Curr Treat Options Cardio Med (2014) 16:317
DOI 10.1007/s11936-014-0317-2

Cardio-oncology (S Francis, Section Editor)

Radiation-Induced Heart Disease: An Under-Recognized Entity?

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Published online: 24 April 2014

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

Keywords Radiation therapy · Radiation-induced heart disease · Cardiovascular disease · Coronary artery disease · Valve disease · Restrictive cardiomyopathy · Pericardial disease · Breast cancer · Hodgkin lymphoma

Opinion statement

Radiation-induced heart disease (RIHD) represents a spectrum of cardiovascular disease in patients who have undergone mediastinal, thoracic, or breast radiotherapy (RT). RIHD may involve any cardiac structure and is a major cause of morbidity and mortality in cancer survivors. While large cohort studies have demonstrated that symptomatic RIHD is a common late finding in this population, the incidence of asymptomatic disease is likely to be even higher. Long-term follow-up with regular screening for RIHD plays an important role in the management of cancer survivors who have undergone RT. Aggressive modification of traditional cardiovascular risk factors such as hypertension, dyslipidemia, and cigarette smoking is essential in patients at risk for RIHD, as these have been shown to potentiate the risks of radiation. In patients with symptomatic RIHD, medical and/or percutaneous therapies are often preferable to surgical interventions in view of the increased surgical risk associated with radiation damage to surrounding tissues. Percutaneous revascularization should generally be favored over surgical revascularization. Transcatheter valve replacements have not been widely used in this population but may offer an alternative to high-risk surgical valve procedures. Pericardiectomy is usually associated with extremely poor short-term and long-term outcomes in patients with RIHD and should be avoided in most cases. Heart transplantation is also higher risk in patients with RIHD than in patients with other etiologies of heart failure, but may be considered in young patients without other comorbidities.

Introduction

Advances in the diagnosis and treatment of malignancy have resulted in dramatic improvements in survival for many cancers. Five-year survival rates after breast cancer (BC) and Hodgkin lymphoma (HL) are now approaching 90 %. The improved survival rates can be partially attributed to advances in radiation therapy (RT), which is a fundamental component of the treatment strategy for many patients with BC, HL, and other malignancies. One implication of this improvement in survival is that many cancer survivors will live long enough to develop late effects of their cancer treatments.

Cardiac complications of RT are recognized as one of the major late effects in BC and HL survivors. Radiation-induced heart disease (RIHD) may manifest as pericardial disease, myocardial disease, valvular disease, conduction abnormalities, coronary artery disease, or cardiovascular death. Recent evidence suggests that RIHD may be more common than was previously believed, and also addresses controversies regarding the risks associated with modern RT techniques and the existence of a minimum threshold radiation dose. This review will discuss our present understanding of the epidemiology of RIHD as well as its pathogenesis, diagnosis, and current treatment options.

Pathogenesis of RIHD

Although cardiac myocytes are relatively resistant to radiation due to their postmitotic state, vascular endothelial cells remain susceptible to RT-induced damage. Endothelial damage in small capillaries results in capillary loss and small-vessel ischemia [1]. In the epicardial coronary arteries, endothelial damage results in increased capillary wall permeability and local inflammation [2]. Inflammatory pathways involving nuclear factor κ-B (NF-κB) and endothelial dysfunction result in the formation of atherosclerotic lesions [3]. Morphologically, RT-induced CAD is identical to typical atherosclerotic CAD, characterized by intimal proliferation, accumulation of lipid-laden macrophages, and plaque formation [4]. Patients with RIHD are more likely to develop coronary lesions in specific patterns that correspond to areas receiving the highest doses of radiation. In left-sided BC patients, the tangential beam involves the anterior wall of the heart and the left anterior descending (LAD) coronary artery [5], and the LAD and distal diagonal branches are frequently diseased in this population [6–8, 9•]. RT of mediastinal lymph nodes (as in HL) and internal mammary chains (in BC) results in higher radiation doses to basal cardiac structures, leading to ostial coronary artery lesions [6, 10–12]. Mediastinal radiation may also be associated with alterations in autonomic tone, with reduced heart-rate variability reflecting a relative excess of sympathetic over parasympathetic activity [13], potentially further increasing the risk of ischemic heart disease in this population.

