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Valvular Heart Disease (J Dal-Bianco, Section Editor)

# Radiation-Associated Cardiac Disease: From Molecular Mechanisms to Clinical Management

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## Abstract

*Purpose of review* Radiation-associated cardiac disease (RACD) is an increasingly recognized latent manifestation of chest and mediastinal radiation therapy. The delayed presentation reflects increased survival rates from malignancies successfully treated decades previously. However, individuals are now presenting with multiple coexistent manifestations of RACD and pulmonary disease as a consequence of high-dose radiation administered prior to the routine institution of modern dose-modulating regimens. Increased awareness of RACD is critical for implementation of appropriate screening algorithms and for specific management strategies involving the timing and strategies of intervention in these patients.

*Recent findings* Recent advances in multimodality cardiac imaging have demonstrated pathognomonic findings of RACD, which can predict outcomes including mortality. Accurate diagnosis of these typically concurrent manifestations is critical and should prompt referral to a center experienced in managing RACD as surgical risk is significantly increased for this patient cohort, particularly for those undergoing redo operation.

*Summary* The latent effect of RACD and its unique combination of manifestations means that these patients will increasingly present with challenging management issues, resulting in increased rates of morbidity and mortality. Timing of treatment intervention must be carefully considered, although percutaneous options may provide alternative future strategies for this higher risk cohort.

## Introduction

Radiation-associated cardiac disease (RACD) is a late manifestation of radiation therapy for a variety of thoracic malignancies including breast cancer, Hodgkin's and non-Hodgkin's lymphoma, lung cancer, esophageal cancer, and numerous other mediastinal tumors [1••]. Improvements in chemotherapeutic and radiation regimens over the past several decades have resulted in dramatic increases in long-term survival from these malignancies [2]. This prolonged longevity, however, has come at the cost of an increasing prevalence of RACD [3•]. The short-term cardiac manifestations of radiation therapy have been recognized since the early 1900s, when high-dose, wide-field mediastinal radiation for thoracic malignancies were commonplace. However, the longer-term cardiac effects of radiation have only come to light in recent decades given the significant lag between radiation treatment and clinical presentation. The absolute risk of cardiac morbidity and mortality in patients with a history of prior mediastinal radiation therapy is 2% at 5 years and 23% at 20 years compared to non-irradiated patients [4]. Modern thoracic radiation therapy regimens strive to minimize the cardiotoxic effects of radiation through provisions such as respiratory gating techniques including deep inspiratory breath-holds and activated breath control, shielding techniques and using treatment algorithms utilizing narrow tangential beams [5]. Despite these advancements, current clinical practice in managing patients with RACD is largely shaped by antiquated practices.

RACD can involve any cardiac structure and covers an array of cardiovascular disorders involving the pericardium, myocardium, coronary arteries, valvular apparatus, and conduction system in addition to the aorta, pulmonary arteries, carotid arteries, and the lungs. In this article, we will review the clinical and imaging manifestations of RACD and offer a clinically focused approach to diagnosing and managing the cardiac manifestations of radiation therapy. We identified data for this review using MEDLINE, Current Contents, and PubMed using the screening terms "radiation" and "heart disease."

# Molecular mechanisms and risk factors

Due to their postmitotic state, cardiac myocytes are fairly resistant to the toxic effects of radiation therapy. Endothelial cells, on the other hand, are sensitive to radiation and the pathogenesis of most RACD appears to be mediated by endothelial damage. This endothelial damage is compounded and accelerated by conventional cardiac risk factors including smoking, hypertension, hyperlipidemia, and diabetes [6]. Radiation exposure results in increased reactive oxygen species formation and a consequent inflammatory response resulting in increased production of nuclear factor-kappa beta. This inflammatory milieu results in higher expression of adhesion molecules, matrix metalloproteases, and pro-inflammatory cytokines in addition to the downregulation of nitric oxide [7].

