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Chapter 14: Radiation-Induced Heart Disease: Long-Term Manifestations, Diagnosis, and Management.

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ISBN

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Publication Date

2017-11-01

Peer reviewed

CHAPTER 14

Radiation-Induced Heart Disease

Long-Term Manifestations, Diagnosis, and Management

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INTRODUCTION

Radiation therapy (RT) is an important cause of cardiovascular disease in patients treated for cancer, especially in those receiving chest radiotherapy for Hodgkin disease or breast cancer (Table 14.1) as well as after total body irradiation for bone marrow transplantation.[1] Factors that influence the development of cardiotoxicity include the total radiation dose and the dose fractionation. Radiation damage may involve the pericardium, myocardium, valves, coronary arteries, and the conduction system (Box 14.1, Fig. 14.1).[2,3] Injury to the endothelial cells in these compartments, inflammation, and fibrosis are key elements. Diagnosis and treatment do not differ from conventional heart disease; however, screening for radiation-induced heart disease (RIHD) should be pursued even in asymptomatic patients in an effort to ameliorate at least some of the disease manifestations.

RT is commonly used as an adjuvant treatment modality in patients with breast cancer (nearly 40% in the Surveillance Epidemiology, and End Results registry).[4] Randomized trials and meta-analyses confirm that radiation exposure, especially of the left chest, is associated with an increased cardiovascular mortality, attributed mainly to ischemic heart disease and acute myocardial infarction.[4–6]

In patients who received mediastinal RT for Hodgkin disease, cardiovascular mortality becomes a leading cause of death over time.[7,8] Extending prior studies,[9–11] the most recent and comprehensive analysis of more than 2500 patients who underwent mediastinal RT between 1965 and 1995 and had survived more than 5 years reported a cumulative incidence of any cardiovascular disease of 54.6% after 40 years.[12]

Mediastinal RT increased the hazard for any type of cardiovascular disease by a factor of 3.6 (95% confidence interval [CI] 2.8–4.6). The highest risk was found for valvular heart disease (hazard ratio [HR] 6.6, 95% CI 4.0–10.8), followed by an equivalent risk of coronary heart disease or CHF. At 20 years out from RT, childhood cancer survivors develop clinically relevant valvular heart disease at a cumulative incidence rate of 6% versus 3% for other RIHD manifestations (Fig. 14.2).

There is little discussion in the literature on the impact of radiation from diagnostic imaging studies on the heart.[13,14] However, doses of RT are frequently greater than 10 Gy, compared with the radiation dose of a computed tomography (CT) scan of around 0.01 Gy. Therefore, it is unlikely that the radiation from diagnostic CT is cardiotoxic.

RELATION OF RADIATION FIELD, DOSE, AND FRACTIONATION TO RADIATION-INDUCED HEART DISEASE

Both the cumulative radiation dose and the dose fractionation (the division of the total dose into smaller fractions separated by time) are factors in the development of radiation cardiotoxicity. In animal studies, single (unfractionated) radiograph doses of 35 to 40 Gy caused severe heart failure (HF) after several months, whereas 10 to 15 Gy caused only minor HF after 1 year.[15] Cardiotoxicity likely develops with single doses of less than 10 Gy, whereas cumulative doses of 50 to 70 Gy (in fractions of 2, 3, or 4 Gy) cause myocardial

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TABLE 14.1
Malignancies whose treatment may include radiation therapy at the outlined doses and generation of a radiation risk to the heart

Malignancy	Dose (Gy)
Hodgkin lymphoma	30–36
Breast cancer	45–50
Gastric carcinoma	45–50
Esophageal carcinoma	45–50
Lung cancer	50–60
Thymoma	60

cytolysis.[16] Pericardial fibrosis and HF occurred earlier when larger fractions were used. In a human autopsy study, significant myocardial fibrosis was observed only in patients that received greater than 30 Gy.[3] This being said, in recent years there has been a shift from an exponential model with a "safe" threshold value for radiation dose to a more linear model.

BREAST CANCER

The radiation dose that the heart receives varies depending on the type and location of tumor being treated. As described above, there is a higher risk for cardiac disease after RT for cancer of the left breast when compared with irradiation of the right breast.[4] This finding is not surprising given the radiation dose the heart receives for

BOX 14.1
Cardiac disease associated with radiation exposure

Pericardial disease
   Pericardial effusion
   Acute pericarditis
   Constrictive pericarditis
Cardiomyopathy
Vascular disease
   Coronary artery disease
Microvascular coronary disease
Carotid artery disease
Valvular disease
Conduction abnormalities
   Bundle branch blocks
   Atrioventricular block

left-sided tumors is more than double that received for right-sided tumors.[17] With irradiation of the left breast, the left anterior descending artery (LAD) is the structure that receives the highest radiation dose.

Changes to contemporary RT regimens for breast cancer have improved cardiac outcomes. Tangential radiation fields rather than anterior fields result in lower cardiac doses,[18] and CT radiation planning can exclude the heart from the treatment field.[19] These changes have produced a steady decline in the laterality of coronary artery disease (CAD) observed with left-sided versus right-sided irradiation since 1979, and laterality was no more seen in a modern cohort study.[20,21] Although early randomized controlled trials of RT for breast cancer found a higher risk of ischemic heart disease in the RT than in the surgery-only arm, the Danish Breast Cancer Cooperative Group 82b and 82c trials randomized patients to surgery with or without RT and found no increased risk of ischemic heart disease.[18,21–23] In these trials, cardiac radiation protection blocks, lower volume of heart irradiated, and RT treatment planning using ultrasound measurement of chest wall thickness were contributing factors to reduced cardiotoxicity. However, a more recent retrospective analysis of women who underwent RT for breast cancer in Sweden and Denmark between 1958 and 2001 revealed a linear relationship between major coronary events and radiation dose (7.4% risk increase per gray) with no obvious threshold. This increase started within the first 5 years after radiotherapy and continued into the third decade. In addition, patients with pre-existing cardiovascular risk factors had a greater absolute risk of death from ischemic heart disease and/or coronary events compared with patients who did not have risk factors.[24] Avoidance of internal mammary lymph node irradiation reduces cardiac radiation dose; however, recent trials of internal mammary node irradiation for breast cancer have shown benefits in terms of disease-free survival.[25,26] At a follow-up time of 10 years, there were no significant increases in cardiac disease; however, longer-term follow-up of these patients is warranted.

