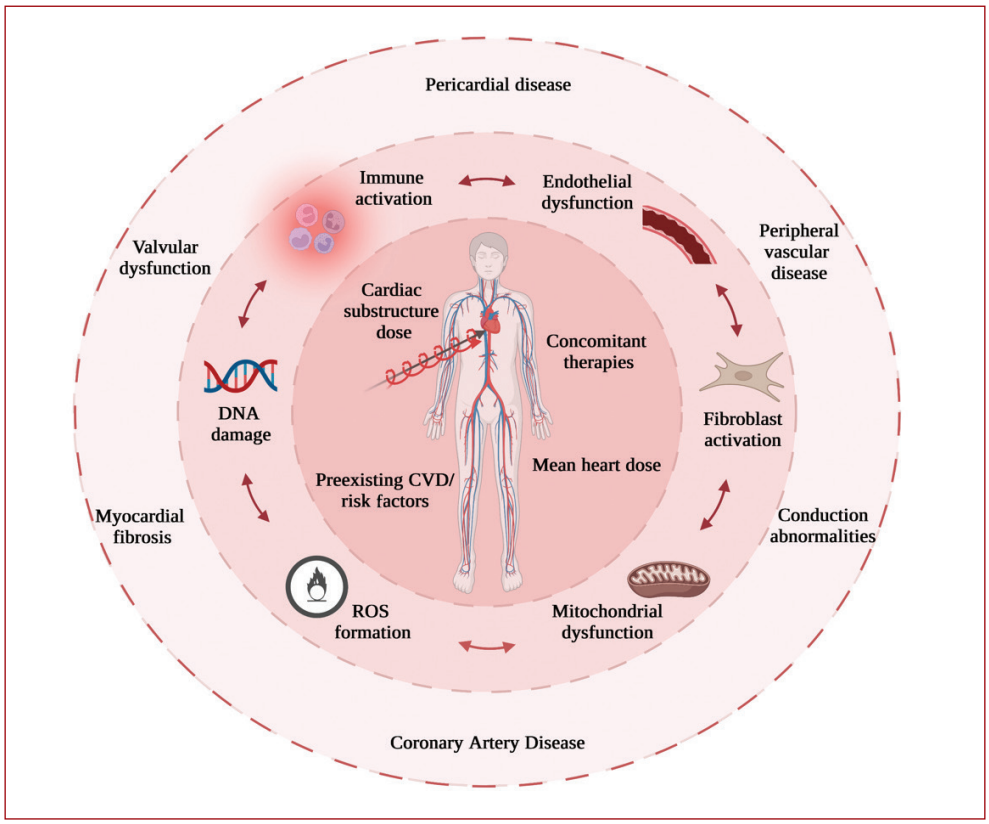

Figure 1. Interaction of mechanisms and factors contributing to radiation-induced cardiac dysfunction. Treatment- and host-related factors influence cardiac injury resulting from radiation therapy, including mean heart dose, dose to cardiac substructures, other cancer therapies, and preexisting CV risk (inner circle). These factors influence the degree and progression of radiation-induced cardiac damage, which is mediated by interactions among immune activation, endothelial dysfunction, fibroblast maturation, mitochondrial dysfunction, ROS formation, and DNA damage (middle ring). Radiation injury to the heart can ultimately lead to several forms of cardiovascular dysfunction, including pericardial effusion, peripheral vascular disease, conduction abnormalities, coronary artery disease, myocardial fibrosis, and valvular dysfunction (outer ring)

Abbreviations: CV, cardiovascular; CVD, CV disease; ROS, reactive oxygen species

ed breaks, with double-stranded breaks being most integral to lethal damage to cells after radiation [2]. In addition, radiation-induced hydrolysis of water and other cellular molecules yields reactive oxygen species (ROS), which can alter many cellular processes and preferentially degrade DNA telomeres and cellular organelles [3]. Radiation-induced destabilization of the mitochondria is particularly important, as disruption of oxidative metabolism can be both a cause and consequence of ROS production [4]. Following genomic damage, DNA repair systems are activated, and a network of genes encoding for cellular apoptosis and senescence are transcriptionally upregulated [5]. Many of the products of DNA repair act locally as danger-associated molecular patterns (DAMPs), inducing both pro-inflammatory and senescence-associated secretory phenotypes (SASP) in nearby cardiac cells [6]. Unresolved immune responses resulting from radiation injury are also likely critical drivers of late cardiac dysfunction [7].

