Curr Treat Options Cardio Med (2019) 21: 31
DOI 10.1007/s11936-019-0737-0

Cardio-oncology (M Fradley, Section Editor)

Cardiovascular Complications Associated with Mediastinal Radiation

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Published online: 4 June 2019

This article is part of the Topical Collection on *Cardio-oncology*

Keywords Radiation · Radiation therapy · Heart disease · Cardiotoxicity · Cardio-oncology · Survivorship

Abstract

Purpose of review Radiation-induced heart disease (RIHD) encompasses a broad range of pathologies and is a significant source of morbidity and mortality among cancer survivors. Increased awareness of the early and late consequences of mediastinal radiation has led to the development of strategies for cardiac risk reduction to improve outcomes through active surveillance and early detection of RIHD. This review aims to discuss the current knowledge on the presentation, diagnosis, and management of RIHD.
Recent findings Decades' worth of cohort data demonstrates an increased risk of RIHD as cancer survivors age. Additionally, interventional/surgical management of irradiated patients poses unique considerations and can be technically challenging. Used in conjunction with echocardiography, multimodality imaging for morphologic and functional assessment adds complementary value in screening, surveillance, and targeted symptom

investigation in patients at risk for RIHD. Furthermore, sensitive imaging parameters and biomarkers have shown potential in detecting subclinical RIHD. Despite the development of techniques which minimize cardiac exposure to ionizing radiation, their effects on the long-term development of RIHD remain to be seen.

Summary Due to the morbidity and mortality associated with RIHD, both patients and clinicians should be aware of the lifelong cardiovascular risks of mediastinal radiation exposure. RIHD surveillance should be a consideration throughout the survivorship period. Studies to evaluate the clinical consequences of contemporary radiation therapy strategies aimed at minimizing cardiac doses and the value of novel, more sensitive metrics for the early detection or prognostication of RIHD are ongoing.

Introduction

In the USA, there are over three million cancer survivors who received radiation therapy (RT) as part of their treatment, accounting for almost one third of all cancer survivors; this cohort is projected to grow in both number and age over the coming years [1]. RT remains an important treatment modality for patients with chest malignancies; this is particularly true in patients with breast cancer and Hodgkin lymphoma (HL), and, to a lesser extent, lung, esophageal, and other mediastinal tumors [1, 2]. While advances in cancer treatment have remarkably improved long-term survival, cardiovascular (CV) disease remains the leading non-cancer cause of death among post-RT survivors [3, 4]. Incidental exposure of the heart during mediastinal RT can lead to both acute and chronic CV consequences; the latter is more common and can have latency periods ranging from years to decades after exposure [2, 4]. Consequently, the cumulative incidence of radiation-induced heart disease (RIHD) increases as time from RT elapses [2]. The spectrum of RIHD in a patient can include vascular, myocardial, valvular, pericardial, conduction system, and autonomic disease, or a combination thereof, resulting in significant morbidity and mortality (Fig. 1) [2, 5•].

Mechanism of radiation-induced heart disease

RIHD results from a complex interplay of inflammatory and pro-fibrotic pathways. Direct endothelial injury is evident within minutes of tissue exposure to radiation and is characterized by recruitment of inflammatory cells and the release of proteases and cytokines [6]. Over time, changes in cellular gene expression—with nuclear factor-kappa B (NF-κB) being a key mediator—promote a cycle of sustained inflammation, oxidative stress, and deregulated activation of myofibroblasts, resulting in ongoing collagen deposition and chronic fibrosis [6–9]. In addition, endothelial dysfunction can lead to the activation of the coagulation cascade and result in local tissue hypoxia, further promoting tissue fibrosis [9, 10]. In RT-exposed vessels, endothelial dysfunction and accelerated atherosclerosis contribute to vulnerable plaque formation [4, 6]. In addition, microvascular injury with decreased capillary density can worsen macrovascular ischemia [5•, 11].

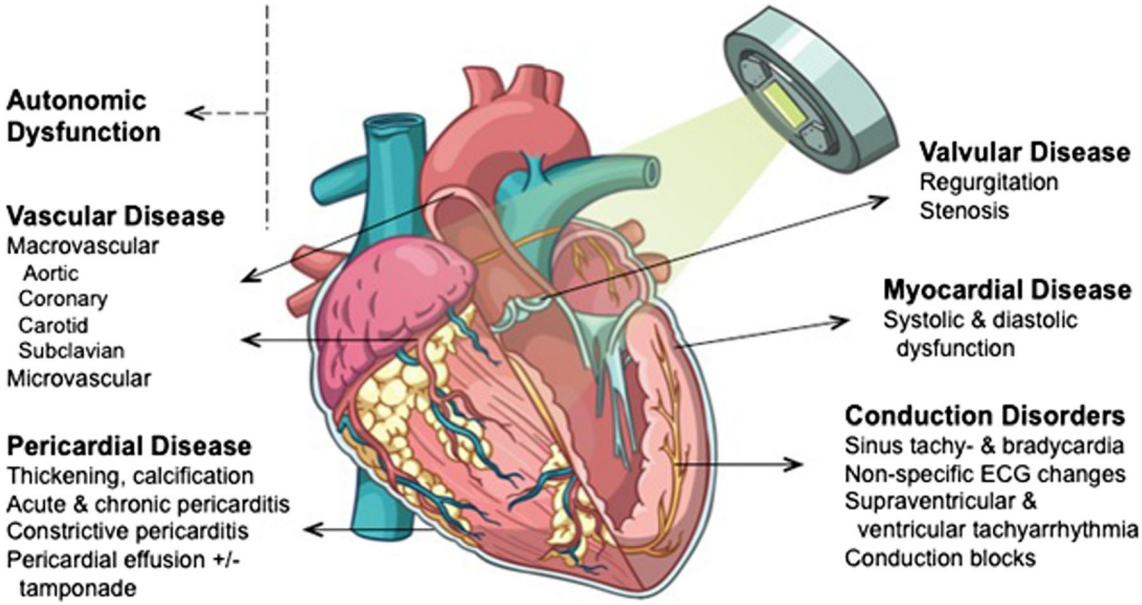

Fig. 1. Radiation-induced cardiovascular disease.