The volume of myocardium exposed to radiation is the most significant determinant for the development of RACD [8]. One randomized controlled trial (RCT) compared pre- or post-operative radiation therapy versus surgery alone in 960 patients undergoing modified radical mastectomy for primary breast cancer. Although there was a trend towards improved survival in the cohort undergoing radiation therapy ($p = 0.09$), there was a significant increase in mortality due to ischemic heart disease in those exposed to higher doses of radiation during a mean follow-up of 16 years (relative hazard 3.2, $p < 0.05$). In comparison, there was no such increase observed in patients with right-sided tumors or in those receiving lower doses of radiation to the myocardium [9].

Concurrent use of cardiotoxic chemotherapeutic agents such as anthracyclines and *HER-2* receptor antagonists also potentiate the deleterious cardiovascular

effects of radiation therapy [10]. Similarly, smoking and metabolic derangement (hypertension, hyperlipidemia, and diabetes) can accelerate the cardiotoxic effects of radiation exposure, while younger age at the time of radiation treatment is associated with the greatest risk of RACD. One retrospective study of 635 patients with Hodgkin's lymphoma treated with mediastinal radiation demonstrated a relative risk of fatal myocardial infarction of 41.5 compared with an age-, race-, and gender-matched control population [11•, 12••].

# Manifestations

## Pericardial disease

The pericardium is affected in as many as 70% of cases of RACD [13]. Radiation-induced pericardial damage results from microvascular injury with increased capillary permeability and consequent formation of a protein-rich exudate which creates a medium for inflammation. This can manifest acutely as an immediate response to radiation therapy as pericarditis or the development of a pericardial effusion, while constrictive pericarditis typically manifests many years later as a consequence of chronic pericardial fibrosis with associated pericardial calcification [14].

Contemporary radiation techniques place an emphasis on minimizing cardiac radiation exposure by ensuring lower radiation doses, equal weighting of the anterior and posterior fields, and subcarinal blocking. With these measures, rates of pericarditis have fallen dramatically [15]. Early acute pericarditis is observed almost exclusively in patients undergoing high-dose mediastinal radiation therapy for Hodgkin's and non-Hodgkin's lymphoma [16]. Although pericardial effusions can be associated with acute pericarditis, delayed chronic pericardial effusions also occur months to years after radiation exposure and are typically followed with serial imaging. Symptomatic effusions causing hemodynamic compromise should be treated with pericardiocentesis or a pericardial window, and concurrent hypothyroidism should be ruled out in these patients as many of these patients may have also undergone neck irradiation [17, 18].

Chronic calcific pericarditis typically presents decades after treatment as a late complication. Manifestations are usually those of right-sided heart failure including jugular venous distention, peripheral edema, ascites, and even anasarca. Given the coexistent restrictive physiology brought about by radiation-induced myocardial fibrosis in many of these patients, it is often difficult to distinguish between restriction and constriction and invasive hemodynamic assessment using concurrent right and left heart catheterization is often required to reliably differentiate between the two. Multimodality imaging techniques including myocardial tissue velocities and strain imaging using echocardiography, computed tomographic (CT) assessment of pericardial thickening and calcification and ventricular deformities with respirophasic septal shift and pericardial delayed enhancement on cardiac magnetic resonance (CMR) are also useful in identifying pericardial pathologies [1].

Radical pericardiectomy is the treatment of choice for patients with chronic pericarditis refractory to conservative measures such as diuretics and a low-salt diet. However, patients with chronic pericarditis typically have other manifestations of RACD including valvular disease and coronary artery disease. These patients have traditionally had poorer outcomes following pericardiectomy