HODGKIN DISEASE

Historically, mantle field irradiation (lymph nodes in the neck, mediastinum, and axillae) with 35 to 45 Gy was used for Hodgkin disease (HD).[27] The whole heart receives a dose of 27.5 Gy with mantle field RT, and some parts receive greater than 35 Gy.[28,29] Most cardiovascular deaths in patients
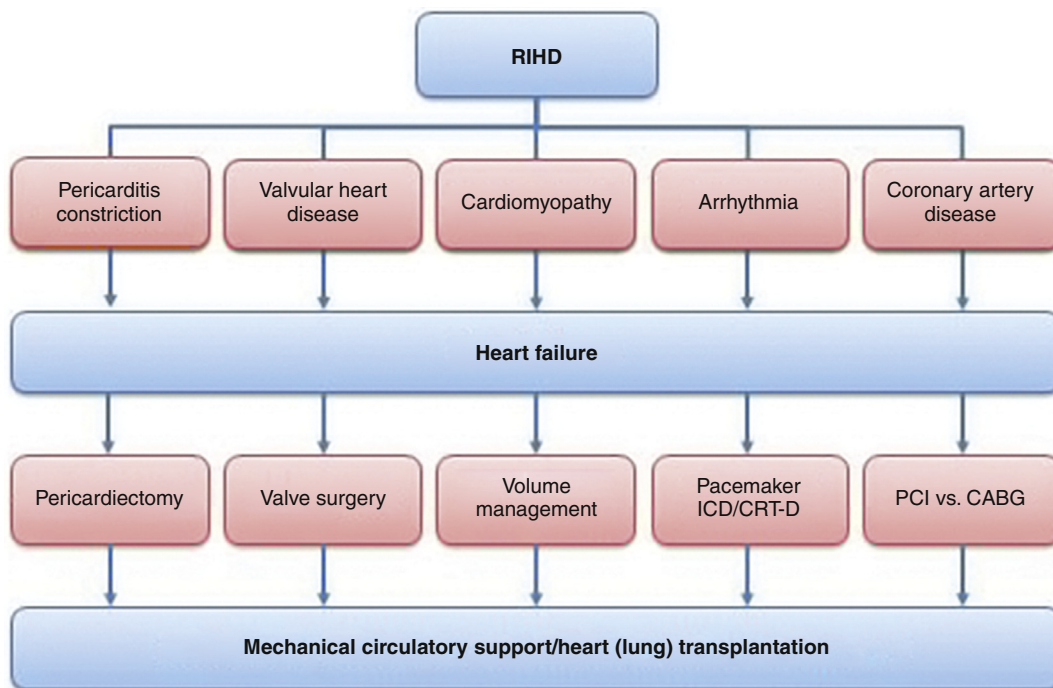
Fig. 14.1 The spectrum of RIHD, common final pathway of presentation with HF, and treatment modalities directed toward the disease aspects. ICD, implantable cardioverter defibrillator.
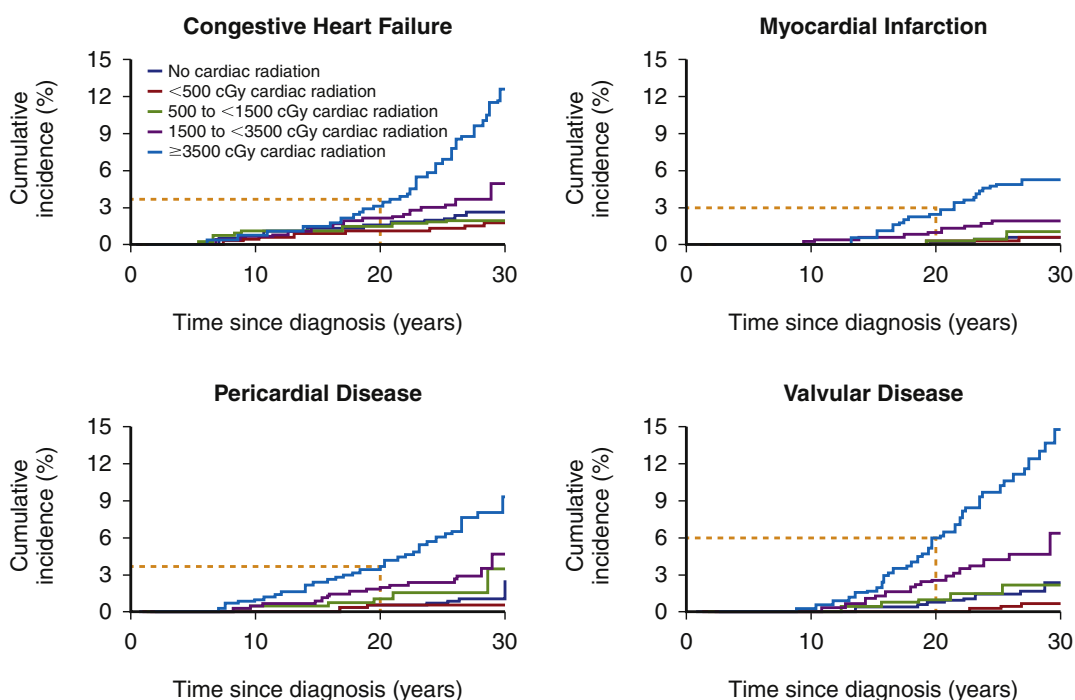

Fig. 14.2 Cumulative incidences of the various aspects of RIHD in childhood cancer survivors. Notice the dose dependency and the timeline of 15 years from diagnosis for clinical appearance. (*From* Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606; with permission.)

with heart disease occur in those that received greater than 30 Gy.[7] Acute pericardial effusion following RT occurred in patients who received an average pericardial dose of 53.25 Gy.[30] A dose of 2.8 Gy was the lowest dose that has been shown to increase the rate of CAD.[31]

RT for HD has been refined since the 1970s. Radiation protection blocks covering the left ventricle limit the total cardiac dose to 15 Gy, and modern-era regimens have used a reduced fraction size.[7,32,33] With these interventions, the relative risk for non-acute myocardial infarction-related cardiac death was reduced from 5.3 to 1.4. Involved-node RT and involved-field RT include the involved nodes and their surrounding regions, respectively.[27,28] These regimens have resulted in further reductions in cardiac radiation dose when compared with extended-field (mantle) radiation.

DOSE FRACTIONATION

Fractionation of total radiation dose is another factor in the development of RIHD, and it is thought that risk of RIHD is higher with a lower number of fractions.[31–34] Indeed, twice weekly fractionation compared with 5 times weekly increases the risk of complications in noncardiac tissues such as pulmonary fibrosis and pathologic fractures.[35,36] Dose plan analysis of hypofractionated RT (larger dose fractions given in fewer treatments) furthermore confirms a lower cardiac radiation dose compared with normofractionated RT.[35] However, hypofractionated RT of 42.5 Gy in 16 fractions versus 50 Gy in 25 fractions, which is commonly used for breast cancer, resulted in no differences in cardiovascular mortality after 10 years.[37,38] Thus, the value of this strategy has yet to be fully defined.