Radiation-induced coronary artery disease

HL and breast cancer survivors with a history of mediastinal RT have a 2- to 12-fold and 1- to 2-fold excess risk of CV mortality, respectively, mostly due to ischemic heart disease [3, 12, 13]. RT-induced coronary artery disease (CAD) usually presents ~ 10–20 years after exposure, although angina may be atypical or silent due to associated damage to nerve endings [14–18]. Excess risk is evident within the first few years and continues for decades [14, 15•, 16, 17•]. In contrast to typical CAD, RT-associated lesions tend to be longer and tubular [4].

Long-term follow-up data from HL survivors who received RT at a median age of 25 years (average mid-mediastinal or mean heart dose of 20–40 Gy) using protocols from 1960 to the mid-1990s demonstrate a 23% cumulative incidence of CAD by 40 years post-RT [14, 19–21]. Mediastinal RT typically spares the left circumflex artery but preferentially affects the ostial and proximal segments of the left main, right coronary artery (RCA), and left anterior descending (LAD) artery [18, 20, 22–24]. Compared to HL patients without prior mediastinal RT, HL patients who received RT have an increased risk of developing CAD (2- to 4-fold), myocardial infarction (2- to 5-fold), and angina (4- to 11-fold) [15•, 19]. Furthermore, HL survivors who received mediastinal RT were 2 to 3 times more likely to undergo coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) [20, 21]. Compared to HL survivors without prior mediastinal RT, HL survivors who received mediastinal RT have a dose-dependent excess CAD risk of 7.4% per Gy of mean heart dose with no safe threshold [15•]. The pattern of CAD lesions predisposes these survivors to an increased risk of myocardial infarction and sudden cardiac death at a relatively young age [18, 22, 24]. The 25-year

risk for death from ischemic heart disease or sudden cardiac death among survivors with prior mantle RT is estimated at ~ 10%, 5 times greater than expected in the general population [22].

Most childhood cancer survivors with a history of mediastinal RT exposure receive an estimated maximum dose of less than 20 Gy, although exposures are variable given the range of diagnoses [25]. The cumulative incidence of CAD among this cohort is approximately 5.3% by 45 years of age [26]. Compared to those who had no mediastinal RT exposure, those exposed to greater than 15 Gy or greater than 35 Gy had a 2.4- or 3.6-fold increased risk of myocardial infarction, respectively [27].

Breast cancer survivors represent a relatively older cohort compared to HL and childhood cancer survivors, and are generally exposed to a lower average dose of RT. Nonetheless, Darby et al. found a 7.4% higher risk of major coronary events per Gy of RT exposure; the risk continued beyond 20 years after treatment and was without a safe threshold [16]. In a study employing a more contemporary RT technique, the risk of major coronary events among breast cancer survivors was approximately 16% per Gy within the first 9 years after RT [28•]. The mid to distal LAD and distal diagonal segments seem particularly vulnerable in left-sided RT and the proximal RCA for right-sided RT [29, 30]. This differential exposure has been associated with a 20–30% greater risk of CAD and CV death with left- versus right-sided RT [12, 16, 17•].

RT dose remains the most significant treatment-specific risk factor for the development of RT-associated CAD, and traditional CV risk factors such as hypertension, hyperlipidemia, diabetes mellitus, obesity, and smoking appear to intensify this risk [2, 15•, 16, 19, 20, 26, 28•]. In one study, HL survivors with traditional CV risk factors had an increased risk of coronary heart disease (rate ratio, 1.5; 95% confidence interval [CI], 1.1 to 2.1) compared to those without CV risk factors [15•]. Armstrong et al. demonstrated that among childhood cancer survivors treated with mediastinal RT, the risk of major cardiac events increased as the number of CV risk factors increased. The highest risk was seen among survivors with at least two CV risk factors, particularly when one was hypertension. The overall effect of mediastinal RT and CV risk factors (that is, hypertension plus either dyslipidemia, diabetes mellitus, or obesity) to major cardiac events was more than additive, with a 27.9 (95% CI, 14.6 to 51.0) relative excess risk of CAD as compared to childhood cancer survivors with mediastinal RT without corresponding CV risk factors [26].On the other hand, greater physical activity was associated with a lower risk of coronary heart disease [15•]. Finally, although prevalence increases over time, the relative excess risk is greater with a younger age at RT exposure [14, 15•, 19, 21].

In a screening study using stress echocardiography and nuclear scintigraphy, Heindenreich et al. estimated that in HL survivors 15 years post-mantle RT, 7.5% had greater than 50% coronary stenosis [31]; furthermore, they estimated a 2.7% prevalence of severe three-vessel or left main CAD. Abnormalities on screening tests were associated with increased risk for cardiac events during follow-up [31]. Of the two screening modalities, nuclear perfusion defects were less specific and had a greater (89%) false positive rate, compared to 11% for stress echocardiography. Perfusion defects seem to be associated with wall motion abnormalities. However, they may not reflect the typical coronary

distribution and are not consistently predictive of post-RT cardiac events, as these changes are likely related to associated microvascular disease and myocardial fibrosis [3, 32–34].

