Cardiac Complications of Thoracic Irradiation

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Adjuvant radiation therapy in the management of early stage breast cancer, Hodgkin’s disease, and to a lesser extent other thoracic malignancies has led to a significant improvement in disease-specific survival. Cardiovascular disease is now the most common nonmalignancy cause of death in radiation-treated cancer survivors, most often occurring decades after treatment. The spectrum of radiation-induced cardiac disease is broad, potentially involving any component of the heart. The relative risk of coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, conduction abnormalities, and sudden cardiac death is particularly increased. Over the years contemporary techniques have been introduced to reduce cardiac morbidity and mortality in radiation-treated cancer survivors; however, the long-term effects on the heart still remain unclear, mandating longer follow-up. Awareness and early identification of potential cardiac complications is crucial in cancer survivors, with the management often being quite complex. This review examines the epidemiology of radiation-induced cardiac disease together with its pathophysiology and explores the available treatment strategies and the potential utility of various screening strategies for affected cancer survivors. (J Am Coll Cardiol 2013;61:2319–28) © 2013 by the American College of Cardiology Foundation

Although the introduction of radiation therapy (RT) into the portfolio of therapies used in the management of thoracic malignancy has led to a significant improvement in disease-specific survival for patients with early stage breast cancer, Hodgkin’s disease (HD), and to a lesser extent lung cancer and some other malignancies involving the thoracic region, the treatment has seen the emergence of a new spectrum of cardiovascular disorders induced by radiation injury. Radiation-induced cardiac disease encompasses a spectrum of deleterious effects on the heart from pre-clinical histopathologic findings in isolation to symptomatic clinical disease. Multiple studies have shown that these patients have an increased risk of coronary artery disease (CAD), congestive heart failure, valvular heart disease, pericardial disease, and sudden death (1–5). This review examines the epidemiology of radiation-induced cardiac disease together with its pathophysiology, therapy, and potential complicating role in the context of cardiovascular interventions.

Epidemiology

Given that survival rates for many forms of thoracic malignancy have improved over the past few decades, sufficient time has now passed for the sequelae of radiation-induced cardiac injury to become clinically evident. Among Hodgkin’s lymphoma and breast cancer patients treated with radiotherapy, cardiovascular disease (CVD) is the most common nonmalignant cause of death (1,6–8). Over the long term, the benefits of radiotherapy might be partially offset by cardiac complications. The late effects of irradiation generally become evident during intervals ranging from 3 to 29 years after treatment (9), usually appearing in the second to third decade post-therapy (1,2,5,10). Contemporary radiotherapy techniques such as reduction in doses and field size have been shown to be safe with no increase in disease relapse in HD (11). However, it is unclear whether such techniques have reduced the risk of late complications in magnitude or simply delayed the time to onset. As such, longer follow-up will be required to determine the pattern and prevalence of radiation-induced CVD with present radiotherapy methods.

Hodgkin’s lymphoma is one of the most common cancers in young adults, with an annual incidence of approximately 3 of 100,000 (5,12,13). Early stage HD has become a highly curable disease, with survival rates approaching 95%, and the overall 5-year survival rate is 85% with modern radiotherapy and chemotherapy used either alone or in combination (13,14). Cardiovascular complications late after mediastinal radiotherapy is the next most common cause of treatment-related morbidity after second malignancy in HD survivors. They account for 25% of mortality in cured patients (15–17). Myocardial infarction is the most common cause of cardiac mortality in this patient subgroup (2,18).
The estimated relative risk of cardiac mortality ranges from 2.2 to 12.7, and the absolute excess risk ranges from 9.3 to more than 28 of 10,000 person years of follow-up (1,2,6,7,10,18,19). An estimated aggregate incidence of radiation-induced cardiac disease is between 10% and 30% by 10 years post-treatment, with up to 88% of patients demonstrating asymptomatic cardiac abnormalities (20). Multiple studies have supported a significant increase in the incidence of CVD in long-term survivors (1,2,10,19), extending to increased requirement for coronary artery bypass grafting (CABG) (3.2-fold), percutaneous coronary intervention (PCI) (1.6-fold), implantable cardioverter-defibrillator (ICD) or pacemaker (1.9-fold), valve surgery (9.2-fold), pericardial surgery (12.9-fold) (19), and heart failure (4.9-fold) (21). Moreover, the increase in cardiovascular morbidity is accompanied by a clear increase in the risk of cardiac mortality (Table 1).