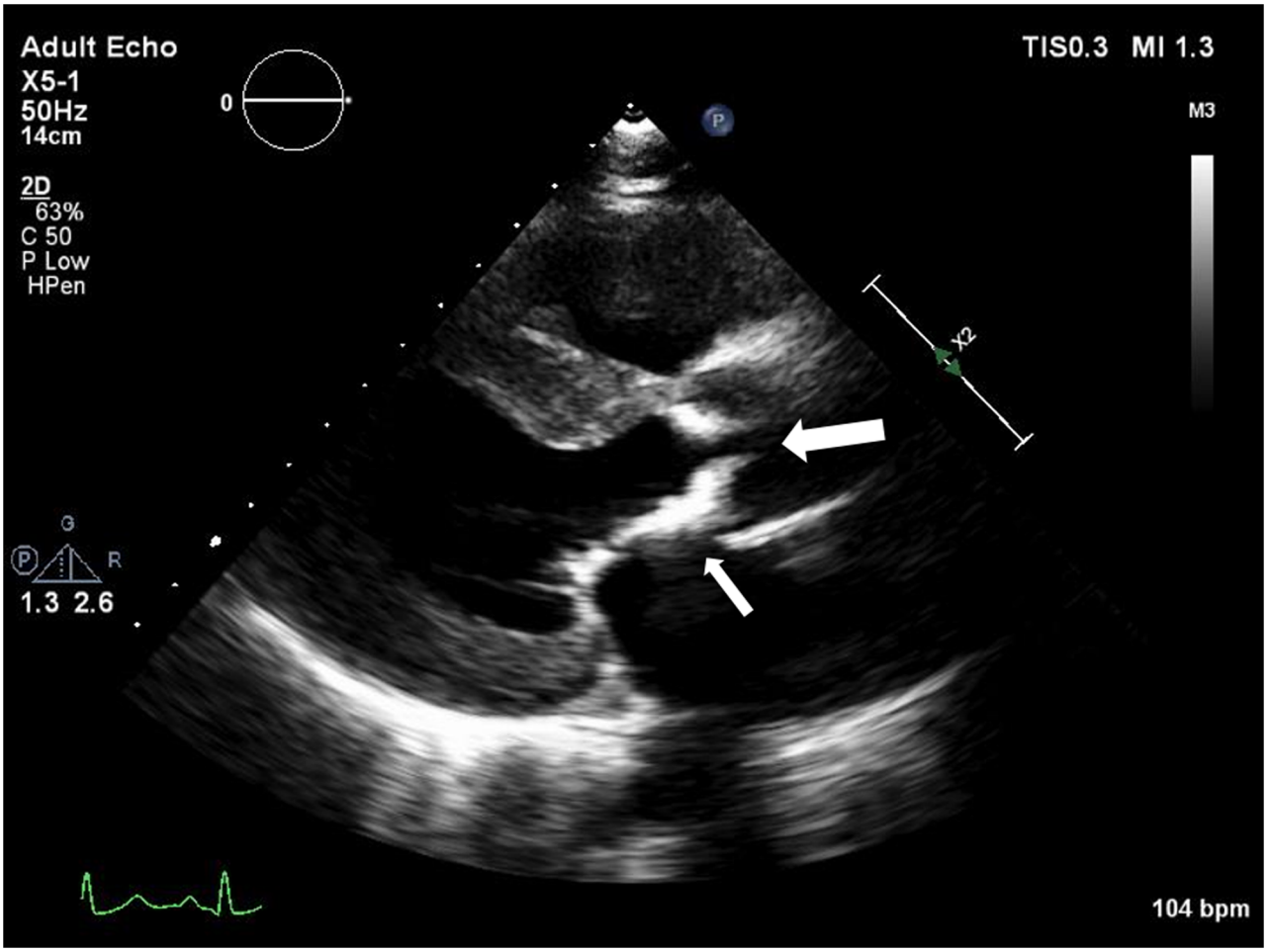


**Fig. 1.** Echocardiogram image from a 52-year-old male treated with mantle radiation for Hodgkin's lymphoma 25 years ago. Parasternal long-axis view demonstrates severe, calcific stenosis of the aortic valve (large arrow), with associated thickening and calcification of the aorto-mitral curtain (small arrow).

with one study of 163 patients with radiation-associated chronic pericarditis showing a 7-year overall survival rate of only 27% [19•].