Importantly, cardiac cells display differential sensitivity to radiation. As cardiomyocytes are terminally differentiated, postmitotic cells, they are relatively resistant to radiation damage [8]. Conversely, coronary endothelial cells, and in particular capillary endothelial cells, are highly radiosensitive [8]. Radiation-induced endothelial injury is thought to be a pivotal consequence of radiation, as disruption of the coronary microvasculature results in vascular insufficiency (Figure 1) [1]. Furthermore, maladaptive responses of the coronary vascular endothelial cells to radiation damage can contribute to a pro-thrombotic state over time [9].

ADVANCEMENTS IN RADIATION THERAPY — A BRIEF HISTORY

The main determinant of RICD development in patients with thoracic cancer is the dose of incidental radiation received by the heart [10]. In recent decades, advances in RT planning and delivery have dramatically decreased heart doses in many thoracic cancer populations, thereby improving the therapeutic ratio of RT in survivors. In the 1990s, traditional two-dimensional radiation field arrangements, which were based on simple x-ray imaging, were largely replaced by three-dimensional conformal radiation therapy (3DCRT) [11, 12]. Unlike its predecessor, 3DCRT relies on computed tomography (CT) imaging to deliver radiation to tumor volumes with a margin for both micro-

scopic tumor extension and uncertainties from the target's motion [11, 13]. This technique also allows accurate determination of the doses received by organs adjacent to the targets, such as the heart. By the end of the decade, even more technological advances were realized, including the wide availability of intensity-modulated radiation therapy (IMRT), owing to the development of computer-controlled multi-leaf collimators and inverse planning software [11, 13]. IMRT delivers multiple radiation beams with varying intra-beam intensities, allowing for radiation doses that conform to irregularly shaped tumor boundaries [11, 14]. Despite its non-tumor tissue sparing capabilities, especially with respect to minimizing high doses to organs at risk, IMRT requires a larger number of radiation beams than 3D-CRT, which substantially lengthens the RT treatment time. Thus, in the mid-2000s, volumetric modulated arc therapy (VMAT), a form of IMRT in which the entire dose volume is delivered in a single gantry arc, was introduced to improve IMRT treatment efficiency [14, 15]. Additionally, more recent technological advances include image-guided radiation therapy (IGRT), which can be used with both 3DCRT and IMRT and aids in the targeting of RT, and stereotactic body radiation therapy (SBRT). IGRT typically uses daily imaging before RT to recognize slight variations in tumor position across treatment fractions due to patient positioning or organ/target movement and uses this information to localize a radiation fraction appropriately [11, 16]. Unlike more traditionally fractionated RT regimens, SBRT precisely delivers highly conformal radiation doses to a small area in one to five large fractions [11, 14]. SBRT has been found to be particularly useful for ablative-type therapy in patients in whom surgical tumor resection is contraindicated, such as some patients with early-stage non-small cell lung cancer [17].