Breast cancer is the most common cancer in women, with 1 in 8 women being diagnosed within their lifetime (22). Breast conservation with post-operative radiotherapy has become the standard of care of treatment for many women with early breast cancer and provides overall survival now equivalent to mastectomy (23). The current 5-year survival of early stage breast cancer is 95% (22). The largest meta-analysis exploring the impact of radiotherapy on breast cancer morbidity and mortality from other causes was conducted by the Early Breast Cancer Trialists Collaborative Group (24). This study showed that in the absence of any breast cancer deaths, the 20-year survival was 69.5% among women treated with chest wall radiotherapy for a left-sided breast cancer compared with right-sided.

A left-sided treated cancer versus 8% of patients with right-sided cancer (p = 0.01) (28). Similarly, in a large study of 4,456 women, Bouillon et al. (29) also found a significant increase in mortality from CVD in irradiated patients versus control subjects, with a particularly strong interaction between smoking and radiotherapy treatment (27). There are conflicting data with regard to increased risk of left- versus right-sided breast cancer with adjuvant radiotherapy. Correa et al. (28) retrospectively studied 961 patients and found that 46 left-sided and 32 right-sided previously treated patients had undergone a stress methoxyisobutylisonitrile at a median of 12 years post-radiotherapy. Positive studies were found in 59% of patients with left-sided treated cancer versus 8% of patients with right-sided cancer (p = 0.01) (28).

Association studies have also examined the relationship between radiotherapy and CVD in pediatric cohorts and patients with lung cancer. Observations made in the pediatric population have provided unequivocal proof that radiotherapy is associated with increased risk of cardiovascular mortality. Tukenova et al. (30) studied 4,122 cancer survivors, <15 years of age at time of recruitment, with a mean follow-up of 27 years. The standardized mortality ratio for death was 4.2 compared with the general population and 5.8 for cardiac death. The relative risk for death was proportional to radiation dose (relative risk: 3 to 25, for 1 to 4.9 Gy to >15 Gy, respectively) (30). There have been multiple case reports in radiation-treated children as young as 12 years old suffering sudden cardiac death with autopsy-proven critical left main stenosis (31). Cardiac injury is less commonly reported in patients who receive RT for lung cancer, because most patients who receive RT for unresectable lung cancer do not live long enough to experience late-term toxicities or already have significantly reduced cardiopulmonary reserve (32).

### Developments in Radiotherapy

Historically, thoracic radiotherapy techniques for cancer treatment involved relatively high doses being delivered to a high volume of the heart, with the dose varying depending on the cancer targeted. Before the late 1980s, Hodgkin’s lymphoma patients received between 35 and 45 Gy over the dedicated treatment regime. In more recent years, doses of 30 Gy have been shown to yield similar results, and in combined modality treatment this has become the standard.

### Table 1

<table>
<thead>
<tr>
<th>Years Post-Treatment</th>
<th>Aleman et al. (1)</th>
<th>Swerdlow et al. (2)</th>
<th>Castellino et al. (10)</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
<td>AR</td>
<td>RR</td>
</tr>
<tr>
<td>0-5</td>
<td>7.7</td>
<td>6.1</td>
<td>1.7</td>
</tr>
<tr>
<td>5-10</td>
<td>7.0</td>
<td>10.6</td>
<td>2.3</td>
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<tr>
<td>10-15</td>
<td>4.5</td>
<td>10.7</td>
<td>1.9</td>
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<tr>
<td>15-20</td>
<td>6.8</td>
<td>28.7</td>
<td>4.1</td>
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<tr>
<td>&gt;20</td>
<td>8.3</td>
<td>53.9</td>
<td>3.1</td>
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</table>

AR – absolute risk; RR – relative risk.
of care in most countries (11,33). Lower doses of 20 Gy in combined modality treatment are currently under investigation, with encouraging preliminary results (11). In the breast cancer population, up to 45 to 50 Gy of radiation might be used in the treatment of cancers at high risk of regional recurrence (26,29). In Hodgkin’s survivors, Schellong et al. (34) found that the cumulative incidence of cardiac disease after 25 years exposure to a mediastinal radiation dose of 36 Gy was 21%, significantly decreasing to 6% and 5% to those exposed to 25 Gy and 20 Gy, respectively.

Over the years, improved irradiation techniques have been introduced to minimize irradiation to the heart; however, the existence or magnitude of the residual risk is still uncertain. Techniques to further reduce cardiac exposure such as image-guided therapy; 3-dimensional treatment planning; respiratory gating; and intensity modulated RT, aiming to deliver radiation more precisely to the tumor while relatively sparing the surrounding normal tissue, show promise and are still under investigation (20,35,36). Data from Campbell et al. (36) support further targeted field reduction from involved-field RT to involved-nodal RT as a component of adjuvant therapy for early HD and have found no statistical difference in progression-free survival and overall survival at 10 years. Other modern techniques employed to minimize radiation exposure include cardiac shielding (with lead blocks), reduced fraction size (<2 Gy/day), reduced total dose of radiation (<30 Gy/day), and relative field weighting (aimed to minimize overexposure to the anterior mediastinum) (20,37). The clear goal is to decrease the intensity of therapy without sacrificing long-term disease control.