In the pre-modern era, the pericardium was the most frequently involved cardiac structure after RT [14, 15]. Microvascular injury to the pericardium causes increased capillary permeability, which leads – often rapidly – to the development of a protein-rich effusion. In addition, local inflammation may result in pericarditis, and the long-term sequelae of this may include constrictive pericarditis in up to 25 % of patients with late pericarditis [16, 17].

In the myocardium, microvascular injury results in chronic ischemia, subsequently leading to diffuse myocardial fibrosis [1, 18]. This primarily manifests as diastolic dysfunction [19]. In the pre-modern era, higher cardiac radiation doses resulted in systolic dysfunction in over half of patients [20],

but more recent literature suggests that fewer than 5 % of patients develop reductions in left ventricular ejection fraction [21].

RT may directly damage cardiac valves, resulting in both stenotic and regurgitant lesions. Pathologic findings include leaflet retraction, fibrotic thickening, and late calcification [22]. Left-sided valves are affected more often than right-sided valves [23], although pulmonic and tricuspid valve disease have been described [24, 25].

Epidemiology

By the 1960s, the increased risk of cardiac morbidity and mortality following RT were widely recognized. Early work from Stanford University concluded that RIHD was more common than had been believed, and described particularly high rates of pericardial disease [16]. In contrast, RT was not thought to be a common cause of coronary artery disease (CAD) until the 1990s, when the high prevalence of CAD was described in patients treated with RT for BC [26] and HL [27]. Analyses of randomized trials and large observational cohorts have now confirmed that ischemic heart disease is the most common cause of cardiovascular mortality in post-RT patients [9•, 28, 29•].

The risk of RIHD is dependent upon the volume and region of heart that falls within the radiation field, the total RT dose, additional insults such as cardiotoxic chemotherapy or traditional cardiovascular risk factors, and time since exposure [17, 28]. In a retrospective study of HL patients treated with RT between 1962 and 1998 at the University of Florida, 10 % of patients developed symptomatic CAD at a median nine years after treatment [11]. The only treatment-related risk factor for CAD was higher radiation dose. All patients who developed symptomatic CAD had at least one traditional cardiovascular risk factor.

In a meta-analysis of randomized trials initiated between 1976 and 1991 evaluating the effect of RT on local recurrence and survival after BC, the incidence rate ratio for heart disease mortality was 1.27 (surgery and RT vs. surgery alone) [30]. Using data from the Surveillance, Epidemiology, and End Results (SEER) database, Henson and colleagues demonstrated an increased risk of mortality from heart disease within the first decade after diagnosis in women treated with RT for left-sided vs. right-sided BC between 1973 and 1982 (RR 1.19) [31]. Mortality ratios progressively increased with each additional five years of follow-up, with a ratio of 1.90 at >20 years from diagnosis.

In a cohort of 157 patients treated with mediastinal RT for HL between 1972 and 1985, the standardized mortality ratio for death from ischemic heart disease was 5.0 [32]. In another large study of the long-term effects of RT for HL, 3.9 % of patients died of cardiac causes after a median follow-up of 9.5 years; the relative risk of cardiac death among those receiving >30 Gy compared to the general population was 3.5 [28].

Diastolic dysfunction and valvular disease are also important sources of morbidity in cancer survivors who have received RT. In a study of 294 HL patients who had undergone mediastinal RT at Stanford, diastolic dysfunction was detected by echocardiography in 14 % of patients after a mean follow-up of 14 years [19]. Perfusion defects were more common in patients