At present, there are several cutting-edge RT modalities at the forefront of cardiac-sparing treatment for patients with thoracic cancer. In pre-clinical models, the use of FLASH-RT has shown great promise in improving normal tissue tolerance [18]. Unlike traditional RT that delivers radiation dose over the span of minutes, FLASH-RT delivers a milliseconds-long, ultra-high radiation dose [18]. This instantaneous radiation delivery has been found to induce a protective metabolic response in non-tumor tissues, which may allow for higher radiation doses to be delivered to a tumor without additional normal tissue toxicity [18]. The first clinical trial implementing FLASH-RT began in 2020 to assess the feasibility and toxicities of this modality in cancer patients with bone metastases, but at this time FLASH-RT is not readily available outside of a clinical trial [18]. Proton therapy, which delivers positively charged particles rather than photons, is also a therapy with large cardiac-sparing potential [19]. However, the availability of proton centers in the US is limited, although the number of facilities has greatly increased over the past decade. Protons offer a physical advantage over photons due to their ability to be deposited at a specific tissue depth with little spread beyond this point [19]. Clinical trials in non-small cell lung cancer and esophageal cancers comparing mean heart dose (MHD) between photon (e.g. IMRT, SBRT) and proton therapies have demonstrated reductions in MHD with the use of protons. However, in the non-small cell lung cancer trial there was no reduction in lung toxicity or improved survival in the proton arm, while the esophageal cancer trial demonstrated a reduction in overall toxicities and a numerical decrease in cardiac toxicities, with no change in cancer outcome [20]. To date, the widespread implementation of proton therapy is limited due to expense and limited facilities offering this modality, which may change as more clinical trial data become available and more proton centers continue to open.

In addition to these technological developments, changes in patient setup and positioning during RT have helped to substantially reduce the heart dose. In breast cancer patients, alternative (e.g. prone vs. supine) positioning differentially displaces both the heart and breast tissue, which may distance the heart from the radiation field [21, 22]. Benefits derived from such positional changes in breast cancer patients appear to be in part dependent on tumor laterality and breast volume [22]. A large body of evidence supports the use of organ motion management techniques during cardiac sparing during RT. In particular, implementation of deep inspiration breath hold (DIBH) techniques in breast cancer patients receiving RT markedly reduces MHD (approximately 25%–67% reduction), as well as left anterior descending artery (LAD) dose (approximately 20%–73% reduction), compared to free breathing [23, 24].

MODERN RADIATION THERAPY — WHERE ARE WE NOW?

Collectively, the advancements discussed above have led to modern RT treatments that minimize, but often do not fully eliminate, incidental radiation received by the heart. Studies suggest that RICD can occur even with low levels of cardiac radiation exposure [25]. The cardiac-sparing capacity of current RT regimens varies among thoracic cancer populations, resulting in heterogenous RICD presentations. Additionally, it is important to recognize that these advanced techniques are not broadly available at all centers or appropriate for all patients. There also continue to be many survivors previously treated with RT who may have been exposed to higher doses than are seen using modern techniques.

In breast cancer patients treated with modern 3D-CRT, only a small percentage of the heart (e.g. anterior aspect) typically receives radiation, although left-sided breast tumors place the heart closer to the radiation field [23, 26]. Despite reductions in MHD, breast cancer survivors treated with RT are still at risk for developing late manifestations of RICD, such as myocardial fibrosis and coronary artery disease [27–29]. These chronic complications, in particular, are mechanistically linked to radiation-induced coronary microvascular destruction and consequent vascular insuf-

ficiency (discussed above) [27]. In contrast, patients with lung, esophageal, and gastric cancers frequently receive high doses of fractionated RT to small regions of the heart, leading to more acute forms of cardiac dysfunction (~2 years post-RT) [1, 30, 31]. Importantly, radiation dose to critical cardiac substructures may be more predictive of RICD development than MHD alone [12, 23]. For example, radiation exposure to the LAD and left ventricle has been found to associate with adverse cardiac outcomes in breast cancer survivors [31, 32]. In esophageal cancer patients, associations have been reported between radiation dose to the pericardium rim and risk of pericardial effusions, which is the most frequently observed form of RICD in this population [33, 34]. Finally, in patients with early-stage lung cancer, RT exposure to substructures, such as the left atrium, superior vena cava, LAD, heart base, and bilateral ventricles, has been linked to all-cause mortality during the survivorship period [30, 35–37].

