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THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Prevention, Diagnosis, and Management of Radiation-Associated Cardiac Disease

JACC Scientific Expert Panel

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) discuss the state-of-the-art diagnostic techniques for detection of radiation-associated cardiac disease; 2) discuss the current management strategies of treating patients with established radiation-associated cardiac disease; and 3) discuss current radio-oncologic strategies to reduce radiation dose and minimize chances of future development of radiation-associated cardiac disease.

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ABSTRACT

Radiation-associated cardiac disease, a heterogeneous and complex disease, manifests years or even decades following radiation exposure to the chest. It is associated with a significantly higher morbidity and mortality. Often, the presentation is vague and overlaps with many diseases, presenting unique diagnostic and management issues. As a result, a high index of suspicion followed by multimodality imaging is crucial, along with comprehensive screening to enable early detection. Timing of intervention should be carefully considered in these patients, because surgery is often complex with an emerging role of percutaneous interventions. (J Am Coll Cardiol 2019;74:905–27) © 2019 by the American College of Cardiology Foundation.

Radiotherapy (XRT) is frequently used as an adjunct to surgery/chemotherapy in thoracic malignancies and lymphomas. Although XRT results in significantly improved survival of cancer patients, the irradiation of healthy surrounding tissues results in long-term side effects. Radiation-associated cardiac disease (RACD) and radiation-associated pulmonary disease (RAPD) can develop immediately or gradually, often several years following XRT. Although modern XRT delivery techniques have significantly reduced the dose and cardiac involvement, a major issue remains: the development of RACD decades following high-dose XRT. Also, clinicians often do not associate XRT exposure in the distant past with current cardiac manifestations (which range from pericarditis, coronary artery disease [CAD], valvular heart disease, nonischemic cardiomyopathy, and conduction abnormalities) (**Central Illustration**). Unfortunately, the presenting picture may be clouded by the contribution of shared common risk factors of cardiovascular disease, making precise diagnosis difficult. This document represents a consensus effort by a broad range of experts to provide a focused overview of RACD, including prevalence, clinical/imaging manifestations, screening recommendations, and therapeutic options based upon cumulative experience over the last 20 years.

PREVALENCE AND RISK FACTORS

Despite data from many large observational studies, the exact prevalence of RACD is difficult to determine because of heterogeneity of presentation, underrecognition of manifested disease and improvement of XRT delivery techniques over the years. Most studies report prevalence based on XRT exposure from decades ago; and the prevalence using modern XRT protocols is still poorly defined and would take years to determine. As shown in **Table 1**, there are varying degrees of data related to prevalence of various manifestations of RACD and RAPD (1–14), with most of the data reported from XRT for treatment of breast cancer and Hodgkin's lymphoma decades ago. However, on the basis of available data, mediastinal XRT is associated with significantly increased risk of heart failure with predominantly preserved EF, ischemic heart disease, left-sided

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HIGHLIGHTS

- RACD, a heterogeneous disease that can manifest years or decades following radiation exposure to the chest, is associated with high morbidity and mortality
- It is crucial to develop comprehensive multimodality imaging-based screening protocols to adequately identify those at risk, plan interventions, and evaluate treatment responses.
- Coordinated management by an experienced team of providers at a center of excellence is strongly advocated with individualized timing of surgery or percutaneous interventions.
- The longer-term goal should involve developing radiotherapy protocols that minimize the chances of developing RACD.

valvular heart disease, electrical abnormalities (including autonomic dysfunction), pericardial disease, and porcelain aorta. **Table 2** lists the potential risk factors for RACD.

EVOLUTION OF RADIOTHERAPY

The guiding principle in XRT is to give a therapeutic dose to the tumor and minimize unwanted exposure to surrounding normal tissues. Cardiac exposure is nearly always the result of "stray" radiation as the heart is almost never the actual target, except for rare sarcomas or metastases. The primary ways in which cardiac exposure has been reduced are better patient selection, newer XRT technology, reducing field size, and lowering the target dose (when appropriate). The major cancers where cardiac exposure is a significant clinical challenge are discussed in the following.