**Pathophysiology and Histopathology**

Irradiation can damage all cells, both cancer cells and healthy cells, and can affect blood vessels of all sizes. Radiation therapy causes an increase in capillary wall permeability, with dilation of vessels leading to the characteristic radiation erythema. Radiation treatment causes direct damage to blood vessels by the generation of reactive oxygen species that disrupt DNA strands leading to an inflammatory cascade (38). The same process occurs in the vasculature of the heart. This inflammatory cell infiltrate disturbs the filtration properties of the endothelium, and the basement membrane of the capillary wall thickens as a result of collagen deposition and fibrosis (16). Endothelial dysfunction is believed to be a precipitating factor in the development of cardiac sequelae (39) and is most likely a combination of impaired endothelial function, stimulation of growth factors, and eventual fibrosis (40). Analogous to atheromatous plaques, however differing in their microvascular location, there is progressive hypoperfusion with microvascular thrombosis and ischemia, with eventual small vessel occlusion and cell death. The pathohistologic hallmarks include diffuse fibrosis of the interstitium of the myocardium and arterial lumen narrowing (41).

Thoracic RT can affect all of the structural components of the heart, including the pericardium, myocardium, heart valves, coronary arteries and capillaries, and conducting system (2,5,21) (Table 2). Pericarditis is the typical acute manifestation of radiation injury, whereas chronic pericardial disease, CAD, valvular heart disease, systolic and diastolic cardiomyopathy, and conduction abnormalities (complete heart block, sick sinus syndrome, prolonged QTc) might manifest years or even decades after treatment exposure (5,9,19). Several risk factors for the development of radiation-associated cardiotoxicity have been identified (Table 3). Systemic chemotherapy, particularly anthracycline agents and trastuzumab (even more potent in combination), can also have a dose-dependent synergistic impact on cardiac dysfunction (20,42).

**Pericardial disease.** Acute radiation pericarditis might be one of the earliest cardiac complications of radiotherapy and was historically the most common cardiovascular manifestation of radiation therapy, typically manifesting a few weeks after treatment. Modern methods of implementation, including lower doses (including equally weighted anterior and posterior beams) and shielding methods (like subcarinal blocking) have decreased the incidence from 20% to 2.5% (43,44), with the incidence being proportional to dose and treatment volume (17). Pericarditis is usually self-limiting, however, 10% to 20% of patients develop a chronic or constrictive pericarditis 5 to 10 years after treatment (16). Associated pericardial effusions are characterized by fibrous adhesions, high protein count, and an increase in serum inflammatory markers. Chronic pericarditis might occur even if the patient did not experience an acute event. Fibrotic fusion and thickening of the visceral and parietal layers in the presence of a tense effusion in the free pericardial space is referred to as effusive-constrictive pericarditis and has been well-described in radiation-treated cancer survivors (45,46).

**CAD.** Pathologically, vascular radiation injury is accompanied by an increase in capillary wall permeability, the generation of reactive oxygen species, and activation of an inflammatory cascade (38). This subsequently leads to