with diastolic dysfunction, and after adjusting for important covariates, diastolic dysfunction predicted worse event-free survival. In another study by the same investigators, 60 % of HL survivors had mild-or-greater aortic insufficiency and 16 % had aortic stenosis [33]. In a University of Florida study, 6.2 % of HL patients developed symptomatic valvular disease at a median follow-up of 22 years [11]. The most common valve lesion was aortic stenosis, and the observed-to-expected ratio for valve surgery (based on a matched general population) was 8.42. Importantly, valvular disease may not develop for more than 20 years after radiation exposure. In a Norwegian study, 116 HL survivors underwent echocardiography at a median of 10 years after exposure and then underwent repeat echocardiography 12–14 years later [22]. Of the patients with mild-or-less regurgitation of the aortic and mitral valves on the initial echocardiogram, 37 % had developed moderate-or-greater regurgitation of one or both valves by the time of the repeat study.

Younger age at time of treatment is also a risk factor for RIHD [17]. In an analysis of 25-year survivors of childhood Wilms tumor in the Childhood Cancer Survivor Study (CCSS), the hazard ratio of congestive heart failure among survivors treated with RT in the absence of anthracyclines compared to sibling controls was 6.6 [34]; this increased to 18.3 among survivors who also received >250 mg/m2 of doxorubicin with RT. In another CCSS study of adult survivors of a variety of childhood cancers, compared to those who received no RT, the hazard ratios among those who had received ≥35 Gy were 4.5, 3.6, 4.8, and 5.5 for congestive heart failure, myocardial infarction, pericardial disease, and valvular disease, respectively [35]. Among those who had received 15–35 Gy, the respective hazard ratios were 2.2, 2.4, 2.2, and 3.3.

Much of the data regarding risk of RIHD is based on patients who received RT in the 1970s and earlier. Doses of RT for many malignancies have decreased since the early 1980s, and novel RT methods have been designed to minimize the dose reaching the heart. It has been suggested that the excess risk of cardiac mortality is negligible with modern RT techniques and at low heart doses [36–40]. The incidence of pericardial disease has been reduced from as much as 20 % to less than 5 % with modern RT methods [41]. In the SEER database study described above, no excess mortality was seen in the first decade after diagnosis among those treated for left-sided vs. right-sided BC between 1983 and 1992 [31]. In a retrospective study of BC patients treated in Toronto, Canada, between 1982 and 1988, no excess cardiac morbidity or mortality was observed in patients with left-sided vs. right-sided disease after a median of 10.2 years' follow-up [37]. In an analysis of the DBCG 82b and 82c randomized trials conducted between 1982 and 1990, there was no excess mortality from ischemic heart disease associated with radiation after breast-conserving surgery over a median of 10 years of follow-up [42].

More recent data have challenged this hypothesis. In a large population-based case-control study of coronary events in 2,168 women with a history of BC treated with RT, Darby and colleagues demonstrated increased cardiac risk at any level of RT, even among those treated between 1990 and 2001 [29•]. In this study, rates of major coronary events (myocardial infarction, coronary revascularization, or death from ischemic heart disease) increased in a linear fashion by 7.4 % per Gy, with no apparent threshold, and ap-

peared within five years of RT, while smaller studies had previously suggested that no excess risk occurs until at least 10 years post-RT [43].

The incidence of RIHD is likely to be greatly underestimated by studies of symptomatic disease. In a study of 294 asymptomatic patients treated for HL at Stanford University between 1964 and 1994, echocardiography revealed resting abnormalities of left ventricular (LV) function in 21 % of patients, and 14 % had stress-induced wall motion abnormalities on stress echocardiography or perfusion defects on nuclear scintigraphy. Of 40 patients in the study who also underwent coronary angiography, 22 had ≥50 % stenosis of at least one coronary artery [44].