## Myocardial disease

Mediastinal radiation may cause systolic or diastolic dysfunction. Myocardial damage results from microvascular injury which results in ongoing ischemia and consequent myocardial fibrosis. Concurrent radiation-associated stenosis of the epicardial vessels can result in infarction and regional replacement-type fibrosis. Systolic dysfunction occurred in almost half of patients historically when high-dose, wide-field mediastinal radiation was the norm [20]. However, using modern radiation delivery techniques, systolic dysfunction occurs in fewer than 5% of patients and the vast majority of cases of radiation-associated myocardial dysfunction have a restrictive pattern. Systolic dysfunction is observed almost exclusively in patients undergoing concurrent chemotherapy with cardiotoxic agents [21]. One single-institution study of 294 patients with

Hodgkin's lymphoma treated with radiation found that 14% developed some degree of diastolic dysfunction during a mean follow-up of 3.2 years [22].

Treatment of radiation-associated myocardial disease mirrors that of other forms of cardiomyopathy with a focus on symptom relief. Advanced hemodynamic support such as left ventricular assist devices and heart transplantation may be an option for carefully selected patients, although cardiothoracic surgery may be more technically challenging in the setting of prior radiation and immunosuppression cannot be considered if there is any likelihood for cancer recurrence. One study explored outcomes of cardiac transplantation in 12 patients with RACD, 10 of whom had restrictive lung disease. They demonstrated a 5-year survival of only 46.7% after transplant, illustrating the high risk associated with this patient population [23].

## Valvular disease

Valvular heart disease occurs in as many as 81% of patients with RACD [24]. Both stenotic and regurgitant lesions have been described and the left-sided valves are affected far more commonly than the right-sided valves. Radiation exposure results in leaflet retraction, fibrotic thickening, and eventual calcification [25]. Radiation also affects surrounding peri-valvular structures including the valve annulus, subvalvular apparatus, and aorto-mitral curtain (Fig. 1). Thickening and calcification of the aorto-mitral curtain is a hallmark of RACD and has been found to be an independent predictor of outcomes in these patients [26•]. Radiation-associated valve disease is thought to result from radiation-induced expression of osteogenic factors such as bone morphogenic protein 2, osteopontin, alkaline phosphatase, and runt-related transcription factor 2 by valvular interstitial cells bringing about a phenotypic change from a myofibroblast- to an osteoblast-like cell [27].

There is a significant lag time between radiation exposure and clinically apparent valve disease with symptoms occurring 10 to 20 years after therapy [28]. This is important clinically as asymptomatic patients treated more than 20 years ago remain at markedly elevated risk of aortic regurgitation (60% vs 4%), aortic stenosis (16% vs. 0%), mitral regurgitation (52.1 vs. 26.3%), and tricuspid regurgitation (4% vs. 0%) compared to those treated within 10 years [29].

The choice of valvular intervention in patients with severe symptomatic disease is often challenging in RACD given the extent to which other cardiac structures are involved as well as the high peri-operative morbidity and mortality. One study demonstrated a long-term mortality rate of 45% in RACD patients undergoing surgery on a single valve and 61% in those undergoing surgery on multiple valves compared to 13 and 17%, respectively, in patients without a history of mediastinal radiation [30]. Valve replacement is preferred to repair due to the high failure rates of repair attributed to ongoing radiation-induced valvular changes after repair such as leaflet thickening, restriction, and calcification [31].

Due to the high morbidity and mortality associated with surgical intervention in RACD, such operations should be carried out at high-volume centers by surgeons experienced in managing RACD. The timing of surgery is also critical, as if there are multiple concurrent manifestations, it is better to try and address all issues during a one time surgery, rather than subject these already high-risk patients to the increased morbidity and mortality of reoperation. In addition to