<table>
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<th>Table 2</th>
<th>Effects of Radiation Therapy on the Heart</th>
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<tbody>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
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<tr>
<td>Coronary artery disease</td>
<td>Microvascular dysfunction</td>
</tr>
<tr>
<td><strong>Structural</strong></td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Mitral stenosis and insufficiency</td>
</tr>
<tr>
<td>Aortic stenosis and insufficiency</td>
<td>Pericardial disease</td>
</tr>
<tr>
<td>Conduction system disease</td>
<td><strong>Myocardial</strong></td>
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<tr>
<td>Systolic dysfunction/systolic heart failure</td>
<td>Diastolic dysfunction/heart failure with preserved ejection fraction</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>Myocardial fibrosis/scar</td>
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shown that diastolic dysfunction is seven-fold more common than systolic dysfunction (53,54). The result is an alteration in the compliance of the myocardium itself relatively radiation resistant. However, intimal proliferation with collagen deposition and fibrosis (16). As such, initial endothelial dysfunction is believed to be a key factor in the development of cardiac sequelae (39). In the case of CAD, the stenoses might be due to intimal proliferation, damage to the intima, or atherosclerotic lesions (9). This initiates a cascade of events that is typical of atherosclerosis, including replacement of damaged cells with myofibroblasts along with platelet deposition. In vitro studies have also revealed the pro-thrombotic effect of radiation associated with higher release of von Willebrand factor which can provoke and contribute to coronary thrombosis (47,48). Ultimately, the mechanism involved in plaque formation is thought to mirror spontaneous atherosclerosis; however, plaques in irradiated patients have been found to be more fibrous with a decreased lipid component (17,49–51). Ostial stenoses are typical for radiation-induced CAD. Macroscopically, there is a significantly higher incidence of severe left main disease, followed by ostial right coronary artery and left anterior descending artery stenoses correlating with the anatomic location of radiation treatment (9). In general, the lesions are consistently longer, more proximal, smoother, concentric, and tubular (9). The incidence of radiation-induced CAD is increased by the standard cardiac risk factors. Hull et al. (52) studied 415 patients post-RT for Hodgkin’s lymphoma and found that 10.4% of patients developed significant CAD (defined as having history of myocardial infarction/CABG/>75% luminal stenosis on angiography or autopsy) at a median of 9 years of follow-up.

**Myocardium.** The lack of myocyte cell division makes the myocardium itself relatively radiation resistant. However, diffuse interstitial fibrosis occurs after relatively low doses of radiation through microvascular insufficiency and ischemia, involving damage to the capillary endothelial cells (53,54). The result is an alteration in the compliance of the myocardium, leading to both systolic and diastolic dysfunction. Most patients with myocardial involvement have some degree of interstitial fibrosis (55), typically developing at radiation doses above 30 Gy. It has been shown that diastolic dysfunction is seven-fold more common in individuals treated with thoracic radiotherapy population compared with community control subjects, and the presence of diastolic dysfunction is associated with stress-induced ischemia, a worse prognosis, and event free survival (56).

**Valvular dysfunction.** Radiotherapy might directly damage cardiac valves and surrounding myocardium, leading to fibrotic thickening, valvular retraction, and late calcification (5). The incidence of valvular dysfunction has been reported to increase during the second decade after mediastinal radiotherapy for HD (5). Wethal et al. (5) found that, of 116 patients observed approximately 10 years after treatment, 36 (31%) demonstrated moderate valvular regurgitation in 40 valves, primarily either the aortic or mitral valve, whereas none had evidence of stenosis. Interestingly, in the same cohort 39% of patients still available for follow-up 12 years later had developed aortic stenosis, including some of a moderate to severe degree (35%) (5). The valves were found to be thicker with reduced leaflet motion and calcification (5). These results suggest that valve retraction is the predominant early change that causes regurgitation and that it might take in excess of 20 years for the valves to become significantly thickened, calcified, and stenotic. It is hypothesized that a higher pressure system on the left side of the heart compared with the right accounts for why the mitral and aortic valves are affected more than the pulmonary and tricuspid. Multiple studies have supported the higher incidence of aortic and mitral valve disease (4,5,57). Consistent with these observations, another study found that, of asymptomatic patients previously treated with at least 35 Gy of radiation, 6% had clinically significant dysfunction, and 26% had >grade II aortic regurgitation. This equated to a 34-fold increased risk compared with the Framingham population (4). Also, 26% demonstrated marked calcification of the aortomitral curtain (4).

**Conduction system.** Abnormalities along the entire conduction system have been described in the setting of radiotherapy, including varying degrees of atrioventricular block, sick sinus syndrome, prolonged QTc, supraventricular arrhythmias, and ventricular tachycardia (53,58). Right bundle branch block is more commonly observed than left bundle branch block post-RT, likely due to higher radiation exposure of the right ventricle due to its anterior location. Ventricular ectopy might occur in up to 50% of patients exposed to mediastinal irradiation, often secondary to ventricular fibrosis (53,58). Crestanello et al. (59) found a high post-operative prevalence of conduction disease after valvular surgery in this patient cohort, with 27% of patients requiring permanent pacemaker placement. Dysfunction of the autonomic nervous system, leading to persistent tachycardia, loss of circadian heart rhythm, and respiratory phasic heart rate variability has also been described after irradiation (60). The latter clinical picture is similar to heart transplant patients who have a denervated heart (60). Persisting tachycardia might further increase the patient risk of developing a tachycardia-mediated cardiomyopathy.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Risk Factors for Radiation-Induced Cardiotoxicity</th>
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<tbody>
<tr>
<td>Total dose &gt;30–35 Gy</td>
<td>Higher dose/fraction &lt;2 Gy/day</td>
</tr>
<tr>
<td>Field size (volume of heart irradiated)</td>
<td>Relative field weighting (anterior/posterior positioning)</td>
</tr>
<tr>
<td>Presence of tumor next to the heart</td>
<td>Younger age at exposure</td>
</tr>
<tr>
<td>Time since exposure</td>
<td>Type of radiation source (cobalt)</td>
</tr>
<tr>
<td>Cardiotoxic chemotherapy (e.g., anthracycline)</td>
<td>Other cardiovascular risk factors (e.g., diabetes, smoking)</td>
</tr>
<tr>
<td>Technique (reduced with CT plan)</td>
<td>Adapte...</td>
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Prevention of Radiation-Induced CVD