Diagnosis of RIHD

Guidelines for the identification and monitoring of RT-induced heart disease were recently jointly published by the European Association of Cardiovascular Imaging and the American Society of Echocardiography (Fig. 1) [45•]. The European Society of Medical Oncology also recently issued clinical practice guidelines for the prevention, diagnosis, and management of cardiovascular disease associated with cancer therapy [46]. In asymptomatic patients, screening echocardiography is recommended every five years, beginning five years after exposure in high-risk patients and beginning 10 years after exposure in all others [45•]. Functional non-invasive stress testing is also recommended every five years in asymptomatic high-risk patients, beginning 5–10 years after exposure. Nuclear scintigraphy is not recommended as a stress imaging method due to the additional radiation exposure involved with this modality. All patients should have annual clinical evaluations, and appropriate investigations should be performed in symptomatic patients or those with new clinical findings suggestive of structural heart disease. Magnetic resonance imaging (MRI) is particularly useful in the evaluation of pericardial anatomy, although computed tomography is also helpful in patients with contraindications to MRI.

Troponin I levels are elevated immediately following RT for left-sided BC [47], but are not elevated at later points [48]. NT-proBNP levels are elevated 5–22 months after RT for left-sided BC, and are more elevated in patients in whom a greater heart volume was included in the treatment field [48]. Although natriuretic peptide and troponin measurements have been suggested for early risk stratification of patients undergoing RT [49], the long-term implications of these early elevations are not clear, and a role for biomarker measurement in the early diagnosis of RIHD has not been established.

Novel methods of cardiac imaging may allow detection of RT-induced heart disease earlier and with greater sensitivity. Using echocardiography with strain-rate imaging in BC patients, Erven and colleagues demonstrated significant changes in myocardial strain immediately post-RT in myocardial segments receiving >3 Gy [50]. In follow-up, these abnormalities remained at 14 months post-RT [47]. In another study, small but statistically significant changes were seen 4–6 weeks after RT in systolic and diastolic function by echocardiography as well as in the corrected QT interval on ECG in patients receiving RT for breast or lung cancer [51]. Similarly to biomarkers, the long-term clinical significance of these early changes is uncertain. Advanced im-