Given its high sensitivity for detecting CAD, coronary CT angiography (CCTA) with coronary artery calcium scoring can be a useful adjunct in screening young adults for premature atherosclerosis [3, 24, 35]. Studies demonstrate a CAD prevalence ranging from 20% to nearly 90% among relatively young HL survivors who underwent CCTA; the wide range is likely due to baseline differences and interval from time of RT [24, 35–37]. Compared to non-irradiated controls, lymphoma survivors were found to have higher coronary calcium scores, more left main or multi-vessel CAD, and a 3-fold odds ratio of developing proximal obstructive disease based on CCTA. Of note, the average survivor had a low prevalence of traditional CV risk factors and had an average age of 45 years at the time of CCTA [24]. The Children's Oncology Group recommends periodic evaluation for cardiac toxicity, including CAD, with consideration for referral to cardiology 5 to 10 years after RT, for survivors who were exposed to greater than or equal to 35 Gy of chest RT alone, or greater than or equal to 15 Gy if therapy included an anthracycline [3, 38].

Radiation-induced valvular disease

RT exposure results in valvular thickening, calcification, and fibrosis, with progression from regurgitation to stenosis [5•, 39]. Thickening of the aortomitral curtain is the key feature of RT-induced valvular disease [5•]. The risk is higher for left-sided valves, with the aortic valve being the most commonly affected, likely due to the high-pressure transvalvular gradient coupled with proximity to the RT field [40–42]. In contrast to rheumatic heart disease, radiation injury involving the mitral valve typically spares the leaflet tips and valve commissure [3].

Up to 81% of patients with RIHD develop valvular disease, with 6% experiencing clinically significant valvular dysfunction, often requiring intervention [39]. Among HL survivors, Wethal et al. demonstrated regurgitant lesions in 31% of HL survivors at 10 years after RT, and in over 90% by 22 years after RT [43]. Aortic regurgitation was the most common lesion found among asymptomatic HL survivors who received greater than or equal to 35–40 Gy of mediastinal RT, with risk of moderate to severe disease being 34 times higher as compared to the Framingham population [42, 44]. Compared to HL survivors without mediastinal RT exposure, the risk of any valvular disease is 5- to 7-fold greater in HL survivors who received mediastinal RT, and they are about 9 times more likely to require valve surgery [14, 19–21]. Likewise, childhood cancer survivors who were exposed to greater than or equal to 15 Gy and greater than or equal to 35 Gy of mediastinal RT had a corresponding 3.3- and 5.5-fold greater risk of valvular disease than non-irradiated counterparts [27].

Though valvular dysfunction can occur at any RT dose, there appears to be an accelerating risk above 30 Gy; risk increased from 2.5% per Gy for mean valve dose of less than or equal to 30 Gy, to 24.3% per Gy for mean valve dose greater than 40 Gy [14, 40]. Concurrent anthracycline treatment further increases the risk of valvular dysfunction 2- to 4-fold [19, 45]. Traditional CV risk factors further increase the risk of valvular disease, especially when one of those

risk factors is hypertension [19, 26, 40]. Clinically significant valvular disease characteristically occurs later than RT-induced CAD [19, 20], and lower doses of RT exposure are associated with an even more prolonged latency period, often extending decades post-treatment [46].

Echocardiography remains the cornerstone for diagnosing and evaluating valvular heart disease. The expert consensus statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommends initial screening at 5 to 10 years after RT, then every 2 to 5 years thereafter [3]. Transesophageal echocardiography or 3-D echocardiography is particularly useful when there is limited visualization with 2-D echocardiography [3, 18]. Cardiac CT can provide complementary information such as associated aortic root dilation and LV hypertrophy or dilation [3]. Stress echocardiography for dynamic assessment of valvular disease and detection of myocardial ischemia should be considered when patient symptoms do not appear to correlate with resting valvular gradients [5•].

Radiation-induced myocardial disease

Progressive myocardial fibrosis occurs through RT-induced microvascular damage, leading to decreased capillary density, cardiomyocyte hypoxia and death, and replacement fibrosis, resulting in decreased myocardial compliance and elasticity [6, 11]. Moreover, concomitant RT-induced CAD and myocardial infarction can result in fibrosis [5•]. Radiation-induced myocardial disease typically manifests as diastolic dysfunction and restrictive cardiomyopathy [2, 47].

Among HL survivors who received mediastinal RT with or without anthracyclines, the 40-year cumulative incidence of heart failure (HF) or cardiomyopathy is 8.1% as the first cardiac adverse event, and 24.8% overall [14]. The risk rises sharply after exposure to greater than or equal to 25 Gy, with a latency period of almost 20 years [48]. Depending on the dose exposure, the risk is approximately 3 to 5 times greater in HL survivors who received mediastinal RT compared to HL survivors without mediastinal RT exposure [14, 19]. Heidenreich et al. demonstrated a high prevalence of systolic and diastolic dysfunction at an average of 15 years post-mantle RT compared to the Framingham population (36% versus 3% and 14% versus 6%, respectively); the risk significantly increased with time from treatment [44, 49]. Concomitant doxorubicin treatment, even at lower doses (< 250 mg/m^2), increased the risk by at least 5.4-fold beyond that of survivors who had anthracycline exposure without prior mediastinal RT [14]. Notably, patients with diastolic dysfunction more often had stress-induced ischemia and CAD-associated events [49], underscoring that CAD further contributes to myocardial injury in the setting of RT.