INTERACTION OF RT WITH CONCOMITANT THERAPIES AND PATIENT FACTORS

Concurrent and/or sequential cancer therapies

A number of systemic cancer therapies, including immunotherapy, many types of chemotherapy, and endocrine therapy, have been independently associated with cardiac dysfunction in thoracic cancer survivors [35, 38, 39]. RT is frequently administered concomitantly or sequentially with these therapies, begging the question of whether treatments with both RT and cardiotoxicity systemic therapies produce additive or synergistic cardiotoxic effects. Concomitant RT and immune checkpoint inhibitor (ICI) therapy is relatively uncommon, although sequential therapy can occur in non-small cell lung cancer. Several clinical and pre-clinical studies report enhanced anti-tumor efficacy of combination RT and ICI therapy compared to ICI alone [5, 40]. Indeed, radiation may sensitize tumor cells to immunotherapy and expand the temporal window of immunotherapy efficacy by reducing tumor growth before latent immunotherapeutic effects [41]. More than 40% of cancer patients in the US are eligible for treatment with ICI (e.g. CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors), and ICI treatment is rarely associated with fulminant myocarditis. ICI treatment also has been associated with accelerated atherosclerosis [42–44]. PD-1 blockade after RT appears to enhance cardiac inflammation, which may be due to activation of shared immune pathways in the heart [45, 46].

Chemotherapeutic treatment, especially anthracycline treatment, also increases the risk for cardiac dysfunction in thoracic cancer patients. The risk ratios for cardiomyopathy in anthracycline-treated patients compared to non-treated individuals reveal that this cardiotoxicity is dose-dependent [47]. Typically, anthracycline-induced cardiotoxicity manifests as sub-clinical left ventricular dysfunction progressing to congestive heart failure [48]. Combination RT and chemotherapeutic treatment are widely reported to have a synergistic cardiotoxic effect. Recent analysis of over 36 000 childhood cancer survivor patients treated with combinations of RT and chemotherapy demonstrated the highest and earliest onset of ischemic heart disease compared to individuals treated with one or no therapeutic modality [49].

Pre-existing cardiometabolic risk factors

When assessing patients at risk for RICD, the context of traditional CV risk factors, including hypertension, hyperlipidemia, smoking, diabetes mellitus, age, and preexisting CV disease (CVD) must be considered. Traditional CV risk factors and established CVD increase the risk of adverse CV events in cancer patients undergoing RT, though the relative impact of these baseline risk factors across various cancer subtypes and adjunctive treatments continues to be elucidated. In a study of 963 patients with breast cancer who received RT, baseline traditional CV risk factors were associated with increased rates of ischemic coronary disease, with diabetes, smoking, and obesity corresponding to 3.23, 1.87, and 1.5-fold higher risks of CVD, respectively [25]. In addition, a history of prior ischemic heart disease was associated with a 7-fold increased rate of coronary events after RT [25]. Another study examining 1460 patients enrolled in breast cancer clinical trials found that baseline hypertension and diabetes were each associated with a 2-fold increased risk of cardiac events, while baseline coronary artery disease (CAD) was associated with a nearly 3-fold increased risk [50]. In a case-control study of patients with a history of Hodgkin Lymphoma treated with mediastinal RT, baseline hypertension was associated with an increased risk of CV events (odds ratio [OR], 1.81; 95% CI, 1.26–2.59), as were diagnoses of hyperlipidemia (OR, 2.17; 95% CI, 1.67–1.82) and diabetes mellitus (OR, 1.92; 95% CI 1.38–2.67) at baseline or during follow-up [51]. Similarly, in patients with non-small cell lung carcinoma (NSCLC) treated with thoracic RT, pre-existing CAD, heart failure (HF), peripheral vascular disease (PVD), or stroke were associated with an increased risk of CV events, with a relative risk of 7 (95% CI, 3.2–15.3) [30].