Long-term cardiac injury after radiation treatment depends on several factors, including: total radiation dose; dose of radiation fraction/day; amount and areas of the heart treated; presence of tumor within or adjacent to the heart; left-sided tumors; and the use of concomitant cardiotoxic chemotherapeutic drugs such as the anthracyclines and trastuzumab (16,20,61). In particular, newer approaches to the delivery of more targeted and lower-dose therapy will likely lead to a reduction in the frequency of the cardiac complications of radiotherapy. Conventional risk factors for CAD, including age, increased body mass index, hypertension, hypercholesterolemia, diabetes mellitus, smoking, preexisting CVD, and a positive family history, also compound the risk. Going forward, diagnosis of cancer might also lead patients to adopt unfavorable lifestyle changes such as decreased physical activity and weight gain, which might concomitantly reduce cardiovascular reserve and heighten the risk of CVD.

Cardiac Evaluation of the Post-Radiotherapy Patient

A strategy for prolonged cardiological follow-up and cardiac screening is mandatory in cancer patients who have received irradiation to facilitate early identification of cardiac related complications. As outlined in the following text, strategies for early detection likely provide the best approach in which to reduce the morbidity and mortality caused by radiation-induced heart disease. Before radiotherapy, a comprehensive baseline evaluation including a detailed cardiovascular history, cardiac examination, risk factor profiling, and echocardiography should be performed. In particular, the echocardiographic examination should include a thorough investigation of both systolic and diastolic function. Accordingly, aggressive management of any cardiac risk factors should be implemented. Surveillance monitoring is paramount, because the timing of medical or surgical intervention can be crucial for optimal patient outcomes. In the preoperative setting, smoking cessation, pulmonary rehabilitation, and prophylactic draining of pleural effusions might be beneficial to minimize the frequent and problematic postoperative pulmonary complications (62).

There is a paucity of data to support the optimal method and frequency of screening post-radiotherapy patients. Currently only expert opinion and consensus-based guidelines for cardiac follow-up are available. In 2006, the American Society of Clinical Oncology submitted screening recommendations for both chemotherapy and radiotherapy-induced cardiac and pulmonary late effects (20). The document was not approved, due to lack of direct evidence with regard to the utility, benefit, and harm of screening (20). Beyond this, Byrd and Mendes (63) proposed screening echocardiography 10 years after treatment in the asymptomatic cohort. In addition, the American College of Radiology and National Comprehensive Cancer Network recommends a baseline stress echocardiogram at 5 to 10 years and 10 years, respectively, with 1 to 3 yearly glucose and lipid profile review (64,65). Heidenreich and Kapoor (53) have recommended that stress testing should begin 5 years post-irradiation therapy. The Children’s Oncology Group has also developed guidelines for the surveillance of pediatric patients, recommending second yearly transthoracic echocardiograms for those below 5 years of age at treatment (once yearly if concomitant anthracycline therapy) (66). For children >5 years at age of treatment, recommendations were based on radiation dose, with children exposed to <30 Gy requiring 5 yearly echocardiograms and second yearly for those exposed to >30 Gy (once yearly if moderate-dose anthracyclines were needed) (66).

It might be reasonable to follow a more conservative follow-up approach in the absence of symptoms. We propose that cardiac screening should commence as early as 5 years post-cessation of radiation treatment or after the age of 30, whichever occurs first. We recommend annual specialist review, potentially in a Late Effects or Survivorship Clinic, given the constellation of other sequelae that might manifest, with early referral to a cardiologist should either asymptomatic structural or functional dysfunction be evident or if symptoms arise. In addition to an annual consultation and a meticulous cardiac examination, the focus of screening should ideally incorporate noninvasive, radiation-free modalities in the first instance. Furthermore, it is paramount that any woman who has had thoracic radiation and/or anthracycline treatment have at least their first pregnancy monitored in a tertiary referral center and be assessed by a cardiologist in their second trimester, because underlying cardiac failure can be exposed during this time (67).