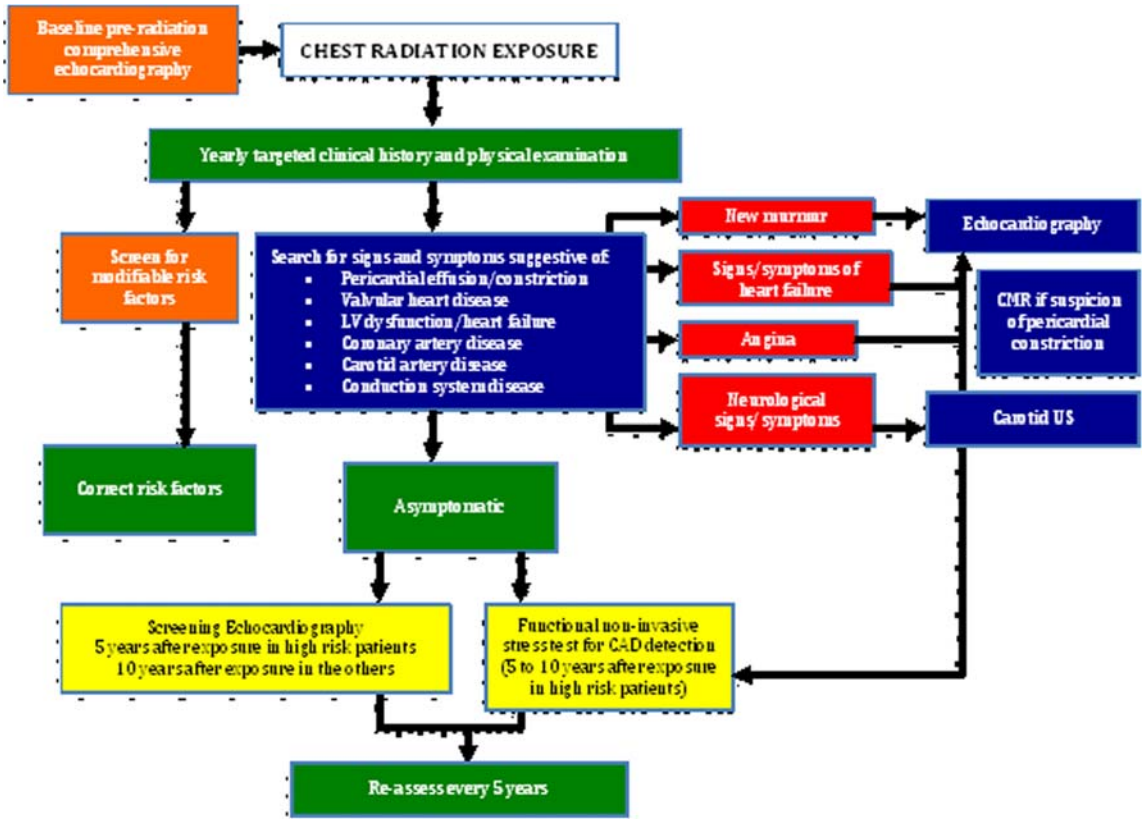

Fig. 1. Algorithm for patient management after chest radiotherapy. LV, left ventricle; US, ultrasound. High risk patients: anterior or left chest irradiation location, high cumulative dose of radiation (>30 Gy), younger patients (<50 years), high dose of radiation fractions (2 Gy/day), presence and extent of tumor in or next to heart, lack of shielding, concomitant chemotherapy, cardiovascular risk factors (diabetes, smoking, overweight, ≥ moderate hypertension, hypercholesterolemia), pre-existing cardiovascular disease. Adapted with permission from Journal of the American Society of Echocardiography, 26(9), Lancellotti et al., Expert Consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography, 1013–1032, Copyright 2013, with permission from Elsevier.

aging techniques may also be useful for detecting long-term sequelae. Cardiac computed tomography angiography (CCTA) has been used to screen for coronary artery disease following RT. In a study of 119 survivors of childhood HL, CAD was detected by CCTA in 16 % [52]. In a study of 31 20-year survivors of HL treated with anterior mediastinal RT between 1978 and 1985, cardiac abnormalities were present on MRI in approximately 70 % of survivors [53]. LV systolic dysfunction was identified in 23 % of survivors, hemodynamically significant valvular disease in 42 %, late myocardial enhancement in 29 %, and any perfusion deficit in 68 %.

Despite this remarkably high prevalence of disease, relatively few patients receive long-term follow-up and screening. In a survey of adult survivors of childhood HL in Norway, 96 % could correctly state whether they had received RT, chemotherapy, or both, but only 34 % were aware that their

treatment was associated with long-term health risks [54]. Fewer than 20 % were aware of late cardiac effects, and only 13 % had attended a follow-up clinic for the purpose of screening for late effects. The use of advanced imaging techniques requires further investigation before it can be recommended for screening in asymptomatic patients.

Management of RIHD

Prevention

Several studies have demonstrated that the risk of RIHD, particularly RT-induced CAD, increases in the presence of traditional risk factors and that the greatest risk of cardiac mortality in this population is the presence of pre-existing heart disease [11, 27, 28, 29•, 55]. High-risk patients should be identified prior to making treatment decisions, and management plans should take this elevated baseline risk into account. Cardiovascular risk factors should be aggressively controlled in patients who have undergone RT with cardiac irradiation. Specific chemopreventive agents for RIHD have not been identified. Thalidomide [56] and pentoxifylline [57] have not been effective at preventing RT-induced cardiac damage in animal models. This remains an area of active research.

Modern radiation techniques

In recognition of the late cardiac effects associated with RT, techniques were developed in the early- to mid-1980s to reduce the dose of radiation received by the heart. Deep inspiration breath hold (DIBH) [58–60], prone positioning [61], three-dimensional conformal radiotherapy (3D CRT) [60, 62], intensity modulated radiotherapy (IMRT) [63, 64], volumetric-modulated arc therapy (VMAT) [62], and proton therapy [62, 65] have been shown to reduce the cardiac dose during RT for BC, HL, and distal esophageal cancer. Many of these methods are designed to minimize the volume of heart falling within the radiation field; others, such as IMRT, expose a larger heart volume to a lower peak radiation dose [66].