PATHOPHYSIOLOGY OF RADIATION-INDUCED HEART DISEASE

Human autopsy studies have characterized the pathologic findings of RIHD, and pathophysiologic concepts have been described (Fig. 14.3).[2,3] It is unlikely that age-related CAD or degenerative changes are responsible for the
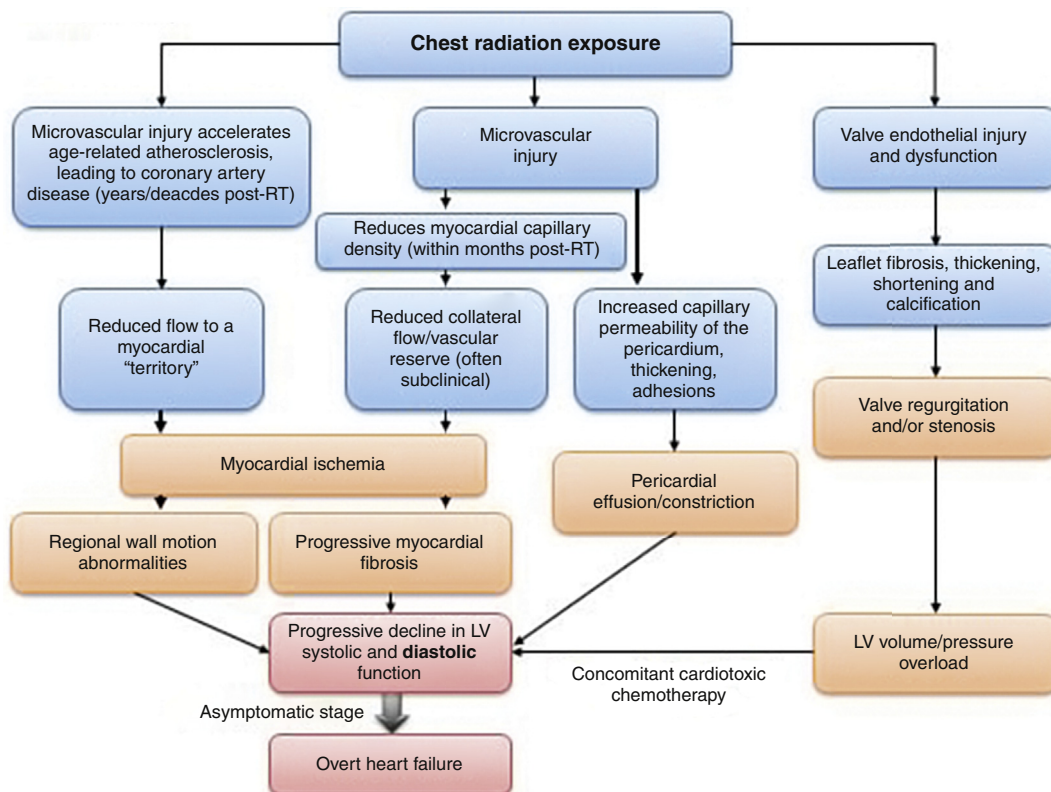

Fig. 14.3 Outline of the pathophysiology of RIHD. (*From* Lancellotti P, Nkomo VT, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2013;14(8):723; with permission.)

lesions observed given the young age of many of these patients. Pericardial disease was the most common finding, with 70% to 100% of patients having an abnormal pericardium. Some of the lesions observed include constrictive pericarditis, fibrinous pericardial adhesions, and pericardial fibrosis. Pericardial effusions and thickening with fibrous tissue were seen in most patients. Diffuse fibrosis and calcification were found in each of the 4 valves, and some surgically removed specimens were severely fibrosed and stenotic. Myocardial interstitial fibrosis was also found in most patients, although necrosis of myocardial cells was not observed. Up to a third of autopsies revealed severe CAD (>75% stenosis) attributable to radiation. Although conventional atherosclerosis was often present, fibrous tissue was a dominating feature in essentially all 3 layers of the arterial wall.

Fibrosis becomes the dominant pathologic feature 1 year after radiation, whereas inflammation is the dominant finding early on.[15,16,39] This also has been attributed to injury of the endothelial layer with subsequent activation and release of cytokines as well as loosening of tight junction and increased permeability. This process is pertinent to the process of acute and constrictive pericarditis but also affects the valves and the capillaries in the myocardium. Cytokines such as tumor necrosis factor-α and transforming growth factor-β have been implicated in increased type I and III collagen deposition and thus fibrosis.[40–43]

However, because interstitial fibrosis is often perivascular, some investigators have hypothesized that tissue hypoxia from capillary damage may be the primary insult causing radiation-induced tissue fibrosis.[15,16,37,42–45] Endothelial damage exposes von Willebrand factor, which stimulates thrombus formation and can occlude myocardial capillaries.[46,47] The theory that ischemia is a key factor in RIHD is supported by the observation that histopathological changes are most evident in the subendocardium. However, direct radiation injury appears to affect the intercalated discs and mitochondria of myocytes.[48–52] Reactive oxygen species are produced by inhibition of mitochondrial respiration, which is associated with radiation-induced myocardial dysfunction.[41,48–54] The renin-angiotensin-aldosterone system is also activated by this oxidative stress, and angiotensin II is another profibrotic mediator.[55,56] In addition, studies have suggested that angiotensin-receptor blockers and angiotensin-converting enzyme (ACE) inhibitors can potentially inhibit the development of radiation-induced fibrosis.[55–59] Finally, there is also the potential for direct injury of the cardiomyocytes (myocytolysis).[16]

Radiation exposure accelerates atherosclerosis by causing direct endothelial injury. Intimal cholesterol plaques may occur rapidly when lysosomal enzymes are activated and endothelial permeability is increased following coronary irradiation.[60–65] Furthermore, there is endothelial activation with expression of adhesion molecules and release of von Willebrand factor.[46,66–69] These processes favor inflammation, plaque progression, and vulnerability as well as thrombosis.[70,71] A unique observation is the presence of fibrotic changes of all 3 layers of the epicardial coronary arteries.[2,3] However, changes of the microvasculature are also observed after chest irradiation.[72,73]

Structural alterations of the valves seem to be stimulated by conversion of interstitial cells into an osteoblast-like cell.[74,75] In addition, multiple osteogenic proteins, including osteopontin and bone morphogenetic protein 2, are upregulated and likely play a role in the development of calcific aortic stenosis following cardiac irradiation.

PERICARDIAL DISEASE

Radiation-induced pericardial disease ranges from acute pericarditis and pericardial effusions to constrictive pericarditis. Historically, with older, more radiation-intense protocols, pericardial disease was one of the most frequent cardiac complications of RT.[76,77] Pericardial effusions with cardiac tamponade were among the first case reports of RIHD following thoracic radiation. Acute pericarditis presenting with chest pain and friction rubs was also reported.[77,78] Management of these cases does not differ from management of acute pericarditis and includes nonsteroidal anti-inflammatory drugs.

Although pericardial disease-related sequelae is less frequently encountered nowadays due to changes in radiation exposure and techniques, patients may also develop chronic pericardial effusions and/or constrictive pericarditis due to evolving adhesions and fibrosis anywhere from 1 to 20 years following irradiation.[3,77–85] Patients may complain of shortness of breath, increased girth size, lower extremity swelling, and lightheadedness to the point of presyncope and syncope. The physical examination findings include jugular venous distention, Kussmaul sign, ascites, and peripheral edema. Electrocardiogram findings are nonspecific but include low-voltage and T-wave changes. Although echocardiography, CT, or MRI scans may reveal pericardial thickening, these findings can be nonspecific, and cardiac catheterization to evaluate for ventricular discordance and interdependence may aid in the diagnosis.[86]

Pericardiocentesis is sometimes needed for large effusions and pericardial stripping (pericardectomy) for hemodynamically and clinically relevant constriction.[77,86,87] Mortality following pericardial stripping is significantly higher in radiation-induced constrictive pericarditis compared with pericardiectomy performed for other causes (5-year mortality 89.0% vs 35.7%, *P*<.001; **Fig. 14.4**).[86,87] The likely reason for higher mortality rates in this population is due to more extensive pericardial and mediastinal fibrosis as well as fibrosis of the myocardium, and concomitant valvular and ischemic heart disease. Once diagnosed, pericardiectomy should be done sooner rather than later but may only expose the presence of restrictive cardiomyopathy.[86] A thorough preoperative evaluation is therefore needed to determine the value of surgery as is experience with managing these cases in general for best overall outcomes.