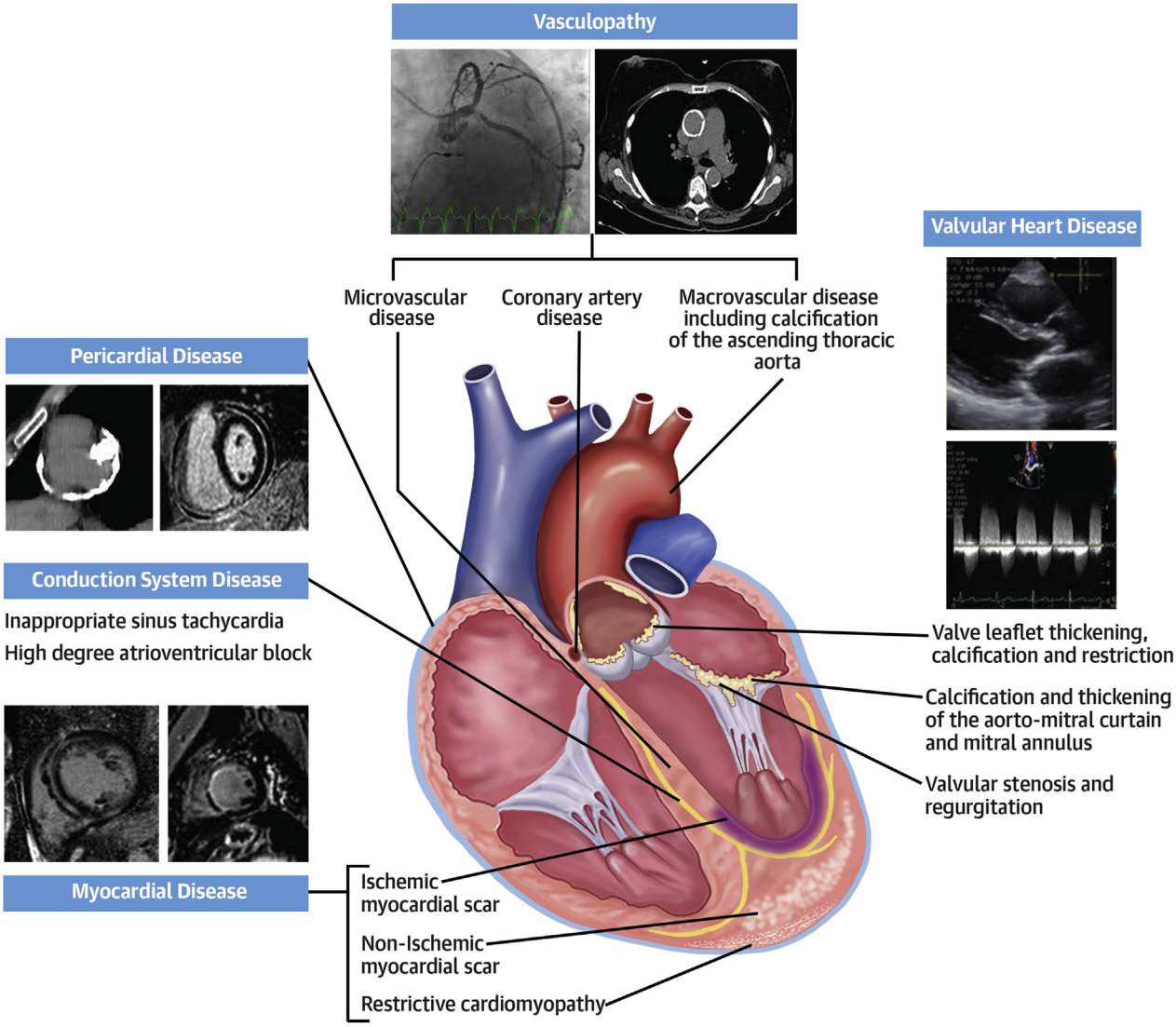
LYMPHOMA. High-dose (≥40 Gy), extended field XRT has played an important role in the curative treatment of lymphoma since the 1960s. A common approach for supradiaphragmatic disease was to irradiate a mantle field (**Figure 1**) using an anteroposterior/posteroanterior technique with tissues (including the heart) receiving a dose of ~30 to 40 Gy (15). Because patients were younger, they survived for many decades after treatment, giving them enough time to manifest RACD. Luckily, the treatment approach has changed, and more recent patients are not exposed to this type of radiation (**Figure 1**). For patients who receive XRT and chemotherapy, extended field is no longer used, and XRT has evolved to small fields (e.g., involved field, involved site, and involved node [16]). However, these techniques still require radiating sites of pre-chemotherapy disease. Most recently, a concept of irradiating only sites of residual abnormalities after chemotherapy has emerged (17). Through successive clinical trials, the prescription XRT dose has been lowered from >40 Gy to 20 to 30 Gy, depending on risk factors (17). In addition, advanced delivery techniques like deep inspiratory breath hold (DIBH) (18) and proton therapy (19) have been used in select cases to further reduce cardiac exposure. DIBH pulls the heart inferiorly and allows treatment of upper mediastinum with less cardiac exposure. Because protons can stop at a finite distance, normal tissue distal to the target is avoided. All these modifications have reduced exposure in many patients to close to zero with almost no risk of RACD. However, in some patients, even with all modern treatment planning, especially those with lower mediastinal disease, there can still be significant cardiac exposure with mean heart doses >10 Gy (20,21). When evaluating these patients, discussion with the radiation oncologist to understand RACD risk is important.