The 30-year cumulative incidence of HF among survivors of childhood cancer is approximately 4%, a 15-fold increased risk compared to the general population [27, 50••]. RT doses greater than or equal to 15 Gy increase the risk for HF 2-fold [27, 45]. The presence of hypertension in combination with another CV risk factor increases this risk beyond additive effects, up to a factor of 18 [26].

Despite lower RT exposure, breast cancer survivors are also at an increased risk for HF. A case-control study on older women who received contemporary conformal RT with a dose less than 5 Gy showed that cases of heart failure

mostly had preserved ejection fraction (HFpEF) that developed at an average of 5.8 years post-RT. The risk of developing HFpEF was 16 times greater than controls, developed more commonly in patients with ischemic heart disease or atrial fibrillation, and increased with RT dose [47].

The American Society of Clinical Oncology and the International Late Effects of Childhood Cancer Guideline Harmonization Group recommend a risk-stratified approach to cardiomyopathy surveillance among childhood and adult cancer survivors. High-risk survivors include those who received high-dose RT (greater than or equal to 35 Gy for childhood and greater than or equal to 30 Gy for adult cancer survivors) or lower-dose RT plus anthracyclines. Low-risk survivors include those who received only low-dose RT. Lifelong echocardiogram surveillance starting no later than 2 years after completion of therapy, at 5 years after diagnosis, and every 5 years thereafter is the recommended minimum investigation among childhood survivors. For adult survivors, an evaluation 6 to 12 months upon completion of cardiotoxic therapy may be considered in high-risk patients [50••, 51••]. Cardiac magnetic resonance imaging (MRI) may be preferred in cases with poor acoustic windows and offers superior image resolution and myocardial tissue characterization [3].

Even with normal left ventricular ejection fraction (LVEF), patients who undergo RT can develop diastolic dysfunction and abnormal myocardial deformation as measured by global longitudinal strain (GLS). Among childhood cancer survivors who received mediastinal RT without anthracyclines, 5.7% had an abnormal LVEF, 22.4% had diastolic dysfunction, and 33% had abnormal GLS, with GLS being the only parameter associated with low doses of RT exposure (1 to 19 Gy) [52••]. Preferential reductions in cardiac apex GLS were also demonstrated among chemotherapy-naïve breast cancer patients, which corresponded to the region of greatest RT exposure [53, 54].

Radiation-induced pericardial disease

Early post-RT changes involve microvascular damage with resultant ischemia and neovascularization of the pericardium, leading to further ischemia and fibrosis. With concurrent damage to the venous and lymphatic drainage, accumulation of a fibrin-rich effusion occurs. Over the long term, this is replaced by collagen, leading to the formation of a thick and rigid pericardium [5•, 6]. Acute pericarditis after high-dose RT exposure has become infrequent with the development of contemporary RT techniques [34]. Pathology reports of RIHD among patients who received more than 35 Gy of mediastinal RT show evidence of pericardial disease in 70–90%, predominantly manifesting as pericardial thickening [55, 56]. Similarly, pericardial thickening was the most common abnormality on echocardiographic screening among asymptomatic HL survivors with prior mantle RT dose greater than 35 Gy. By approximately 15 years post-RT, 21% of screened patients had pericardial thickening, 3% had a small pericardial effusion, and none had developed constrictive pericarditis [44]. Symptomatic pericarditis and pericardial effusion requiring intervention were seen in 1.3% of HL survivors by 25 years after RT, corresponding to almost 13-fold greater risk than the general population [21]. Childhood cancer survivors were found to have an overall low 30-year cumulative incidence of pericardial disease of approximately 3%, although this represents a 6.3-fold

increased risk when compared to sibling counterparts; pericardial disease was significantly associated with increased doses of mediastinal RT and high-dose anthracycline exposure. Compared to childhood cancer survivors with no prior mediastinal RT, doses greater than or equal to 15 and greater than or equal to 35 Gy were associated with a corresponding 2.2- and 4.8-fold increased risk [27].

Patients with esophageal and non-small cell lung cancer (NSCLC) have a relatively poor prognosis; given its long developmental latency, RIHD has generally been less of a concern in this population. Nonetheless, as these patients are typically older and have preexisting CV comorbidities, high-dose RT could still predispose them to adverse CV outcomes. Among 112 inoperable NSCLC patients treated with a total dose of greater than or equal to 70 Gy, 9 (8%) patients developed symptomatic pericardial disease (7 pericardial effusion, 2 constrictive pericarditis) and 33 (29%) were incidentally found to have new pericardial effusions [57]. An association between RT dose and outcomes such as cardiac events and overall survival has not been consistently demonstrated in lung cancer patients treated with RT [57–59]. Among patients with esophageal cancer treated with doses of more than 50 Gy, 28 to 48% developed pericardial effusion at a median of 6 months based on post-treatment surveillance chest CT scans, with a dose dependent increase in risk [60–62]. Symptoms occurred in 4 to 8% of patients at a median of 22 months, with progression to cardiac tamponade among 3 of 11 symptomatic patients in Fukada et al.'s study [61, 62].