CARDIOMYOPATHY

The clinical presentation of radiation-induced myocardial disease is similar to HF of other causes.[88] MRI may show diffuse and patchy fibrosis that does not correspond to a coronary artery perfusion territory. Left ventricular ejection fraction (LVEF), on average, may still be within the normal range but lower than expected in comparison with healthy controls (62%, *P*<.05).[89] The impairment in cardiac function can be more profoundly impaired in patients who also received anthracycline treatment, even when there is temporal separation between these treatment modalities (**Fig. 14.5**).[90–92] The most distinctive feature is the development of restrictive cardiomyopathy as a consequence of endocardial and myocardial fibrosis.[93,94]

As with HF not caused by radiation exposure, ACE inhibitors and β-blockers are the mainstays of therapy.[95] Orthotopic heart transplantation (OHT) is the last resort in cases that are refractory to medical therapy. It may also be preferred to pericardiectomy given the technical difficulties of pericardial stripping in the presence of severe mediastinal fibrosis.[96,97] OHT may also be the only remaining option in the case of diffuse CAD not amendable to coronary artery bypass surgery (CABG), which can similarly be challenged in its technical aspects by mediastinal fibrosis. In the RIHD population, OHT may also carry a significant perioperative risk, although at least one center has reported excellent short- and intermediate-term results in a small cohort of patients.[96,97] Patients should be carefully selected for OHT given the significant perioperative risk.

VALVULAR DISEASE

Most patients develop clinically relevant valvular disease 20 years or more after mediastinal radiation (on average 22 years to symptom development).[98] A cardiac radiation dose of greater than 25 Gy carries the highest risk for radiation-induced valvular disease,[99–102] and in general, the aortic and mitral valves are the most commonly affected valves. Regurgitation is more common than stenosis (aortic regurgitation in 60%, mitral regurgitation in 52%, and aortic stenosis in 16% in one series).[3,11,98,103,104]

Surgical management is the standard of care for radiation-induced valvular disease.[103] The 30-day mortality after valvular surgery for radiation-induced valvular disease (including aortic, mitral, and tricuspid valves) is 12%, whereas the 5-year survival is 66%.[105,106] Constrictive pericarditis significantly raises the 30-day mortality to 40%.[102,105–107] It might be because of a direct role, or more likely, constrictive pericarditis serves as an indicator of higher
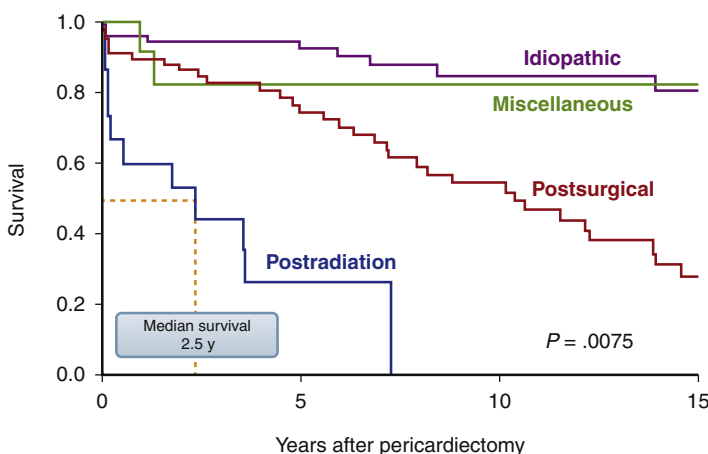

Fig. 14.4 Survival after pericardiectomy by type of pericardial disease. (*Adapted from* Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. J Am Coll Cardiol 2004;43(8):1448; with permission.)
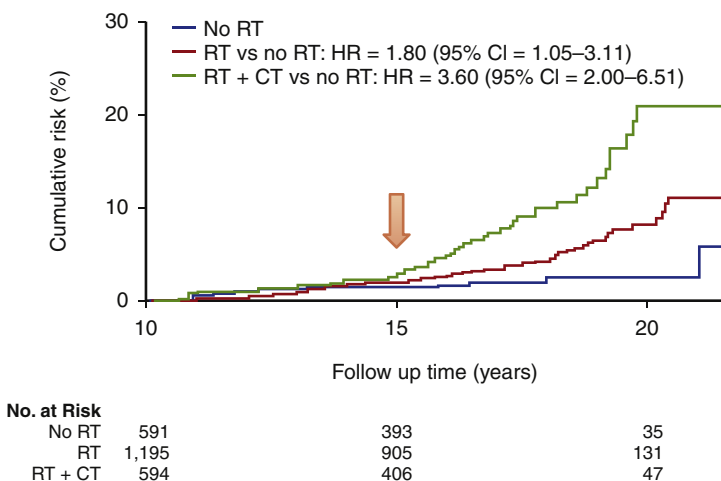
Fig. 14.5 Cumulative incidences of HF in patients with breast cancer. Notice the more than synergistic impact of chemotherapy (mainly anthracyclines) and the emergence of differences after 15 years. (*From* Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;99(5):370; with permission.)

radiation dose exposure and greater burden of cardiac and mediastinal disease. In patients with advanced aortic stenosis who are poor surgical candidates due to comorbidities such as radiation pulmonary fibrosis and severe aortic calcifications (ie, porcelain aorta), transcatheter aortic valve replacement (TAVR) may be a less invasive option.[108] Intervention for radiation-induced valvular disease should be individually tailored to the valve involved and the patient's other comorbidities.

CORONARY ARTERY DISEASE

Irradiation of the coronary arteries rapidly accelerates atherosclerosis. CAD is the most common clinically significant manifestation of RIHD, with acute myocardial infarctions occurring even in young patients without traditional cardiac risk factors (see Fig. 14.3).[11,77,109] The distribution of CAD reflects the radiation field.[110] Accordingly, the mid to distal segments of the LAD are the most likely areas to be involved with left-breast irradiation.[111] On the contrary, ostial right and left main lesions have classically been reported with mediastinal, mantle, or involved field radiation. A third of patients screened with coronary angiography will also have 2- or 3-vessel disease with stenoses 70% or greater.[112–114] Concerns for aggravation of in-stent restenoses after thoracic radiotherapy have been raised but not always confirmed.[115–117]

Radiation-induced CAD typically presents clinically with angina or myocardial infarction, just like conventional CAD.[113,118] The diagnostic workup is in keeping with published guidelines, and coronary angiography remains the reference standard.[109,113] Consideration has to be given to

the presence of microvascular disease, ideally assessed by regional myocardial perfusion imaging with PET or invasive measures of coronary flow reserve and vasoreactivity. Under these circumstances, technetium-99m tetrofosmin perfusion may show reversible perfusion defects that do not correspond to coronary artery distribution territories but microvascular dysfunction.[119,120] Stress echocardiography is generally not as sensitive but more specific for regional perfusion defects, which may not be present with microvascular disease. Computed tomography angiography (CTA) with or without coronary artery calcium (CAC) scoring is an alternative imaging technique. The prevalence of coronary calcium in patients who received RT for Hodgkin disease is overall higher, and the overall plaque burden is more quantifiable; however, no systematic studies have yet been performed.[121–123] In one of the most comprehensive studies thus far, conventional functional stress testing underestimated the burden of CAD in these patients (Fig. 14.6).