Coronary artery calcification (CAC) on cardiac gated and non-gated computed tomography (CT) of the chest identifies patients with underlying coronary artery disease who are at higher risk for CV events in the setting of RT [52]. In one retrospective study examining non-gated CT imaging in breast cancer patients, the presence of CAC was associated with post-cancer treatment CV events with an odds ratio of 4.9 [53]. Another study of patients with breast cancer found a similar correlation, with a 4.95 increased risk in patients with intermediate or high CAC scores prior to RT [54]. Indeed, vascular calcifications on baseline imaging may serve as a better predictor of future risk for CV events than traditional risk stratification based on laboratory and

Table 1. Imaging modalities and screening intervals for assessment of radiation-induced cardiac dysfunction

	Coronary artery disease	Cardiomyopathy	Valvular disorders	Constrictive pericarditis
Initial imaging modality and screening interval	CCTA/ CAC Within 5 years of RT, then every 5 years	TTE Within 6-12 months of RT[a], then every 5 years	TTE Within 5 years of RT, then every 5 years	TTE Within 5 years of RT, then every 5 years
Characteristic findings	CCTA: calcified or noncalcified plaque CAC: calcified plaque	Impaired GLS > –18% Reduced LVEF <50% Diastolic dysfunction[b]	Valve leaflet and annulus calcification Valve stenosis and/ or regurgitation	Ventricular septal shift Annulus reversus[c] Diastolic flow reversal in hepatic vein on expiration
Strengths	Early identification of CAD	Can identify CV dysfunction prior to HF symptoms	Accurate gradient assessment with Doppler	Noninvasive High specificity
Weaknesses	CAC on non-gated imaging may lead to false negatives	Limited views in some patients Cannot identify myocardial fibrosis	Limited views in some patients MV not as well assessed as TEE	Invasive hemodynamics may be needed to differentiate constriction vs. restriction

[a]Baseline screening is recommended at 6–12 months in high-risk patients; otherwise, initial screening within 5 years of RT is reasonable; [b]Measures of diastolic dysfunction include E/A reversal, E/A >2, reduced medial and lateral mitral annulus tissue Doppler velocities (medial e' <7, lateral e'< 10); [c]Annulus reversus is characterized by medial > lateral mitral annulus tissue Doppler velocity; alternatively, a medial e' of >9 cm/s in the setting of ventricular septal shift is 87% sensitive and 91% specific for constriction [61]

Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; CCTA, coronary computed tomography; CV, cardiovascular; E/A, E wave/A wave; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; MV, mitral valve; RICD, radiation-induced cardiac dysfunction; RT, radiation therapy; TEE; transesophageal echocardiogram; TTE, transthoracic echocardiogram

demographic data, as it objectively categorizes existing atherosclerotic burden, is readily obtainable, and does not rely on prior evaluation and diagnosis of traditional CV risk factors.

Cancer survivors receiving RT, especially survivors of childhood cancers, are also at increased risk for developing CV risk factors that can further impact the risk for future CV events. In pediatric cancer survivors, hypertension, diabetes, dyslipidemia, and obesity were more prevalent and were found to disproportionately increase the risk of adverse CV events compared to sibling controls with similar traditional CV risk factors [55]. In a large retrospective study of childhood cancer survivors who underwent thoracic RT, post-treatment hypertension was strongly associated with the risk of developing any CV event (risk ratio [RR], 37.2; 95% CI, 22.2–62.3), most notably CAD, HF, and valvular heart disease, which had the highest relative excess risk due to interaction with RT. Diabetes, obesity, and dyslipidemia also conferred excess CV risk in these patients, though to a more modest extent [55]. Notably, cancer survivors with a history of childhood cranial RT involving the hypothalamic-pituitary axis have been found to develop metabolic syndrome at a higher rate. In a study of childhood survivors of acute lymphoblastic leukemia patients receiving hypothalamic-pituitary axis-involved RT were more likely to have a higher body mass index and insulin dysregulation [56]. Thus, in survivors of childhood cancers, in particular, RT may potentiate the early development of traditional cardiometabolic risk factors, increasing the risk for CV events in adulthood.