In the survivorship setting, pericardial effusions are typically progressive, recurrent, or both, and are associated with serositis and impaired lymphatic drainage [63, 64]. About 20% of patients with pericardial effusions progress into chronic constrictive pericarditis with or without tamponade [2, 6]. Echocardiography can assess for pericardial thickening, effusion, and hemodynamic consequences of constriction and tamponade. CT and cardiac MRI provide better assessment of pericardial calcification and residual inflammation. Likewise, the presence and degree of pleural effusions can also be evaluated via these modalities [3].

Radiation-induced conduction system disease

Almost 75% of HL survivors have some form of conduction abnormality or cardiac arrhythmia, which can result from fibrosis of the conduction system with or without coexistent myocardial ischemia [6, 65]. Electrocardiogram (ECG) abnormalities range from brady- and tachyarrhythmias to conduction blocks; the right bundle branch is most commonly affected due to its anterior location [44, 65]. Compared to the general population, HL survivors are twice as likely to need a pacemaker or automatic implantable cardioverter defibrillator (AICD) [21].

Radiation-induced carotid and cerebrovascular disease

Concurrent exposure of the mediastinal and lower cervical regions increases the risk of non-coronary vascular disease. In addition, radiation-induced myocardial infarction and valvular disease can predispose to embolic stroke [66]. About 5 to 8% of HL survivors treated with RT developed ischemic stroke,

transient ischemic attack, carotid artery stenosis, or subclavian artery stenosis, which is about 2.5 to 3 times greater when compared to HL survivors without prior cervical/mediastinal RT and the general population [20, 66]. Among childhood cancer survivors, the risk of stroke was 4 to 5 times that of siblings [67]. Ischemic stroke occurred approximately 17 years post-RT [20, 66, 67], and similar to other RIHD, the excess risk was greater among those with hypertension [20, 66]. Notably, cerebrovascular ischemic events in HL survivors mostly occurred among patients who were older at time of RT, suggesting a role for preexisting vascular disease [20, 66]. The European Society of Cardiology suggests inclusion of carotid ultrasound as part of a comprehensive screening assessment among patients with prior neck RT [18].

Radiation-induced autonomic dysfunction

Damage to the carotid sinus or aortic arch baroreceptors and autonomic dysregulation, characterized by an elevated resting heart rate, dampened heart rate variability, blunted blood pressure and/or heart rate response during exercise, abnormal heart rate recovery after exercise, labile blood pressure, and orthostatic intolerance can occur in patients treated with mediastinal or neck RT [34, 44, 65, 68, 69]. These changes are common among HL survivors, associated with increasing RT dose and longer latency period, and are associated with impaired exercise capacity, poor quality of life, and increased mortality [34, 65]. Management of baroreceptor failure is complex and should be approached with a combination of non-pharmacologic and pharmacologic measures [69].

Risk reduction and Management of Patients with RIHD

Knowledge of treatment- and patient-related risk factors is paramount to guide prevention and management of RIHD. Established risk factors include older RT techniques, greater total heart or fraction doses, larger irradiated heart volume, anterior or left chest RT, concomitant cardiotoxic therapy, time elapsed since RT, younger age at treatment, and the presence of traditional CV risk factors [2, 3, 26, 38, 70]. All patients should undergo a comprehensive evaluation prior to initiation of RT that includes a medical history, a physical examination, and a baseline echocardiogram, with emphasis on CV assessment of preexisting risk factors and CV disease prior to, during, and throughout the survivorship period for management and optimization of CV risk [71]. Annual physician visits, scheduled screening and surveillance for RIHD, and targeted symptom investigation are essential during follow-up [5•, 38, 50••, 51••]. Healthy lifestyle habits such as keeping a healthy weight, diet, regular exercise, and abstinence from smoking should also be promoted [38, 72]. Management of traditional CV risk factors and CV disease should align with American College of Cardiology/American Heart Association guidelines. Although prior mediastinal RT is not considered a traditional CV risk factor and has yet to be incorporated into conventional risk prediction models, it appears to comparably raise the risk of cardiac disease. We recommend having a low threshold to initiate high-intensity statin therapy [73]. While conventional risk calculators may not be applicable to young adult cancer survivors, prior RT exposure has been incorporated into a clinical CV risk score that includes age at diagnosis, sex, race, and

diagnosis of lymphoma [74•]. Furthermore, a HF risk prediction model incorporating sex, age at diagnosis, and anthracycline use in addition to mediastinal RT has been validated in several cohorts of childhood cancer survivors [75•].

Patients with RIHD who undergo cardiothoracic surgery are typically younger but have had prior cardiac surgery or require complex surgery and have worse outcomes than their non-RIHD counterparts (Table 1). Epicardial adhesions and mediastinal fibrosis can limit surgical manipulation [76–78], and extensive RT-induced aortic calcification (i.e., porcelain aorta) may preclude cross clamping during cardiopulmonary bypass or induce embolism upon manipulation [5•]. Wu et al. demonstrated that patients with RIHD undergoing cardiac surgery had greater short- and long-term mortality compared with matched controls—4% versus 0.3% within 30 days and 55% versus 28% by 7.6 years; this relationship held even in subgroups who underwent isolated CABG, who were younger (< 65 years old), and who were at lower surgical risk [76]. In addition, patients with RIHD experienced longer hospital stays and more post-operative events such as atrial fibrillation, permanent pacemaker implantation, and ventricular dysfunction. Aortomitral curtain thickness, degree of pulmonary fibrosis, and GLS are associated with mortality after cardiac surgery specific to the RIHD cohort [79–81]. The timing of surgery needs to be carefully planned, as repeat cardiac surgery is associated with greater long-term mortality in post-RT patients compared to non-RT patients (71% versus 43%, respectively). Damage to the internal thoracic artery due to RT or during mediastinal biopsy (performed for diagnosis of HL) can preclude its use as a bypass conduit. Therefore, preoperative assessment of vessel integrity is recommended; normal appearing arteries have been utilized with good long-term outcomes [78, 82].