Guidelines for management of stable CAD and acute coronary syndromes do not specifically address RIHD; however, it is reasonable to follow the existing recommendations for conventional CAD.[124,125] Either percutaneous coronary intervention (PCI) or CABG may be considered for complex, multivessel CAD, although if valve surgery or pericardiectomy is needed, then CABG may be done concurrently to avoid reoperation.[126,127] The internal mammary artery (IMA) is in the radiation field of some RT regimens, and there have been concerns that it may be potentially a dysfunctional conduit.[128] The IMA, however, was found to be free of radiation-induced injury in one study of

Duke Treadmill Score

Stress Echocardiography
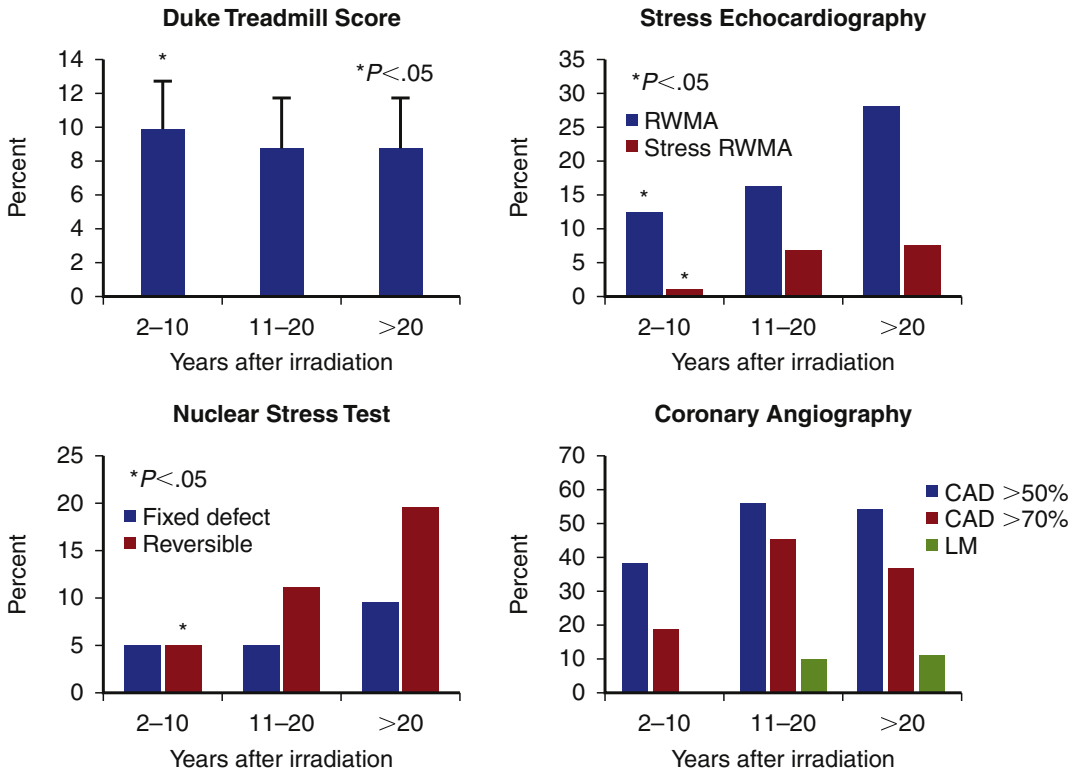
Nuclear Stress Test

Coronary Angiography

Fig. 14.6 Prevalence of stress test and coronary angiography findings in patients who received mediastinal RT (≥35 Gy) for Hodgkin lymphoma. LM, left main coronary artery; RWMA, regional wall motion abnormalities. (*Data from* Heidenreich PA, Schnittger I, Strauss W, et al. Screening for coronary artery disease after mediastinal irradiation. J Clin Oncol 2007;25:43–9.)

125 patients who had received thoracic RT[129]; thus, no definitive conclusions can be made about IMA graft patency in the setting of mediastinal radiation. It may, however, be prudent to perform angiography on any potential mammary grafts to exclude pre-existing disease before surgery. In general, PCI and CABG are both reasonable options for the management of severe radiation-induced CAD, but the final decision is case based.[130,131]

NONCORONARY ATHEROSCLEROTIC DISEASE

In addition to CAD, atherosclerosis affects the carotid and subclavian arteries following thoracic radiation as well.[11] Stenosis of 40% or greater of the carotid or subclavian artery was observed in 7.4% of patients with prior RT for Hodgkin disease at a median of 17 years after treatment. The median age of patients at the time of radiotherapy was 34 years, and the median time from treatment to diagnosis of carotid or subclavian arterial disease was 17 years. Patients who developed subclavian stenosis were exposed to a higher

median low-cervical radiation dose than those who did not (44 vs 36 Gy, P = .002).

RT for head and neck tumors also increases the risk of carotid artery stenosis. Patients who had received a mean radiation dose of 56.4 Gy to the neck for nasopharyngeal carcinoma had a prevalence of carotid stenosis of 79% compared with 21% in controls.[132] Ten years after RT to the neck, the relative risk of stroke was 10.1 (95% CI 4.4–20.0).

Carotid endarterectomy and carotid artery stenting are options for severe carotid artery stenosis, and stenting of the subclavian artery or bypass subclavian artery bypass grafting are options for subclavian artery stenosis.

ELECTROPHYSIOLOGIC ABNORMALITIES

Cardiac irradiation may cause damage to the conduction system, such as atrioventricular (AV) block and bundle branch blocks.[98,133] Although most patients are asymptomatic, the most common clinical presentation reported in the literature is syncope. In one study of patients who presented with complete heart block, the average latency

period from irradiation to clinical presentation was 12 years. Ostial stenosis of the right coronary artery (RCA) from radiation exposure has been reported to cause AV block from exercise-induced AV nodal ischemia.[134,135] Radiation-induced fibrosis may also disrupt the conduction system.[136,137] Calcifications of the mitral-aortic junction are a peculiar sign to note on imaging studies as associated with complete heart block in these patients (Fig. 14.7). Patients with high-degree AV blocks may require pacemakers.[133,134] Treatment with anthracyclines in addition to RT may increase the risk of developing supraventricular tachycardia and ventricular tachycardia.[138]

AUTONOMIC DYSFUNCTION

Patients treated with thoracic RT may also develop autonomic dysfunction, likely due to the disruption in the parasympathetic and sympathetic regulatory mechanisms. In fact, in Hodgkin lymphoma survivors after mediastinal RT, autonomic dysfunction ranks second after electrocardiogram (ECG) abnormalities as one of the most common abnormalities (Fig. 14.8). A more recent retrospective study of 263 patients with Hodgkin lymphoma evaluated the resting heart rates and heart rate recovery before and during exercise treadmill testing. Compared with control patients, patients that had received RT a median of 19 years prior (median radiation dose 38 Gy) had an elevated resting heart rate.[139] In addition, after 1 minute of recovery from Bruce protocol, a significantly greater percentage of RT patients had an abnormal heart rate recovery (31.9% vs 9.3%, P<.0001). An abnormal heart rate recovery was associated with higher all-cause mortality (HR 4.6, 95% CI 1.6–13.0), as has previously been described in patients without radiation history or known heart disease.[140] The authors of this study hypothesized that radiation injury to the autonomic nervous system is disruptive of the sympathovagal balance.

SCREENING AND PREVENTION

Although modern RT has become more sophisticated and results in lower radiation doses, patients are also living longer after treatment of cancer, increasing the likelihood of developing clinically significant RIHD. Prevention of radiation exposure by excluding the heart from the radiation field with radiation planning or use of radiation protection blocks (shielding) is the primary method of preventing RIHD.