complex surgeries, these patients can also have protracted post-operative recuperation due to their concurrent radiation-associated pulmonary disease, poor chest wound healing, recurrent pleural effusions from impaired chest lymphatic drainage after radiation and other comorbidities. Many of these factors likely contribute to the significantly higher longer-term mortality we demonstrated in patients with RACD undergoing cardiac surgery compared to an age- and gender-matched cohort without prior mediastinal radiation (55% vs. 28%, $p < 0.001$) [32••]. We also studied long-term outcomes of patients with radiation-induced severe symptomatic aortic stenosis undergoing surgical aortic valve replacement (SAVR). At a mean follow-up of 6 years, 48% of patients in the RACD group died compared to 7% of those without RACD [33••]. We subsequently studied the rate of progression of aortic stenosis in RACD to determine whether this accounted for the disparity in mortality between the groups. We found no significant difference in the rate of progression but found that significantly more patients in the RACD group underwent AVR (80% vs. 50%, $p < 0.01$) at a much shorter time from the initial echocardiogram (2.9 ± 1.6 years vs. 4.1 ± 2.4 years; $p < 0.01$) [34•].

In light of the unacceptably high morbidity and mortality rates after surgery in RACD, transcatheter aortic valve replacement (TAVR) had been highly touted as an alternative to SAVR. A percutaneous approach would theoretically mitigate several problems encountered during open heart surgery including radiation-induced fibrosis of surrounding structures, adhesions, and restrictive pulmonary disease. We studied 98 patients with RACD undergoing TAVR at our institution compared to 172 undergoing SAVR and found an in-hospital, 1- and 2-year survival of 96%, 91%, and 86% in the TAVR group compared to 96%, 86%, and 80% respectively in the SAVR group indicating that TAVR may offer a short-term survival benefit [35••]. Longer-term TAVR outcomes remain undefined in the RACD population.

## Vascular disease

Coronary artery disease (CAD) is the most common cause of mortality in patients with RACD. The morphologic features of atherosclerotic disease in RACD are the same as those in non-irradiated patients including intimal proliferation, lipid-rich macrophage accumulation, and plaque formation [36]. Radiation doses as little as 0.5 Gy can initiate atherosclerosis through radiation-induced inflammation, and radiation is an independent risk factor for accelerated atherosclerosis [37]. The risk of radiation-induced vasculopathy is accentuated by conventional cardiac risk factors [38]. The time from radiation exposure to the development of clinically significant coronary artery disease is approximately 9 years and coronary artery disease occurs in approximately 10% of patients within 20 years of radiation therapy [28]. Hence, screening for underlying radiation-induced hemodynamically significant CAD is usually recommended earlier than screening for valvular heart disease, which typically manifests a decade later. The risk for epicardial coronary disease is directly proportional to the dose and duration of radiation. One study of more than 2000 women with breast cancer showed that the risk of coronary disease increased by 7.4% per Gy of thoracic radiation without an obvious ceiling dose [39].

The distribution of coronary involvement usually reflects the area irradiated, with the ostia of the epicardial vessels affected most frequently. For example, the

left anterior descending artery and the distal diagonal vessels are more commonly involved in patients with a history of left-sided breast cancer, where the left ventricular apex and anterior wall are typically exposed to the highest doses of radiation [40].

As mentioned previously, prior mediastinal radiation creates a hostile surgical environment with fibrosis of the chest and surrounding structures, poor wound healing, adhesions, and concurrent large-vessel vasculopathy. Similarly, inclusion of the internal thoracic arteries in the radiation field may result in atherosclerosis of these vessels, thereby making them unsuitable for harvesting as bypass graft conduits. Although percutaneous coronary intervention (PCI) is generally preferred where possible in RACD, CAD in this setting involves multiple coronary arteries and is usually a more diffuse process, thereby making it not ideally amenable to PCI. The preponderance of concurrent valvular lesions and pericardial involvement in RACD also means that coronary artery bypass grafting (CABG) may be the more logical management strategy. One study of 157 patients with RACD undergoing PCI at our institution found that 38% of these patients died during a mean follow-up of 6.6 years compared to 27% of age- and gender-matched controls without prior radiation therapy ($p = 0.04$). Balloon angioplasty and bare-metal stent placement (HR, 2.50; 95% CI, 1.61–3.97; $p < 0.0001$), a higher SYNTAX score HR, 1.99; 95% CI, 1.32–3.04; $p < 0.001$), older age (HR, 1.70; 95% CI, 1.07–2.07; $p = 0.024$), and a history of smoking (HR, 1.88; 95% CI, 1.10–3.09; $p = 0.022$) all portended worse outcomes [41]. Another recent study comparing 116 patients with RACD with 408 control patients undergoing PCI found no difference in mortality between the two groups during a median follow-up of 6.3 years [42].