Due to these unique surgical challenges, percutaneous intervention may be favored in patients with RIHD, although consideration of coronary calcifications is relevant. Compared to patients without prior RT, Reed et al. demonstrated an estimated twofold increased risk of all-cause and CV mortality over an average of 6.6 years post-PCI [83]. The risk was independent of clinical characteristics, complexity of cardiac lesions, and type of stent. In that study, the use of balloon angioplasty or bare metal stent was associated with a significantly greater risk of all-cause and CV mortality as compared to drug eluting stent placement. In contrast, over a similar period, Fender et al. found no difference in rates of all-cause mortality, CV mortality, or post-PCI complications in patients with RIHD compared to those without [84]. Likewise, Liang et al. showed that mediastinal RT before or after PCI was not associated with increased long-term risk of stent restenosis, stent failure, CV mortality, or myocardial infarction [85].

Among patients with RT-induced valvular disease, Paven et al. [86] demonstrated that patients without any history of mediastinal RT undergoing valve surgery had a long-term mortality rate of 17%, while their counterparts with a history of mediastinal RT had a mortality rate as high as 61%. A study by Crestanello et al. of 22 patients found that continued effects of RT on the valves, even after completion of treatment, led to high rates of failure after mitral and tricuspid valve repair that required further surgery [87]. As such, valve replacement is the preferred intervention even though it is associated with significant morbidity and mortality [86]. There is limited data on the long-term efficacy of transcatheter interventions in this population, although this may be a reasonable alternative to surgery in select patients with RT-induced valvular disease

Table 1. Outcomes of percutaneous and surgical interventions in radiation-induced heart disease

	Study type	Patient/diagnosis (average RT dose)	Procedure(s)
Coronary artery disease			
Reed et al. 2016	Retrospective observational matched cohort	*N* = 314 (157 RT) 61% breast (50–60 Gy) 14% HL (40–45 Gy) 15% lung (60 Gy) 10% NHL (40–50 Gy) 17% others (40–50 Gy)	Post-RT PCI (RT vs. non-RT) LM 4% vs. 6% LAD 52% vs. 69% LCx 25% vs. 37% RCA 38% vs. 53%
Fender et al. 2017	Retrospective observational matched cohort	*N* = 524 (116 RT) 51% breast 11% esophageal 9% HL 3% NHL 16% lung 11% others	Post-RT PCI (RT vs. non-RT) LM 4% vs. 3% LAD 39% vs. 41% LCx 32% vs. 29% RCA 37% vs. 41% Vein graft 1% vs. 0%
Liang et al. 2014	Retrospective observational matched cohort	(A) *N* = 115 Pre-RT PCI (1930 controls (B) *N* = 45 post-RT PCI (439 controls)	Pre- and post-RT PCI
Wu et al. 2013	Retrospective observational matched cohort	*N* = 478 (173 RT) 53% breast (50–60 Gy) 27% HL (40–45 Gy) 7% lung (60 Gy) 6% NHL (40–50 Gy) 8% others (40–50 Gy)	CABG 15% CABG +1 Vsx 22% CABG +2+ Vsx 21% 1 Vsx 22% 2+ Vsx 16% Other 4%
Valvular disease			
Donnellan et al. 2017	Retrospective observational matched cohort	*N* = 344 (172 RT) 55% HL (40–45 Gy) 30% breast (50–60 Gy) 6% NHL (40–45 Gy) 3% lung (60 Gy) 7% others (40–45 Gy)	Severe aortic stenosis, surgical replacement SAVR 39% SAVR + CABG 27% SAVR + aorta 34%
Dijos et al. 2015	Prospective case control	*N* = 198 (19 RT) 42.5% HL 36.8% left breast 10.5% lung	Transcatheter aortic valve implantation for aortic stenosis
Crestanello et al. 2004	Retrospective	*N* = 22 (post-RT); 14 mitral, 6 tricuspid, 2 both 45% breast 36% HL 18% NHL	Surgical mitral and tricuspid valve repair
Buzzatti et al. 2016	Case series	*N* = 6	MitraClip repair for symptomatic inoperable RT-induced mitral regurgitation
Pericardial disease			
Bertog et al. 2004	Retrospective	*N* = 163 (15 RT, 75 idiopathic, 60 post-surgical) 73% lymphoma 13% breast	Pericardiectomy for constrictive pericarditis
George et al. 2012	Retrospective	*N* = 98 (17 RT, 44 idiopathic, 30 post-surgical; 6 others)	Pericardiectomy for constrictive pericarditis
Murashita et al. 2017	Retrospective	*N* = 1066 (A) *N* = 259 historical pre-1990 (9 RT)	Pericardiectomy for constrictive pericarditis

Table 1. (Continued)

	Study type	Patient/diagnosis (average RT dose)	Procedure(s)
		(B) $N = 807$ contemporary 1990–2013 (92 RT)	
Carotid disease			
Kasivisva-nathan et al. 2012	Systematic review of 21 studies	Surgery: 211 procedures in 179 patients; stenting: 510 procedures in 482 patients	Surgical revascularization vs. carotid artery stenting for post-RT carotid stenosis
End-stage heart failure			
Uriel et al. 2010	Retrospective	$N = 1886$ (9 RT; 8 HL, 1 NHL)	Heart transplant
Saxena et al. 2014	Retrospective	$N = 12$ post-RT (8 HL, 4 NHL)	Heart transplant
Al-Kindi et al. 2016	Retrospective	$N = 45{,}041$ (87 RT-RCM, 1049 RCM, 44,805 other)	Heart transplant