There are limitations to cardiac dose estimation during treatment planning. In one study, Goody et al. demonstrated that unintended cardiac irradiation was a common occurrence in patients receiving RT for left-sided BC [67]. Among patients who had no heart included in their planned radiation fields, 49 % had heart present in the actual treatment field detected by electronic portal imaging at RT delivery. Several authors have suggested that the LAD rather than the heart should be considered the organ at risk, and that evaluating the dose to the LAD may alter treatment plans [68, 69]. In a study by Vennarini and colleagues, however, the LAD could be identified in only one-third of CT slices that included the heart, and the addition of IV contrast did not improve the ability of radiologists and radiation oncologists to identify the vessel prior to RT [70]. This issue may be resolved using cardiac-gated CT during RT planning [69]. It remains uncertain whether modern RT techniques will reduce the incidence of late cardiac damage to the degree that is currently suggested [66].

Historical RT regimens employing larger fraction sizes for early-stage BC have been associated with increased risk of cardiac mortality [71]. Recently, studies of more moderately hypofractionated regimens have not found cardiac mortality in excess of that seen in standard regimens [72, 73]. A recent study by Appelt and colleagues demonstrated that moderately hypofractionated radiation schedules resulted in a lower mean fraction size-corrected heart dose than normofractionated schedules, suggesting cardioprotection with these regimens [74]. The benefits of hypofractionated RT remain controversial.

Management of established RIHD

General principles of treatment for RIHD do not differ significantly from those in patients with non-RT-associated heart disease. The management of these patients, however, is often complicated by the surgical risks associated with RT-induced damage to surrounding tissues.

Patients with symptomatic bradyarrhythmias or high-grade conduction blocks should receive pacemakers as per current guidelines [75]. Implantable defibrillators may be indicated in patients with ventricular arrhythmias or aborted sudden cardiac death.

In patients with RT-associated CAD, percutaneous coronary intervention (PCI) may be preferable to coronary artery bypass surgery (CABG) for several reasons. In general, RT-induced fibrosis of surrounding tissues makes surgical procedures more difficult [12], and inclusion of internal mammary arteries in the radiation field often results in stenosis [76], rendering them unsuitable for revascularization. Furthermore, patients with RIHD often have RT-induced lung disease as well, increasing the risk of perioperative pulmonary complications [77]. In patients who are not candidates for percutaneous revascularization and in whom the potential benefits of CABG outweigh the risks, a careful evaluation for concomitant valve disease is recommended prior to surgery, and moderate-or-greater valve disease should be repaired or replaced at the time of CABG to prevent the need for repeated surgery [78]. In one analysis, prior RT was the single greatest risk factor for mortality following redo sternotomy [79]. Variable results have been reported in patients undergoing coronary artery bypass surgery after thoracic RT, which may be dependent upon the degree of damage to the internal mammary arteries [80–84]. A major limitation of these studies, as well as studies of cardiac surgery after radiation in general has been small sample size, with typically fewer than 20 and often fewer than 10 patients in each series. A notable example is the recent single-center cohort study by Wu and colleagues that demonstrated increased short- and long-term mortality in patients with radiation-induced heart disease undergoing a variety of cardiac surgeries [85•]. During a mean follow-up of 7.6 years, the mortality of RT patients undergoing isolated CABG surgery was 46 %, while the mortality in a non-RT comparison group was 28 %.

It is unclear whether outcomes in patients with CAD amenable to PCI differ from those in patients with typical atherosclerotic CAD. Increased rates of restenosis after PCI with bare metal stents in patients with RT-associated CAD were reported in two early studies, but these studies had a combined sample size of only 16 patients [15, 86]. Another small study of CV outcomes

following PCI (in which ~20 % of subjects received drug-eluting stents) did not detect any difference in target-vessel revascularization between patients with prior thoracic radiation and controls [87].