There is a dearth of literature regarding prevention of RIHD during or after radiation exposure. Animal studies have demonstrated a cardioprotective effect of ACE inhibitors and angiotensin-receptor blockers after irradiation,
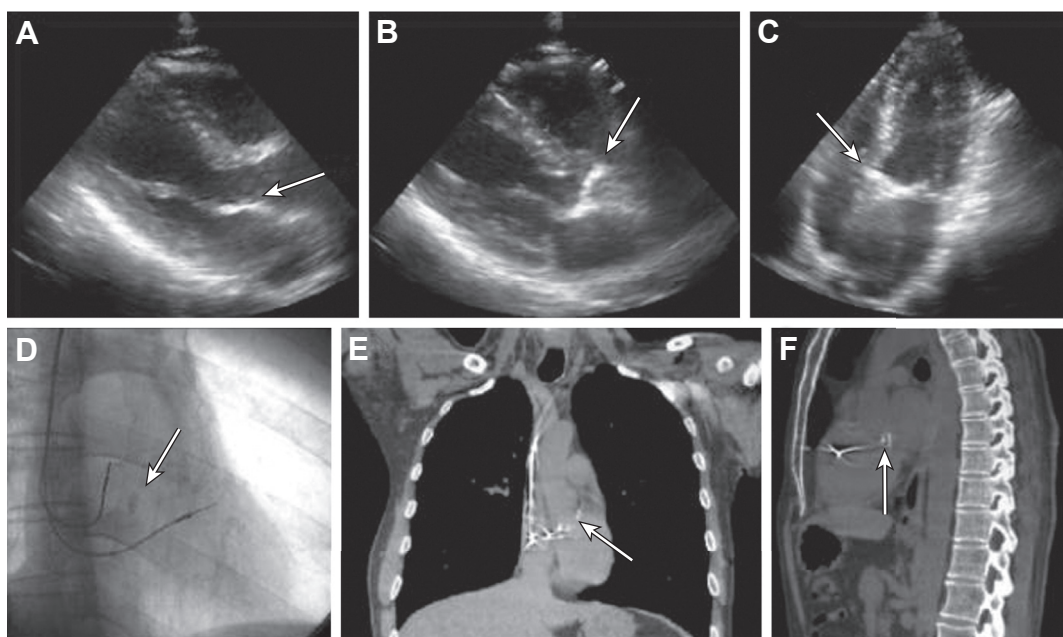

Fig. 14.7 Calcification of mitral-aortic junction. (*From* Santoro F, Ieva R, Lupo P, et al. Late calcification of the mitral-aortic junction (*arrows*) causing transient complete atrio-ventricular block after mediastinal radiation of Hodgkin lymphoma: multimodal visualization. Int J Cardiol 2012;155:e50; with permission.)
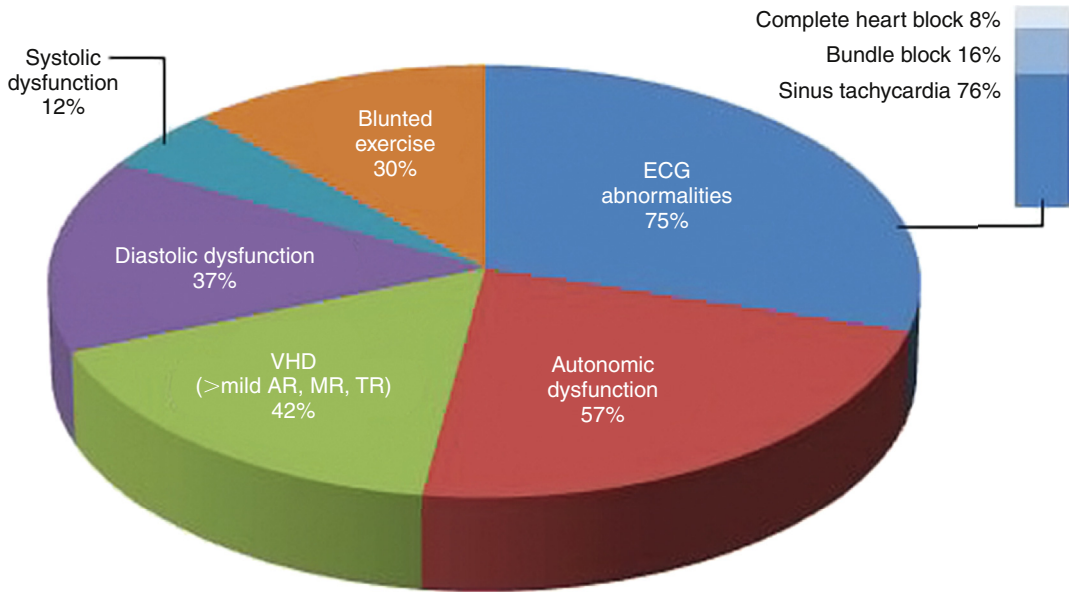
Fig. 14.8 Prevalence of abnormalities and cardiac disease on average 14 years (range 6–27.5 years) after diagnosis in survivors of Hodgkin lymphoma who underwent mediastinal radiation. AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; VHD, valvular heart disease. (*Data from* Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004;22(15):3139–48.)

and patients who are on ACE-inhibitors are at lower risk of radiation pneumonitis.[141–144] HMG-CoA reductase inhibitors (statin drugs) also decrease the degree of cardiac fibrosis due to radiation exposure.[145] Statin therapy should be considered in patients undergoing thoracic RT. Similarly, if patients undergoing RT require antihypertensive treatment, ACE inhibitors or angiotensin receptor blockers (ARBs) should be considered the initial agents. Prospective studies in humans though are needed to confirm the benefits of statins and ACE inhibitors/ARBs in patients with possible cardiac radiation exposure.

Patients with a history of thoracic radiation treatment should be followed by a cardiologist lifelong. This includes asymptomatic patients given that even those without symptoms may have significant cardiovascular disease. The value of brain natriuretic peptide and troponin I is unknown,[146] and the emphasis has been on imaging studies, as endorsed in the European Association of Cardiovascular Imaging and American Society of Echocardiography 2013 consensus statement on follow-up screening after RT.[147] Screening echocardiography is recommended starting 10 years after radiation exposure, or 5 years after RT in higher-risk patients (**Box 14.2**).[98,147,148] Echocardiograms are then to be repeated be every 5 years. Likewise, functional stress tests are recommended 5 to 10 years after RT in high-risk patients to screen for CAD.[148] Other

investigators recommend CAD screening following mediastinal RT >35 Gy.[147] The Society for Cardiac Angiography and Intervention (SCAI) recently further refined screening recommendations after RT as summarized in **Fig. 14.9** (see **Box 14.2**).[149] The SCAI consensus document specifically mentions the use of computerized tomography coronary angiography (CCTA) with CAC scoring and exercise oxygen consumption stress testing with echocardiographic imaging as additional screening techniques. Although CCTA outlines the anatomic burden of CAD more than any other technique, exercise oxygen consumption stress testing evaluates both the cardiac and the pulmonary reserve, which may also be impaired because of concomitant lung fibrosis in these patients. If abnormalities are found on CT or functional stress testing, coronary angiography may be considered. Screening for and treatment of traditional CAD risk factors, including hypertension, dyslipidemia, diabetes, and smoking, are imperative.[91,150] Indeed, RT may be considered as yet another potent cardiovascular risk factor (**Fig. 14.10**), and for instance, the risk of acute coronary events is higher and emerges earlier (<10 years, and even <5 years) in those with other cardiovascular risk factors[24] (**Fig. 14.11**). These observations provide another strong impetus for screening efforts. Even though intuitive and extrapolated from studies on conventional atherosclerotic cardiovascular disease, evidence