At 5 years, then annually. B-type natriuretic peptide (BNP) and troponins might be useful serum biomarkers that might be able to act as early and perhaps pre-clinical markers of myocardial damage. This has been more widely researched in chemotherapy patients; however, Nellessen et al. (54) also evaluated plasma levels of troponin and BNP up to 6 weeks post-RT. Plasma levels of both biomarkers increased over the study period, although without measured impairment in left ventricular (LV) function. This finding supports the potential use of biomarkers in screening post-treatment to potentially identify high-risk patients. In addition to BNP and troponins, blood tests such as fasting serum glucose and lipid profiles should also be reviewed annually. Annual electrocardiography is also a simple investigation that might alert the treating physician to the development of progressive conduction abnormalities. A 24-h ambulatory Holter monitor might also be warranted, depending on the clinical scenario. In one study by Larsen et al. (58), 7% of childhood cancers survivors (mean age 15 years) were found to have ventricular tachycardia on 24-h Holter monitor. Given the sporadic and variable frequency of ventricular arrhythmias, this study might have underestimated the prevalence of ventricular arrhythmias in survivors of childhood cancer.
As outlined in the preceding text, the key late cardiovascular sequelae of thoracic irradiation are the result of coronary, myocardial, and valvular pathology. Most of these complications can be evaluated for using combined rest and stress echocardiography. This approach enables the clinician to assess LV systolic function, diastolic function, valvular function, pericardial integrity, and regional wall abnormalities, both at rest and with exercise. When possible, stress echocardiography should be chosen over a stress thallium/methoxyisobutylisonitrile for the radiation-free and functional advantages, particularly relevant in this patient cohort.

Vigilant screening for athletic participation might also be an important consideration in the pediatric cancer group. In the setting of documented arrhythmias and to further risk-stratify patients, cardiac magnetic resonance imaging (MRI) is an extremely valuable modality to further assess for regional scar, potentially serving as a substrate for ventricular arrhythmias. In patients with nonischemic cardiomyopathy, late gadolinium enhancement on cardiac MRI has been shown to strongly predict adverse cardiac outcomes such as hospital stays for heart failure, appropriate ICD firing, and death (68). There is a growing body of published data supporting a potential role for cardiac MRI and late gadolinium enhancement in the risk stratification and prognostication of patients with cardiomyopathy (68–70), which might have further value in determining the need for device therapy.

Furthermore, cardiac MRI is a highly sensitive modality that potentially provides clinical information beyond the capability of echocardiography, particularly with regard to tissue characterization. Cardiac MRI is particularly useful to assess for regional and, more recently, diffuse myocardial fibrosis with delayed gadolinium enhancement and T1 mapping respectively, with increasing evidence that T1 mapping correlates with diffuse fibrosis and diastolic dysfunction (71,72). Thereby, cardiac MRI might be particularly valuable to diagnose asymptomatic diastolic dysfunction and possibly guide the timing of initiation of anti-fibrotic agents like angiotensin-converting enzyme inhibitors (ACEI) and aldosterone inhibitors. Cardiac MRI might also be useful to evaluate possible diastolic dysfunction in the patient population that cannot undergo tissue Doppler imaging, limited by a heavily calcified cardiac skeleton (Fig. 1), mitral stenosis, or mitral valve replacement.

Coronary computerized topography (CCT) can non-invasively detect and quantify obstructive coronary artery stenoses. Novel prospective gating techniques have significantly reduced radiation dose, making cardiac computed tomography an increasingly attractive and complementary investigative tool for cancer survivors. In the general population, the coronary calcium score is particularly useful (with very little radiation exposure) to predict coronary artery stenosis and cardiac events and adds prognostic value to the Framingham risk score. Yeboah et al. (73) have shown that the coronary calcium score provides superior discrimination and risk reclassification compared with other risk markers in intermediate-risk individuals. However, its utility in the late effects patient cohort is still to be determined. Rademaker et al. (74) retrospectively evaluated the CCT findings of 9 HD survivors, treated with radiotherapy 12 to 35 years ago. This pilot study showed that 8 of the 9 patients were found to have at least mild atherosclerosis, 66% had calcium scores within the 90th percentile for their age, and 2 patients proceeded to coronary angiography (1 requiring PCI, and 1 requiring CABG) (74). Patients with the lowest radiation dose and shortest interval since radiotherapy had minimal or
no findings of CAD. At this early stage, however, we do not recommend that baseline screening stress echocardiography should be substituted for CCT. However, this is certainly a potential focus for further research.