Large-vessel vasculopathy is also seen as a consequence of radiation therapy and can involve the ascending aorta, arch branch vessels, and main pulmonary artery. One study showed that 59% of patients with RACD had ascending aortic calcification and 13% had severe circumferential calcification [41]. This severe "porcelain" aortic calcification may prohibit aortic clamping or cannulation during cardiothoracic surgery, which can have significant technical implications for surgery. Extensive radiation-induced atherosclerotic disease may also be more likely to spontaneously embolize or be disrupted during procedures such as coronary catheterizations resulting in increased likelihood for cerebrovascular accidents and peripheral embolization [43].

## Conduction system disease

Although asymptomatic repolarization abnormalities are commonly observed during radiation therapy, life-threatening arrhythmias after a latent period of several years have been described. Due to the significant lag between treatment and the appearance of electrical abnormalities, it is often difficult to establish causation and define incidence precisely as a result. Infranodal and right bundle branch block are the most frequently encountered conduction abnormalities in patients with RACD given the anterior location of the right bundle [44]. RACD is also associated with prolongation of the QT interval. One study of 134 patients with a history of chest radiation therapy for childhood cancer found that 12.5% had a corrected QT interval on electrocardiogram (ECG) of 440 milliseconds or more [45]. Another study of 69 breast cancer survivors over a 10-year period found that T-wave changes were the predominant ECG

abnormality at 6 months, but at 10 years, these T-wave changes had resolved and ST-depressions predominated [46]. Given the latent period between radiation treatment and ECG manifestations and the inherent difficulty in determining causation as a result of this, the following criteria have been proposed to identify likely causative links between conduction disease and RACD [47]: (1) total radiation dose > 50 Gy, (2) period of 10 or more years since treatment, (3) interval abnormal ECG finding such as bundle branch block, (4) pericardial involvement, and (5) other cardiac or mediastinal findings consistent with RACD.

An overview of the cardiac manifestations of radiation therapy is shown in Table 1.

## Contemporary radiation practices

Given the increased recognition of RACD, there has been a shift in recent decades from high-dose wide-beam radiation therapy to approaches that minimize cardiac exposure to radiation without compromising treatment. This has been achieved through three major principles: reducing the radiation dose, reducing the radiation field or irradiated tissue volume, and through the use of new planning and delivery techniques.

Contemporary radiation therapy has involved a shift from extended-field, mantle-field, and involved-field radiation therapy to far more restrictive strategies such as involved-node and involved-site radiation therapy [48]. One study of patients with Hodgkin's lymphoma found that transitioning from 27.5 Gy using mantle-field therapy to 7.7 Gy with involved-node therapy resulted in a reduction in the 25-year absolute excess cardiac risk from 9.1% to 1.4% and a reduction in cardiac mortality by more than a half from 2.1% to 1% [49]. Furthermore, involved-node and involved-site radiation therapy require precise CT planning which results in more accurate targeting of the tumor and less unnecessary myocardial exposure compared to the two-dimensional planning used for mantle-field and involved-field radiation. Further improvements in conformality have been brought about by intensity-modulated radiotherapy and proton-beam