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BOX 14.2
Screening recommendations for asymptomatic patients with cardiac radiation exposure

Screening for CAD

van Leeuwen-Segarceanu et al

    CT angiography/coronary artery calcium scoring

    Screening recommended for patients receiving ≥35 Gy to the mediastinum (or those who received older RT techniques that do not minimize cardiac irradiation)

    Starting 5 years after radiation exposure for patients 45 or older

    Starting 10 years after radiation exposure for patients less than 45

    Reassess every 5 years

    Lipid panel every 3 years

    Blood pressure and fasting blood glucose screening annually

European Association of Cardiovascular Imaging and the American Society of Echocardiography (EACVI/ASE) consensus statement

    Functional noninvasive stress test

    Screening recommended in high-risk patients[a]

    Starting 5 to 10 years after radiation exposure

    Reassess every 5 years

Screening for valvular disease

van Leeuwen-Segarceanu et al

    Echocardiogram

    Screening recommended for patients receiving 35 Gy or greater to the mediastinum (or those who received older RT techniques that do not minimize cardiac irradiation)

    Starting 10 years after radiation

    Reassess every 5 years

EACVI/ASE consensus statement

    Echocardiogram

    Starting 5 years after radiation in high-risk patients[a]

    Starting 10 years after radiation in all others

    Reassess every 5 years

Screening for noncoronary atherosclerotic disease

Both van Leeuwen-Segarceanu et al and the EACVI/ASE consensus statement do not recommend screening for noncoronary atherosclerotic disease in asymptomatic patients, but recommend carotid artery ultrasonography in patients with carotid bruits or neurologic symptoms. However, given the significant elevation in risk of stroke related to carotid stenosis in patients who have received head and neck radiotherapy, screening with ultrasonography in select asymptomatic patients is reasonable.

[a] High-risk patients were defined as having had anterior or left chest irradiation as well as one of the following risk factors: dose greater than 30 Gy, dose fraction greater than 2 Gy, age less than 50 years, lack of shielding, concomitant anthracyclines, cardiovascular risk factors, or known cardiac disease.
Data from Nellessen U, Zingel M, Hecker H, et al. Effects of radiation therapy on myocardial cell integrity and pump function: which role for cardiac biomarkers? Chemotherapy 2010;56:147–52; and Lancellotti P, Nkomo VT, Badano LP, 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. J Am Soc Echocardiogr 2013;26:1013–32.

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is yet to be provided that this knowledge and re-action to this knowledge yield improved cardiovascular outcomes in patients who underwent RT. Until this proof is provided, all patients may be considered to be at higher risk in the respective radiation territories than captured by conventional risk calculators and should be proactively managed with aspirin and statins. Experimental studies indicate that these medications may not be as efficacious for radiation-induced
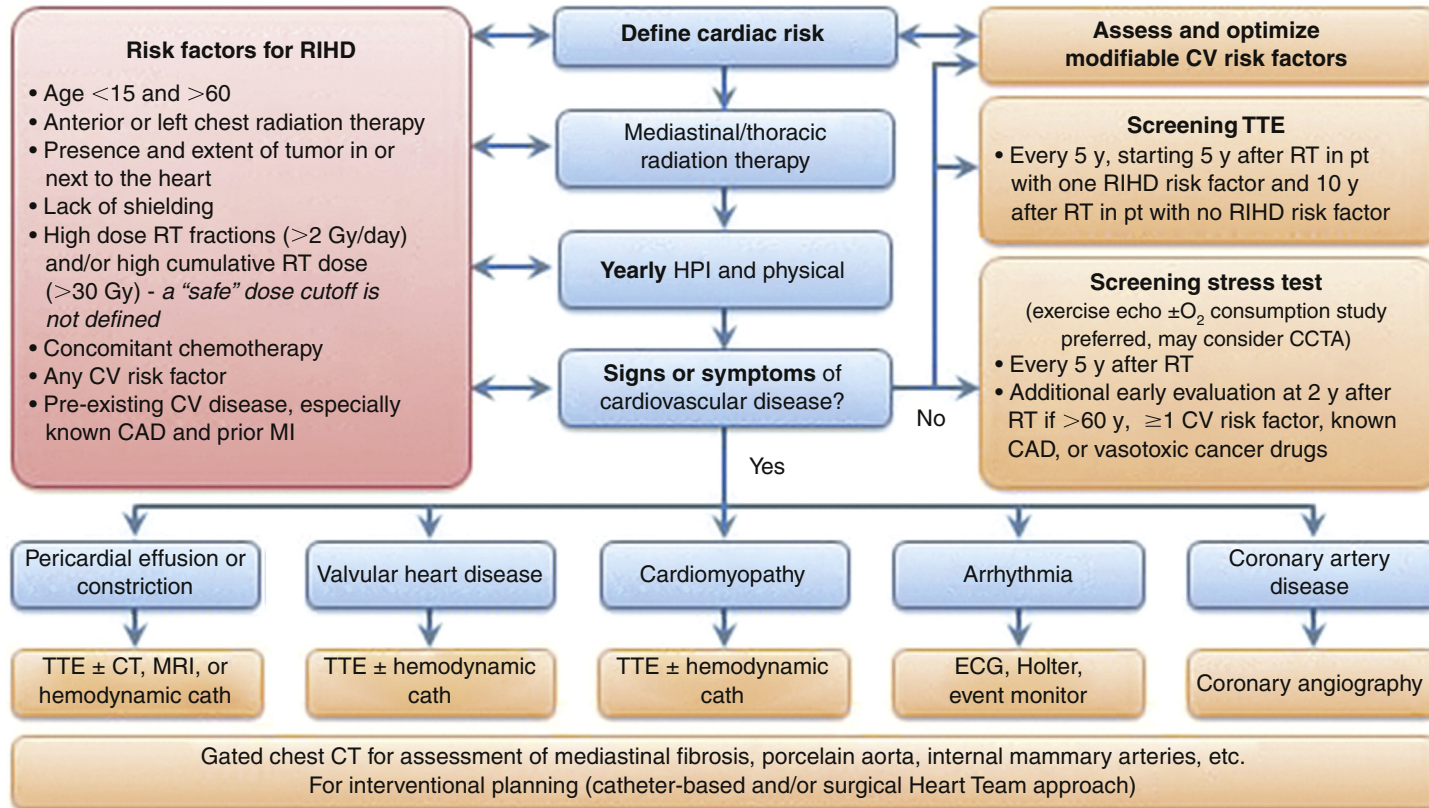
Risk factors for RIHD

- Age <15 and >60
- Anterior or left chest radiation therapy
- Presence and extent of tumor in or next to the heart
- Lack of shielding
- High dose RT fractions (>2 Gy/day) and/or high cumulative RT dose (>30 Gy) - *a "safe" dose cutoff is not defined*
- Concomitant chemotherapy
- Any CV risk factor
- Pre-existing CV disease, especially known CAD and prior MI

Define cardiac risk

Mediastinal/thoracic radiation therapy

Yearly HPI and physical

Signs or symptoms of cardiovascular disease?