**Therapy**

**Acute and chronic pericarditis.** As outlined in the preceding text, acute pericarditis is relatively uncommon with the use of more contemporary thoracic radiotherapy strategies. Similar to other forms of acute pericarditis, patients might present with fever, pleuritic chest pain, dyspnea, and tachycardia. Typical clinical, electrocardiographic, and biochemical features might be present. Transthoracic echocardiography should be performed to exclude tamponade. Cardiac MRI might also be useful to confirm the diagnosis and establish the degree of pericardial thickening along with an assessment for myocardial involvement. Treatment includes the use of nonsteroidal anti-inflammatory agents. Pericardiocentesis might be indicated if there is an associated large pericardial effusion and if the patient is significantly hemodynamically compromised. Pericardectomy might be required for constrictive pericarditis. It is important to exclude other etiologies in the setting of recurrent pericardial effusion such as infection, tumor invasion or recurrence, and hypothyroidism, which might be seen after mantle irradiation. Constrictive pericarditis has been described as a marker for greater radiation injury to the heart, associated with diastolic dysfunction and high mortality (58). Early pericardial stripping might be supported at the time of planned cardiac surgery to improve post-operative cardiac physiology (62).

**CAD.** In the setting of flow limiting disease of the major epicardial coronary arteries, most lesions have been found to be amenable to treatment with either CABG or PCI dependent upon the specific anatomy. Some early studies have suggested that percutaneous angioplasty seems to have a higher rate of restenosis (75); however, there are no data to incorporate outcomes of newer, second-generation drug-eluting stents. A study conducted by Schomig et al. (76) found significant bare-metal stent restenosis at 6-month follow-up (86%) in patients with radiation-induced CAD (p < 0.001) compared with control subjects (76). The group subjects were also found to have significantly narrower coronary lumen diameters (1.0 ± 0.6 mm vs. 1.9 ± 0.9 mm, p < 0.001). Caution with appropriate patient selection must be exercised for PCI, given that certain post-irradiation complications might preclude surgical candidature for failed PCI. Of note, the internal mammary arteries might be chronically scarred or more friable, making them unsuited for use in bypass grafting. In conjunction, the presence of damaged target vessels might add increasing complexity and risk in patients undergoing CABG (77,78). In one study, the internal mammary artery was an appropriate conduit less than one-half the time, routinely harvested by the same authors in their standard practice (62). Routine angiography of the internal mammary arteries might be useful to guide conduit utility and subsequent treatment options.

To date there are few studies, mostly with small patient numbers, on cardiac surgical outcomes and the post-operative course in this specific patient population. Siregar et al. (79) showed that previously treated patients for Hodgkin’s lymphoma had relatively good early post-operative outcome with a 1-year survival of 86%; however, the long-term survival at 4 years was only 46%. The most common post-operative complication after cardiac surgery (operations included: CABGs, valvular repair, valvular replacement) was atrial fibrillation, however, with a slightly higher incidence than described by large databases in the general population [33% vs. 20%] (79,80). In the post-operative setting these patients are also at increased risk of pulmonary complications, particularly pleural effusions, pneumonia, and respiratory insufficiency, due in part to the presence of pre-existing radiation-induced lung disease and smoking (62,79). Thus pre-operative smoking cessation assumes even greater importance in this patient cohort.

The presence of diastolic dysfunction is another challenging issue in this patient group, with high left atrial pressures contributing to pulmonary congestion, thereby increasing post-operative morbidity. The largest study performed by Chang et al. (62) included 70 patients with previous HD. These authors found that extensive exposure of the heart to radiation increased perioperative morbidity and decreased both short- and long-term survival. The cardiac risk factors included higher central venous pressure, higher left atrial pressure, and lower LV mass (62). Increased central venous pressure as a risk factor also suggests that concomitant right ventricular dysfunction is a complicating factor, and in particular the anterior location of the right ventricle makes it vulnerable to dysfunction post-radiotherapy.

As such, it is clear that, for patients with a prior history of chest irradiation in whom cardiothoracic surgery is contemplated, full consideration should be given to the potential impact of alterations in the structure and function of the skin, mediastinal tissues, lungs, intra-thoracic vessels, and the heart per se require careful consideration (59,81). On balance, an appropriate choice of surgical versus percutaneous interventions balancing the relevant risk/benefit ratio of each approach can then be offered to the patient in the setting of the specific clinical context.