SCREENING AND MANAGEMENT GUIDELINES

Clinical assessment of patients at risk for or with suspected RICD

CV management of patients with a history of RT will always start with prevention. CV risk factors should be assessed and optimized at baseline and throughout survivorship to reduce the risk for subsequent RICD. Importantly, patients undergoing thoracic RT for staging or cancer therapy will have baseline CT chest imaging that should be reviewed for the presence of CAC to screen for evidence of atherosclerosis. The recent consensus statement from the International Cardio-Oncology Society (ICOS) emphasizes the importance of reviewing available CT chest imaging at baseline and in follow-up for all patients undergoing thoracic RT to identify patients with asymptomatic CAD who may benefit from preventative medical therapy [10]. Following RT, an annual CV history and physical exam form the basis of screening and prevention. At that time, CV risk factors can be assessed and optimized, available CT scans can be reviewed for CAC, and patients can be screened for signs and symptoms of ischemic heart disease, peripheral vascular disease (e.g. subclavian stenosis), heart failure, and valvular disorders.

Cardiac imaging used in the screening and diagnosis of RICD includes echocardiography, cardiac magnetic resonance imaging (MRI), CV CT, functional imaging (stress echocardiogram or myocardial perfusion imaging), and left heart catheterization (Table 1). Choosing the optimal imaging study depends on the specific pathology investigated, as well as patient-specific factors, including body habitus, presence of a defibrillator/ pacemaker, baseline heart rate, and coexistent arrhythmias or renal dysfunction. There is also a general appreciation for limiting further radiation exposure, when possible, e.g. stress echocardiogram would be preferred to myocardial perfusion imaging, when feasible when a functional ischemic test is indicated. ICOS and other major society guidelines all recommend cardiac imaging within 5 years after thoracic RT, with imaging as early as 6 months post-RT in high-risk patients [23]. Those at high risk include (1) younger patients less than 50 years old; (2) those receiving high doses of cumulative radiation (>30 Gy); (3) those receiving high doses of radiation fractions (>2 Gy/dose); (4) those with tumor(s) involving the heart or nearby adjacent tissue; (5) patients treated with

a lack of cardiac shielding; (6) patients receiving concomitant cardiotoxic chemotherapy; (7) those with traditional CV risk factors; and (8) patients with pre-existing CVD [10].

Transthoracic echocardiogram (TTE) remains the mainstay in evaluating cardiac dysfunction, pericardial disease, and valvular disorders in patients who have received thoracic RT. Assessment of systolic function includes quantification of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) measurement. GLS measurement is an emerging technique to detect subclinical CV toxicity. In a meta-analysis of 21 studies of patients with breast cancer and hematologic malignancies, a portion of whom underwent RT, GLS provided strong prognostic value for cancer therapy-related cardiac dysfunction [57]. A study of breast cancer patients undergoing RT demonstrated a reduction in GLS at 12-month follow-up despite no change in LVEF [58]. In these patients, GLS reduction was most pronounced in the anterior, anteroseptal and anterolateral walls, which received the highest RT doses. While GLS may detect subclinical cardiomyopathy and be a signal for future heart failure, more research is needed as to whether therapy targeted at an early change in GLS will affect CV outcomes.

TTE is also the primary tool for evaluating RT-related valvular heart disease due to its ready availability, comprehensive cardiac evaluation, and favorable side-effect profile [58]. Characteristic findings include aorto-mitral curtain calcification, as well as calcification of valve leaflets and the subvalvular apparatus, leading to either stenosis or regurgitation [59, 60]. TTE may also assess RT-related pericardial disease, including pericardial effusion and constriction. Mitral and tricuspid inflow variations of 25% and 40%, respectively, are commonly used thresholds to identify hemodynamically significant pericardial effusions [61]. A plethoric inferior vena cava is commonly seen with a hemodynamically significant pericardial effusion or constriction. On the other hand, annulus reversus (mitral annulus medial e' >lateral e'), respiration-related ventricular septal shift (due to ventricular interdependence), and hepatic vein diastolic flow reversal in expiration are characteristic of constriction [62].