	Results	Comments
Coronary artery disease		
Reed et al. 2016	Time from RT: 13 ± 10 years Mean FU 6.6 ± 5.5 years Mortality at FU: 38% vs. 27% RT significant predictor of all-cause (HR = 1.85) and CV mortality (HR = 1.70)	RT added incremental prognostic value (all-cause mortality) beyond clinical variables, SYNTAX ≥ 11, and stent type; BA/BMS had higher all-cause and CV mortality vs. DES.
Fender et al. 2017	Median time from RT: 5.6 years Median FU: 6.3 years NS difference in all-cause or CV mortality	Greater proportion of LVEF ≤ 40 in RT group at time of PCI Different results from Reed et al.'s study probably due to baseline differences between groups.
Liang et al. 2014	(A) Median time to RT: 3.6 years, median FU: 2.1 years (B) Median time from RT: 2.2 years, median FU: 3.1 NS difference in TLR or CV mortality in both groups	(A) ↑ All-cause mortality in RT (48.6% vs. 13.9%)
Wu et al. 2013	Time from RT: 18 ± 12 years Mean FU: 7.6 ± 3 years 30-day mortality: 4% vs. 0.3% Mortality at FU: 55% vs. 28% Predictors (HR): RT (2.47), EuroSCORE (1.22), No β-blocker (0.66)	RT group: cardiopulmonary death in 49%; post-op ↑ LOS, AF, PM, ventricular dysfunction, valve regurgitation; Redo surgery mortality: 71% vs. 43%.
Valvular disease		
Donnellan et al. 2017	Time from RT: 25 years (18, 32) Mean FU: 5.7 ± 3 years 30-day mortality: 2% vs. 0% Mortality at FU: 48% vs. 7% Predictors (HR): ↑STS score (1.14), RT (8.12)	RT group: baseline ↑ LM and 3 vessel CAD, worse PFT; mechanical > bioprosthetic valve; post-op ↑ LOS, readmission within 3 months, AF.
Dijos et al. 2015	NS difference in implantation success (94.7% vs. 93.6%) and 30-day safety points; 6-mortality lower in RT group	RT group younger, ↓ CV risk factors, ↓ EuroSCORE, ↑ porcelain aorta and hostile thorax.
Crestanello et al. 2004	Time from RT: 14.9 ± 9.2 years Mean FU: 3.7 ± 3.3 years Early mortality (LV failure) $N = 3$, late mortality $N = 7$ (4 CV). $N = 6$ with severe dysfunction of repaired valve.	Concomitant CABG 50%, valve replacement 27%.
Buzzatti et al. 2016	100% successful implantation (50% with 1 clip, 50% with 2 clips); $N = 4$ residual MR (1+ in 3, 2+ in 1).	

Table 1. (Continued)

	Results	Comments
	Median FU: 29 months: no rehospitalization for HF, clip detachment, or mitral surgery	
Pericardial disease		
Bertog et al. 2004	Median time from RT: 11 years Median FU: 6.9 years Peri-op mortality: 21.4% vs. 2.7% vs. 8.3% 7Y survival: 27% vs. 88% vs. 66%	High peri-op mortality mostly due to low-output HF; pericardial calcification had no impact on survival.
George et al. 2012	Short-term survival: NS 1-year survival: 58.8% vs. 90.9% vs. 86.7% 5-year survival: 40.3% vs. 79.8% vs. 55.9% 10Y survival: 11.0% vs. 66.5% vs. 55.9%	Pericardial calcification had no impact on survival.
Murashita et al. 2017	RT etiology of constrictive pericarditis with HR 4.35 and 3.93 for 30-day and overall mortality in contemporary era (baseline idiopathic etiology)	
Carotid disease		
Kasivisva-nathan et al. 2012	NS difference in stroke or death rate at 30 days with surgery or stenting; similar rates to non-RT population. Restenosis requiring reintervention 6.1% in both groups.	Surgical revascularization: 66% carotid endarterectomy, 20% interposition grafts, 11% extra-anatomic bypass, 2% other
End-stage heart failure		
Uriel et al. 2010	Time from RT: 26 ± 10 years Mean FU: 10 ± 8 years 4 deaths, 3 in-hospital Survival at FU: 55%	RT group: 5 NICM, 2 ICM, 2 constrictive pericarditis. All deaths non-cardiac. Graft function preserved in all patients.
Saxena et al. 2014	Mean time from RT: 23.2 years Mean FU: 7.7 years Hospital mortality 8.3% ($N = 1$) Survival at 1, 5, and 10 years: 91.7%, 75%, 46.7%	8 RCM, 4 DCM; 75% with prior surgery/sternotomy.
Al-Kindi et al. 2016	Time from RT 6-month survival: 79% vs. 92% vs. 92% 1-year survival: 76% vs. 88% vs. 88% 3-year survival: 66% vs. 79% vs. 82% 5-year survival: 58% vs. 73% vs. 76%	RT-RCM younger and more had prior cardiac surgery, post-op with ↑ LOS vs. RCM and other group.