**Conduction disturbance.** A permanent pacemaker is indicated in the setting of high-degree block or symptomatic sick sinus syndrome, following the routine American College of Cardiology/American Heart Association guidelines. Additionally, after a life-threatening arrhythmia or aborted sudden cardiac death, an ICD is indicated for secondary prevention, upon exclusion of ischemia. For some patients, an electrophysiological study and ventricular tachycardia ablation might be useful.

**Valvular dysfunction.** As outlined in the preceding text, aortic and mitral valve regurgitation and stenosis are well-recognized complications of thoracic irradiation.
Crestanello et al. (59) were one of the first groups to investigate whether conventional reparative techniques could be applied to irradiation related valvular disease. These investigators found that the durability of valve repair in long-term survivors was limited, because severe dysfunction developed in one-third of the patients and with reoperation being required in 16% (59). Accordingly, valve replacement might be preferable to valve repair when considering long-term cardiovascular outcomes. In some cases of severe aortic stenosis with significant extracardiac late sequelae of radiotherapy, transcatheter aortic valve implantation might be the best treatment option.

**Heart failure.** Although no specific therapies for the treatment of radiation-induced heart failure have been identified, therapy of systolic heart failure should follow American College of Cardiology/American Heart Association guidelines, with slow upward titration of ACEI, beta blockade, and aldosterone inhibitors, particularly in patients with reduced LV systolic function. In patients with diastolic dysfunction, the principles of treatment broadly mirror those of patients with heart failure with preserved ejection fraction. Although no treatment has been shown to convincingly improve morbidity and mortality in patients with heart failure with preserved ejection fraction (82), diuretic agents and, more recently, exercise training might be introduced to improve symptoms (83). Hypertension, sinus rhythm, and myocardial ischemia must also be optimized. The same indications for insertion of ICD cardiac resynchronization therapy should apply to patients with radiation-induced heart failure and might additionally prolong survival. If significant subcutaneous skin involvement is observed as a late effect of thoracic irradiation, a sub-pectoral approach for device implantation might be necessary to avoid poor wound healing and infection. In the instance of refractory heart failure, temporary inotropic support for periods of decompensation might be needed. In patients with refractory heart failure the use of LV assist devices and heart transplantation might be considered; however, the decision with regard to the appropriateness of such therapies clearly requires multidisciplinary input, particularly from oncologists.

**Heart transplantation.** For a small patient subgroup with biventricular dysfunction, calcified cardiac skeleton (Fig. 1), previous open-heart surgery, and restrictive or constrictive hemodynamic status, heart transplantation might be the only possible and reasonable treatment option. The largest reported study to date was conducted by Uriel et al. (84). This was a retrospective study of 9 patients with radiotherapy induced cardiac disease who underwent orthotopic heart transplantation. Of these patients, there were 3 in-hospital perioperative deaths, 3 second cancers, and 3 life-threatening infections. Five of the 9 patients (56%) were still alive at a mean follow-up of 10 years post-transplantation (however, 2 with a second cancer) (84). Orthotopic heart transplantation also raises the question of potential cancer recurrence in an immunosuppressed population, with a paucity of data in this area to date.

**Future research.** Large prospective studies still need to be conducted to explore the benefit of prophylactic treatment strategies in asymptomatic patients. For example, the effect of statins, ACEI, or aldosterone inhibitors in asymptomatic radiation-treated cancer survivors to slow/halt accelerated atherosclerosis, myocardial dysfunction, or myocardial fibrosis is not yet known. The clinical benefit of such pharmacological agents in those both with and without additional cardiac risk factors is of particular clinical interest. The impact of newer-generation drug-eluting stents on in-stent restenosis and particularly stent thrombosis in this patient cohort still needs to be clarified. And clearly, the long-term effects of contemporary and refined radiotherapy techniques mandate further analysis with time.

**Conclusions**

It is clear that thoracic radiation, particularly as administered with older treatment paradigms, increases cardiovascular-related mortality in the long term. Presently, the utility and optimal strategy for screening is uncertain. Future prospective long-term studies are needed to directly determine the efficacy of screening asymptomatic cancer survivors to help establish guidelines. However, given the high incidence of such complications, we believe the development of a uniform approach to be potentially beneficial. The use of non–radiation-based techniques such as echocardiography and cardiac MRI provide an opportunity for regular assessment of the heart for the myocardial, valvular, and pericardial complications of thoracic irradiation. In conjunction, serial stress echocardiography could provide a useful means for the detection of developing flow-limiting coronary lesions. The role of preventive therapies is uncertain at this time; however, aggressive risk-factor reduction should be adopted according to published guidelines. Taken together, it is likely that the incidence of the late sequelae of thoracic irradiation might continue to rise for some time, reflecting the prior use of this form of adjunctive therapy in patients with malignancy.

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