RT-associated valve disease presents management problems similar to those encountered in RT-associated CAD. Surgical morbidity and mortality are greater in patients with prior chest RT. In the study by Wu et al., post-RT patients undergoing 1-valve or ≥2-valve surgery had long-term mortality rates of 45 % and 61 %, respectively [85•]. Corresponding mortality rates for patients in the comparison group (no prior RT), with similar EuroSCORE-predicted mortality rates, were only 13 % and 17 %. High failure rates of repaired mitral and tricuspid valves have been reported in patients with RIHD, attributed to ongoing post-RT pathologic changes after valve repair [24]. Therefore, the benefits of repair over replacement that are generally accepted in the non-RT population may not translate to the RIHD population, and valve replacement may be preferable to repair. Transcatheter aortic valve replacement (TAVR) has been an important advancement in the care of patients with aortic stenosis (AS) [88, 89] and has been used successfully in patients with RT-associated AS [90]. A significant limitation of this technique is the exclusion of patients with non-calcified valves from randomized controlled trials [89]. As calcification is a late finding in RT-associated valve disease, TAVR may not always be feasible in this population.

RT-associated acute pericarditis should be managed symptomatically. Non-steroidal anti-inflammatory agents are first-line therapy. Pericardiocentesis may be indicated for large pericardial effusions, and it is always indicated when effusions are hemodynamically significant. Pericardial fluid should be evaluated to distinguish RT-associated effusions from other etiologies common in this population such as infection, hypothyroidism, and malignant effusion. Constrictive pericarditis (CP) is a marker of more extensive radiation injury and predicts mortality in patients with prior RT [91]. Pericardiectomy is an effective treatment for selected patients with CP, but is associated with high morbidity and mortality in patients with RIHD. In a review of 135 patients undergoing pericardiectomy at the Mayo Clinic, prior RT was the single greatest predictor of overall mortality (HR 5.13), late mortality (HR 11.80), late cardiovascular death (HR 20.74), and late NYHA III–IV heart failure (HR 9.47) [92]. Overall, freedom from any cardiovascular event at five years was observed in only 12 % of patients with RIHD undergoing pericardiectomy. As such, this procedure should be considered only under exceptional circumstances in patients with RIHD.

Heart transplantation (HT) may be an option for highly selected patients with end-stage heart failure resulting from RIHD. In a report from the Mayo Clinic, excellent intermediate-term outcomes were reported in a small series of patients who had undergone HT following RT for lymphoma. No graft failures or recurrent malignancies were reported [93]. In contrast, an analysis of data from the United Network of Organ Sharing (UNOS) found that patients undergoing HT for RIHD had an unadjusted hazard ratio of 1.81 for all-cause mortality when compared to patients undergoing HT for other etiologies of restrictive cardiomyopathy [94]. While prior radiation was certainly a contributing cause to excess post-transplant mortality, it should be noted that a larger proportion of patients in the RT cohort had previously undergone cardiac surgery, an established risk factor for adverse post-trans-

plant outcomes [95]. The excess risks associated with prior sternotomy and other comorbidities should be strongly considered when evaluating patients with RIHD for transplantation.

Conclusions

As the survival rates of common malignancies improve, RIHD is becoming increasingly common. Population-based cohort studies have clearly demonstrated elevated risk of cardiac death and symptomatic cardiovascular disease among cancer survivors who have received RT, but the true incidence of asymptomatic disease remains unknown. Screening studies have suggested that the incidence is far higher than has been generally recognized. RT techniques have evolved over the past 30 years, and the long-term effects of current regimens will not be understood for decades to come. The elevated risk of cardiovascular morbidity and mortality in this population warrants improved long-term follow-up programs, with appropriate screening for late effects. Patients at risk for RIHD should have traditional cardiovascular risk factors aggressively treated. Surgical risk is greater in patients with symptomatic RIHD as a result of RT-induced damage to surrounding tissues, and medical or percutaneous therapies should be considered as part of a multidisciplinary approach in these complex patients. In patients undergoing surgical management of RIHD, efforts should be made to avoid repeat sternotomies, although thoracotomy approaches may be feasible in selected patients requiring reoperation.

Compliance with Ethics Guidelines

Conflict of Interest
Dr. Margot Davis and Dr. Ronald M. Witteles each declare no potential conflict 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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