In addition to being the gold standard for LVEF assessment, cardiac MRI provides additional detailed tissue characterization and may specifically evaluate for RT-associated fibrosis with gadolinium enhancement, T1 mapping, and extracellular volume quantification [63]. Cardiac MRI can be especially useful in patients with poor acoustic windows on echocardiograms and can also aid in the evaluation of pericardial disease and valvular disorders [64].

CAC on non-gated CT chest imaging represents an immediately available means of assessing for underlying coronary artery disease in patients with a history of chest RT, and evidence supports a good correlation between CAC assessment on cardiac gated and non-gated imaging, though there remains a 9% false-negative rate on non-gated imaging owing to larger CT slice thickness [65]. CAC on both gated and non-gated imaging enhances the estimation of pretest probability of obstructive CAD. Dedicated CAC measurement is indicated to aid in risk stratification for asymptomatic patients not otherwise on preventive therapy, who are at intermediate risk for CV events, as well as CV risk stratification in low-risk patients with chest pain [66].

Coronary computed tomography (CCTA) allows for noninvasive anatomic assessment of the coronary arteries and can identify both calcified and noncalcified plaque, as well as quantify the degree of stenosis. When available, calculation of fractional flow reserve (FFR) by CTA can also estimate lesion-specific ischemia [66]. The radiation dose for CCTA (2.7–5.1 mSv) is significantly less than myocardial perfusion imaging (12.8 mSV), though notable higher than CAC (1.0 mSv) and stress echocardiogram (no radiation). CCTA is indicated to evaluate for nonobstructive and obstructive CAD in patients with chest pain who have intermediate to high pretest likelihood for CAD [66].

Functional stress testing also continues to remain an option to evaluate for obstructive CAD in asymptomatic patients with a history of RT. Specific tests include stress echocardiography and stress nuclear myocardial perfusion imaging. As in the general population, functional testing provides the advantage of assessing exercise capacity, which adds prognostic value, in addition to evaluating for ischemic CVD. Recent ICOS recommendations deemphasize the role of functional testing in asymptomatic patients in favor of anatomical evaluation, as the former may not capture patients with nonobstructive CAD who will benefit from primary prevention with medical therapy [10]. Additionally, the recent ISCHEMIA trial showed no benefit for an initial revascularization strategy, compared to optimal medical therapy alone, in patients with stable coronary artery disease and moderate to severe ischemia on stress testing [67]. Whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain. These results further highlight the multiple prior trials that support optimal medical therapy and prevention strategies as a first-line approach, especially in an asymptomatic patient [68].

In patients that ultimately require left heart catheterization, intravascular ultrasound (IVUS) may help further characterize RT-associated coronary lesions, which may manifest with heavy calcification or neointimal hyperplasia with negative remodeling [69]. In patients with RICD undergoing left heart catheterization who may be candidates for coronary artery bypass, care should be taken to evaluate the native internal mammary artery, which may become fibrosed or atretic, as the superior internal mammary nodal region is often a target of regional nodal RT in breast cancer patients [70, 71].