**Table 1. An overview of the early and late cardiac manifestations of radiation therapy**

| Cardiac structure | Manifestations of RACD |
|---|---|
| *Pericardium* | Acute or chronic pericarditis, acute or chronic pericardial effusion, cardiac tamponade, constrictive pericarditis |
| *Myocardium* | Diffuse myocardial fibrosis, diastolic dysfunction due to restrictive cardiomyopathy, systolic dysfunction, and congestive heart failure due to ischemic cardiomyopathy |
| *Valves* | Accelerated valvular degeneration (leaflet thickening, restriction, and calcification) resulting in regurgitation, stenosis microvascular disease |
| *Coronary Arteries* | Accelerated atherosclerosis, coronary artery disease (often diffuse and multi-vessel) myocardial infarction, resting and regional wall motional abnormalities |
| *Vascular* | Carotid stenosis, accelerated atherosclerosis of the internal mammary arteries, "porcelain" calcified aorta, pulmonary artery calcification |
| *Conduction system* | Arrhythmias, heart block, sick sinus syndrome, autonomic dysfunction |

therapy in addition to respiratory motion management such as deep-inspiration breath holding and end-inspiration breath holding [50–54].

## Current guidelines and multimodality imaging

Guidelines for diagnosing and monitoring patients with RACD have been published by the European Association of Cardiovascular Imaging and the American Society of Echocardiography and are summarized in Table 2 [12••].

Aggressive lifestyle and cardiovascular risk-factor modification through weight loss, exercise, blood pressure optimization, and smoking cessation are paramount. Baseline comprehensive transthoracic echocardiography (TTE) in addition to a detailed cardiovascular history and physical examination should be obtained in all patients prior to radiation therapy. A comprehensive annual assessment paying close attention to symptoms and signs of cardiopulmonary disease should be carried out, and any new symptoms or signs should prompt reevaluation with TTE. Particular features of RACD on TTE include biventricular systolic and diastolic dysfunction, multi-valvular involvement, prominent calcification, wall motion abnormalities, and pericardial disease. One should also pay close attention to the TTE features of pericardial constriction including biatrial enlargement, pericardial thickening and calcification, myocardial tethering, an early diastolic septal bounce, and plethora of the inferior vena cava and hepatic veins with increased respiratory variation. In patients without signs or symptoms, repeat TTE should be obtained 10 years after the start of radiation therapy and surveillance TTE should be obtained every 5 years thereafter. Patients with at least one risk factor for RACD (Table 1) undergoing anterior or left-sided radiation therapy are considered high-risk and should undergo TTE 5 years after initiating radiation therapy. Given the elevated risk of coronary disease in these patients, noninvasive ischemic evaluation should be obtained 5–10 years after radiation exposure with repeat stress testing at 5-year intervals thereafter. Stress TTE and stress CMR are generally preferred due to their higher

**Table 2. Cardiovascular screening for patients undergoing thoracic radiation therapy. Adapted from the European Association of Cardiovascular Imaging/American Society of Echocardiography Guidelines [12••]. *TTE* transthoracic echocardiogram**

| |
|---|
| *Prior to radiation treatment* |
| • Comprehensive cardiovascular screening and risk factor modification |
| • Baseline TTE to detect abnormalities in cardiac structure or function |
| *Annual follow-up* |
| • History and physical examination |
| • Repeat TTE if murmur detected |
| • Thorough investigation of newly-reported symptoms |
| *5-year follow-up for high-risk patients* |
| • TTE |
| • Stress TTE or stress CMR |
| • Repeat TTE at 5-year intervals thereafter |
| *10-year follow-up for asymptomatic lower-risk patients* |
| • TTE |
| • Repeat TTE at 5-year intervals thereafter |

specificity and radiation-sparing techniques. The routine use of cardiac CT is not advocated, but selective use can be helpful to assess pericardial calcification, great vessel calcification, and peri-operative planning. Screening for associated pulmonary complications of prior radiation therapy should be undertaken in these high-risk patients.

## Conclusion

RACD is increasingly being recognized in cancer survivors as a consequence of prior chest and mediastinal radiation performed decades earlier. Awareness of the potential for cardiac manifestations in these patients is vital so that appropriate multimodality-based screening can be implemented. Those patients needing intervention should be managed by physicians and centers experienced in RACD, as individualized timing and technique of surgery is crucial to try and minimize rates of morbidity and mortality in this high-risk cohort.

## Compliance with Ethical Standards

**Conflict of Interest**
The authors declare that they have no 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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