RT radiation therapy, *HL* Hodgkin lymphoma, *NHL* non-Hodgkin lymphoma, *PCI* percutaneous coronary intervention, *LM* left main, *LAD* left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery, *FU* follow-up, *HR* hazard ratio, *BA* balloon angioplasty, *BMS* bare metal stent, *DES* drug-eluting stent, *NYHA* New York Heart Association class, *NS* non-significant, *TLR* target lesion revascularization, *CV* cardiovascular, *CABG* coronary artery bypass grafting, *Vsx* valve surgery, *LVAD* left ventricular assist device, *LOS* length of stay, *AF* atrial fibrillation, *PM* pacemaker placement, *AVA* aortic valve area, *SAVR* surgical aortic valve replacement, *STS* Society of Thoracic Surgeons, *CAD* coronary artery disease, *PFT* pulmonary function test, *HF* heart failure, *NICM* non-ischemic cardiomyopathy, *ICM* ischemic cardiomyopathy, *RCM* restrictive cardiomyopathy, *DCM* dilated cardiomyopathy

[4]. Dijos et al. prospectively enrolled 198 patients with aortic stenosis ($N = 19$ RT-induced) who underwent transcatheter aortic valve implantation [88]. The RIHD group had lower CV risk score and similar implantation success rate compared to patients without a history of RT (94.7% versus 93.6%) with equivalent 30-day safety points. Similarly, in a case series by Buzzatti et al. of 6 patients with RT-induced mitral regurgitation treated with MitraClip, no rehospitalization for HF, clip detachment, or mitral surgery were recorded at median follow up of 29 months [89].

In patients with pericardial disease, pericardiectomy is indicated when symptoms persist despite medical therapy. Galper et al. demonstrated that HL survivors were 13 times more likely to require pericardial surgery than the general population [21]. Compared to other etiologies of constrictive pericarditis, post-RT carries the worst prognosis over the perioperative and long-term period. RT increases the mortality risk 3- to 4-fold, with approximate survival rates of 60% at 1 year that sharply declines to less than 15% at 10 years [77, 90, 91]. It should be noted that HF symptoms might not significantly improve after pericardiectomy, as these patients can have concurrent restrictive cardiomyopathy. Non-invasive assessments with traditional echocardiographic and myocardial deformation indices, CT, and cardiac MRI can provide diagnostic clues, but hemodynamic evaluation with right heart catheterization is usually necessary to differentiate these entities [5•].

Post-cardiac transplant outcomes among patients are likewise worse among those with RIHD. All-cause mortality is particularly high in the early post-transplant period [92, 93]. A study involving 87 patients with RT-related restrictive cardiomyopathy found a 6-month mortality in 21.2% of patients as compared to 7.6–8.7% among patients without RT-related cardiac disease, with a cumulative survival rate of 58% at 5 years [93]. The majority of deaths occurred during the early post-operative course and was attributed to peri- and post-operative complications, reflecting the challenge of surgical management of RIHD [92, 93].

Post-RT patients with carotid artery stenosis experience similar rates of periprocedural stroke and mortality and of restenosis requiring reintervention after surgical or stent revascularization [94]. However, anatomic challenges due to adhesion of tissue planes and greater risks of post-operative cranial nerve injury and wound complications with carotid endarterectomy make carotid artery stenting the preferred revascularization strategy [94, 95]. The safety of carotid artery stenting with embolic protection has been demonstrated, with no significant differences in periprocedural and 5-year outcomes including target lesion revascularization between post-RT and non-irradiated patients [95, 96].

The introduction of contemporary RT strategies, including total dose reduction, dose fractionation, shielding, CT-based planning, prone imaging (for breast cancer), respiratory gating, and highly conformal techniques such as intensity-modulated RT and volumetric modulated arc therapy [4, 51••, 97], will hopefully alter the risk of RIHD. During the 1960s, high-energy radiation via orthovoltage therapy or cobalt 60 was typical for HL. With the introduction of linear accelerators in the 1970s, 30 to 40 Gy in fractions of 1.5 to 2 Gy were standard doses, most commonly delivered through mantle-field RT [14]. Subsequently, adoption of more contemporary techniques around 1990 led to decreasing cardiac exposure throughout the years, corresponding with decreased rates of RIHD [2]. When comparing mantle RT to involved-node RT, Maraldo et al. demonstrated significant differences in mean dose exposure of

the heart and its substructures and in 25-year absolute excess risk of any cardiac (9.1% versus 1.4%) and valvular disease (16.4% versus 0.8%) [97]. Proton and high linear energy transfer therapies can achieve lower off-target exposure beyond that of photon-based techniques [7]. Nevertheless, the clinical benefits of further reduction in RT dose are unclear at this time. The RADCOMP trial (NCT02603341) will compare 10-year CV outcomes between proton versus photon RT; another ongoing trial (NCT01993810) will compare overall survival and cardiac toxicity among NSCLC patients receiving proton versus photon RT. These important studies will help determine surveillance, management, and prevention of RIHD in the future.

Conclusion

The progressive and irreversible nature of RIHD remains a substantial clinical challenge throughout the survivorship period. Associated morbidity and mortality increases with time from radiation exposure, particularly among survivors treated with high-dose RT. Minimizing or avoiding cardiac exposure is the only known strategy to prevent the development of RIHD, but the importance of modifiable risk factor optimization to mitigate further risk cannot be overemphasized. Likewise, a history of mediastinal RT exposure should be considered a risk factor or risk modifier in the management of CV disease. Serial multimodality testing is indispensable to achieve the goal of early RIHD diagnosis and management. It has yet to be determined if newer RT techniques can improve the cardiac outcomes of patients at risk for RIHD, but long-term studies are currently underway to answer this question.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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