No

Yes

Assess and optimize modifiable CV risk factors

Screening TTE
- Every 5 y, starting 5 y after RT in pt with one RIHD risk factor and 10 y after RT in pt with no RIHD risk factor

Screening stress test
(exercise echo ±O$_2$ consumption study preferred, may consider CCTA)
- Every 5 y after RT
- Additional early evaluation at 2 y after RT if >60 y, ≥1 CV risk factor, known CAD, or vasotoxic cancer drugs

Pericardial effusion or constriction	Valvular heart disease	Cardiomyopathy	Arrhythmia	Coronary artery disease
TTE ± CT, MRI, or hemodynamic cath	TTE ± hemodynamic cath	TTE ± hemodynamic cath	ECG, Holter, event monitor	Coronary angiography

Gated chest CT for assessment of mediastinal fibrosis, porcelain aorta, internal mammary arteries, etc.
For interventional planning (catheter-based and/or surgical Heart Team approach)

Fig. 14.9 SCAI algorithm for the management of patients undergoing chest RT. (*From* Iliescu CA, Grines CL, Herrmann J, et al. SCAI expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiología Intervencionista). Catheter Cardiovasc Interv 2016;87(5):E206; with permission.)
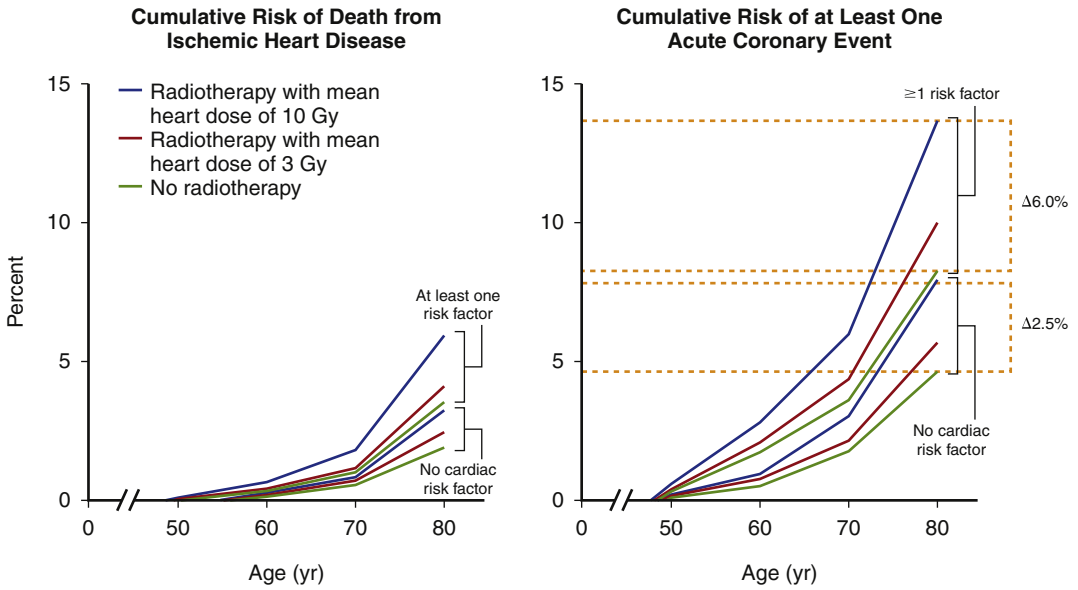
Cumulative Risk of Death from Ischemic Heart Disease

Cumulative Risk of at Least One Acute Coronary Event

Fig. 14.10 Cumulative risk of death from ischemic heart disease (*left*) and of an acute coronary event (*right*) in patients after chest radiation for breast cancer. (*From* Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:997; with permission.)

vascular injury, but there is no substance to these concerns in patients yet.

With regards to the other manifestations for RIHD, there are currently no known strategies that would prevent their development or progression after radiation-induced injury.

SUMMARY

RT is a highly prevalent cause of cardiovascular disease in survivors of breast cancer and Hodgkin disease. CAD, cardiomyopathy, and valvular disease have a high prevalence, so it is recommended that patients with significant prior radiation
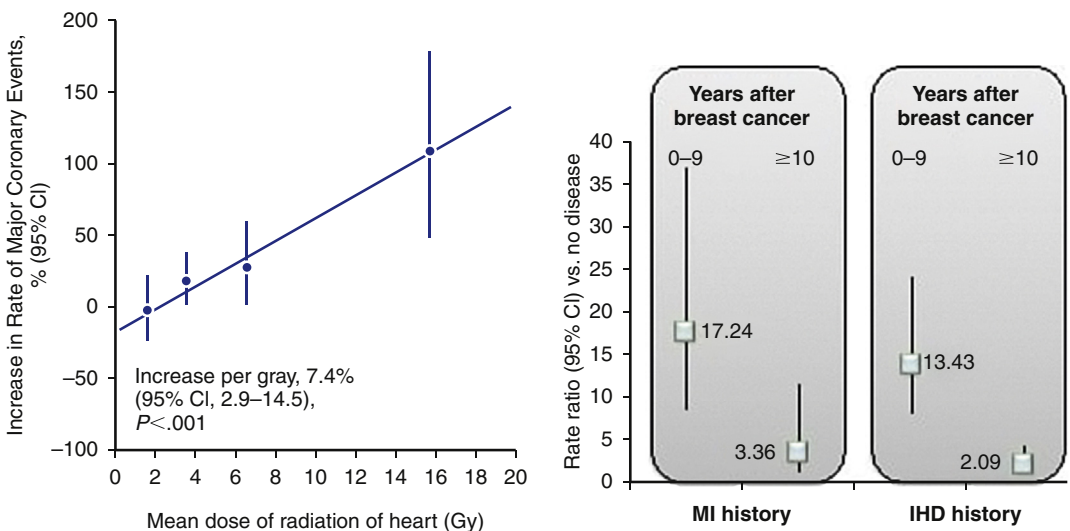
Fig. 14.11 Incidence of major coronary event as a function of radiation dose to the heart (*left*) and the relative risk by time from chest radiation for breast cancer (*right*). MI, myocardial infarction. (*From* Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:993; with permission.)

TABLE 14.2
Commonly used units of radiation exposure

Unit	Type of Unit	Conversion Factor
Rad[a]	Absorbed radiation dose	1 rad = 0.01 Gy
Gray (Gy)[a]	Absorbed radiation dose; SI unit	1 J/kg = 1 Gy = 100 rad
Rem[b]	Dose equivalent	1 rem = 0.01 Sv; 1 rem = 1 rad[c]
Sievert (Sv)[b]	Dose equivalent; SI unit	1 Sv = 100 rem; 1 Sv = 1 Gy[c]

[a] Rad and grays are units of energy per mass.
[b] Rem and sieverts are units of energy per mass adjusted by a dimensionless factor to account for potential for biological damage.
[c] Rem and rad are equivalent and sieverts and grays are equivalent for radiograph and gamma radiation.
   Data from Topolnjak R, Borst GR, Nijkamp J, et al. Image-guided radiotherapy for left-sided breast cancer patients: geometrical uncertainty of the heart. Int J Radiat Oncol Biol Phys 2012;82:e647–55.

exposure be followed by a cardiologist lifelong (Case Studies 1-4, available on Expert Consult, Table 14.2). Screening for RIHD with echocardiograms and for accelerated CAD with either functional stress testing or CT coronary angiography is warranted. Advances continue to be made in reducing cardiac radiation exposure with RT, and with these refinements the incidence of RIHD may decline.

SUPPLEMENTARY MATERIAL
Go to ExpertConsult.com to listen to an interview with the authors.

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