BREAST CANCER. XRT (**Figures 1 and 2**) is used after lumpectomy for most patients treated with breast conservation therapy, because it improves survival (22). Tangential fields used for breast conservation historically extended from the midline to the midaxillary line. For left-sided lesions, the tangent fields often included a small portion of the left heart and left anterior descending artery, leading to cardiac events (23). As a result, historical data showed that patients who received radiation had higher rates of RACD versus those who did not (24). A systemic review of total heart doses delivered from 2014 to 2017 was down to 3.6 versus 5.4 Gy for 2003 to 2013 (25). At an experienced center, it is exceedingly rare to have a mean heart dose of >1 Gy when treating the left breast without any nodal involvement. Only rare patients with challenging anatomy (tumor beds in the medial part of the breast and with the heart hugging the chest wall) have mean heart doses of >1 Gy, despite DIBH. For patients with higher risk and/or advanced disease, in addition to the breast/chest wall, the

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVR = aortic valve replacement
BMS = bare-metal stent
CAD = coronary artery disease
CMR = cardiac magnetic resonance
CT = computed tomography
DIBH = deep inspiratory breath hold
GLS = global longitudinal strain
IMN = internal mammary node
IMN-RT = internal mammary node radiotherapy
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MDCT = multidetector computed tomography
PCI = percutaneous coronary intervention
RACD = radiation-associated cardiac disease
RAPD = radiation-associated pulmonary disease
TAVR = transcatheter aortic valve replacement
XRT = radiotherapy

CENTRAL ILLUSTRATION **Various Manifestations of Radiation-Associated Cardiac Disease**



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regional lymph nodes also often require adjunct radiation (either after lumpectomy or mastectomy). The lymph node region that is most challenging to treat is the internal mammary lymph node (IMN) chain. A variety of techniques have been used to treat IMN (26), but because of their location, it is unavoidable that the cardiac exposure increases (27). Despite evidence that IMN radiotherapy (IMN-RT) was beneficial, most radiation oncologists in the 2000s were not delivering IMN-RT because of cardiotoxicity concerns (28). However, recent data have shown that even patients with relatively early-stage breast cancer benefit from regional node irradiation and IMN irradiation is increasing (29,30). Multiple techniques have been developed to limit cardiac exposure with significant dose reduction over a few decades (27,31). Current techniques are 3-dimensional conformal radiation with heart blocking, DIBH, and prone positioning. Intensity-modulated radiation/arc therapy uses more beams than 3-dimensional approach and improves high-dose conformality while preserving target coverage. Lastly, proton therapy can further limit cardiac exposure in breast cancer patients (32). Dosimetric studies have shown the proton therapy can significantly reduce the heart exposure versus photon therapy (33). The benefit of protons is most