Biomarkers remain understudied in RICD, but current evidence does not support their routine use in the screening of subclinical disease. Recent ICOS guidelines suggest that N-terminal pro-B-type natriuretic peptide (NT-proBNP)

is reasonable to screen asymptomatic patients at risk of HF, based on population data, but studies have not consistently shown that rise in cardiac markers specifically after RT can otherwise predict future cardiovascular outcomes [10]. In a study of 87 patients who underwent thoracic RT for multiple cancer types, NT-proBNP and high sensitivity troponin T did not significantly change pre- and post-RT. Placental growth factor (PIGF) and growth differentiation factor 15 (GDF-15) were found to be elevated post-RT in a small subgroup of 27 patients with lung cancer and lymphoma; however, these changes did not correlate with new clinical or echocardiographic findings [72]. In a study of 129 patients with breast cancer undergoing RT, NT-proBNP, troponin, and C-reactive protein were not found to significantly change pre- and post-RT. However lipopolysaccharide-binding protein (LBP) was found to correlate with MHD and post-RT diastolic dysfunction on TTE in a study of 129 patients, a finding that awaits confirmation in larger studies [73].

A yearly history and physical exam are recommended to monitor patients with a history of cardiovascular RT exposure, and a screening interval of approximately 5 years is generally felt to be appropriate for repeat imaging to evaluate radiation-associated CAD, cardiomyopathy, valvular disorders, and/or pericardial effusion and constriction, depending on a patient's specific risk factors and comorbidities [10]. There is a paucity of data to guide specific reassessment intervals, but there should be a low threshold to investigate clinical changes, as the time course of RICD presentation is highly variable. Additional research is needed to determine the appropriate timing of reassessment after baseline imaging and biomarkers are obtained. Throughout survivorship, however, there should be a continuous focus on CV risk factor optimization and appropriate preventative therapy.

Management of RICD

Optimal medical therapy, including statin treatment and consideration for aspirin therapy, should be initiated in patients identified as having asymptomatic CAD on screening imaging. Patients with a history of RT and symptoms of acute or chronic chest pain should be managed according to the current guidelines. For patients requiring intervention for obstructive CAD, percutaneous intervention (PCI) is often favored over coronary artery bypass graft (CABG) due to the higher risk of surgery in patients with a history of thoracic RT, though diffuse disease is often encountered in this patient population, and PCI may be technically difficult [74]. Similarly, surgical valve intervention carries a high risk of morbidity and mortality compared to non-RT-exposed controls [60]. Calcification and fibrosis of the aortomitral curtain may complicate single valve replacement and can necessitate combined aortic and mitral valve replacement with extensive reconstruction (also known as a "commando" procedure). Transcatheter aortic and mitral valve replacement (TAVR, TMVR) may be preferred in patients at high risk for perioperative complications, and assessment by a multidisciplinary valve team is recommended to determine the optimal approach. In a retrospective study of 110 patients undergoing TAVR and surgical aortic valve replacement (SAVR) after mediastinal RT, TAVR was associated with lower 30-day mortality [75].

Guideline-directed medical therapy is recommended for RT-associated cardiomyopathy presenting as HF with reduced or preserved ejection fraction (HFrEF, HFpEF), though data are needed to best understand optimal therapeutics in this specific population. Importantly, restrictive and constrictive physiology should be considered in patients presenting with HFpEF. For patients with symptomatic constrictive pericarditis who fail to improve with medical therapy, pericardiectomy may be considered, though this procedure carries a high postoperative mortality rate approaching 20%, as reported in a retrospective study of 97 patients with chronic pericarditis (9 of whom had prior thoracic RT) [76]. When pericardiectomy is indicated, there may be some improvement in outcomes when the procedure is done earlier in the course of the disease.

CONCLUSIONS

The therapeutic ratio of RT for thoracic cancers has dramatically improved in recent decades, with modern RT retaining potent anti-cancer effects and improving upon the ability to spare non-tumor tissues. Despite RT advancements, many patients with thoracic cancers still receive radiation exposure to the heart, which damages cardiac tissue through both direct and indirect mechanisms. As a result, RICD is still a critical health concern facing patients who have received RT of the thorax, and the development of RICD in these patients is dependent upon numerous host- and treatment-related factors, including concomitant anti-cancer therapies and pre-existing CV risk factors. It is incumbent upon CV healthcare providers to conduct appropriate RICD screening and management measures to improve the quality of life and survival of patients treated with thoracic RT.

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