TABLE 1 Prevalence of Various Manifestations of RACD in Observational Studies

	Type of Cancer and Number of Patients	Prevalence/Incidence of Disease		Long-Term Cumulative Risk	
Congestive heart failure	• HL (91 cases and 278 controls of 2,617 survivors between 1965 and 1995) (1) • Mean LV dose 16.7 Gy	Mean LV dose, Gy	Rate ratio of disease	Mean LV dose, Gy	25-yr cumulative risk
		1-15	1.27	1-15	4.4%
		16-20	1.65	16-20	6.3%
		21-25	3.84	>20	13.3%
		>25	4.39		
	• BC (59 cases and 111 controls, between 1998 and 2013) (2) • Mean cardiac dose 2.5 Gy		Odds ratio		
		HF	9.1		
		HF preserved EF	16.9		
		HF reduced EF	3.17		
Valvular	• HL (89 cases and 200 controls of 1,852 Hodgkins survivors between 1965 and 1995) (3)	Mean LV dose, Gy	Relative risk of disease	Mean LV dose, Gy	30-yr cumulative risk
		<30	1.4	<30	3%
		31-35	3.1	31-35	6.4%
		36-40	5.4	36-40	9.3%
		>40	11.8	>40	12.4%
Ischemic	• HL (325 cases and 1,204 controls of 2,617 Hodgkins survivors between 1965 and 1995) (4)	7.4%/Gy, no upper threshold, linear risk			
	• BC (963 cases and 1,205 controls of 2,168 breast cancer survivors between 1958 and 2001) (5) • Mean cardiac dose 4.9 Gy	7.4%/Gy, no upper threshold			
CV diseases (CHF, ischemic, valvular, pericarditis)	• HL (2,524 patients between 1965 and 1995) (6)		Odds ratio	For patients treated before 25 yrs of age, cumulative incidences at ≥60 yrs were 20%, 31%, and 11% for ischemic, valvular, and HF as first events, respectively.	
		Ischemic heart disease	2.7		
		Valvular heart disease	6.6		
		HF	2.7		
	• BC (34,825 women 1976-2006) (7) • Mean cardiac dose 6.3 Gy for left-sided and 2.7 Gy for right-sided tumors	Higher incidence ratios for left- vs. right-sided tumors: acute myocardial infarction 1.22, angina 1.25, pericarditis 1.61, valvular heart disease 1.54 No difference in mortality			
CV events	• BC (meta-analysis of 289,109 patients from 13 observational studies) (8)	Left-sided breast cancer had a higher risk of CV death than those who received XRT for a right-sided breast cancer (RR: 1.12; $p < 0.001$)		Difference in CV mortality between left- vs. right-sided breast XRT was more apparent after 15 yrs of follow-up (RR: 1.23; $p < 0.001$).	
Electrical abnormalities	• BC (44,423 patients between 1982 and 2005) (52)	The unadjusted IRR was 1.09 (95% CI: 0.91–1.30) for CIED implants among women receiving XRT compared with nonirradiated women and the IRR was 1.13 (95% CI: 0.93–1.38) when adjustments were made.		XRT for breast cancer does not increase the long-term risk of severe ventricular arrhythmias or cardiac conduction abnormalities.	
Autonomic dysfunction	• HL (263 patients 19 yrs after XRT) (10)	Elevated resting heart rate and abnormal heart rate recovery increased in XRT patients: odds ratio: 3.96 and 5.32, respectively.		Abnormal heart rate recovery associated with increased all-cause mortality (hazard ratio: 4.60)	
Pericardial diseases	• HL (377 patients) (11)	Pericarditis observed with irradiation of the entire pericardium was 20%. With left ventricle shielding, this rate was decreased to 7%, and with subcarinal block, it was further reduced to 2.5%			
	• Esophageal cancer (214 patients between 2001 and 2010) (12)	Patients who receive high doses of radiation are at risk for pericardial effusions (incidence of 36%, 8% symptomatic)			
Aortic calcification	• Various cancers receiving mediastinal XRT (13)	In the inoperable Placement of Aortic TraNscathetER valve trial cohort, 15% had a porcelain aorta, with a high proportion likely due to prior mediastinal radiation.			
Pulmonary function abnormalities	• HL (145 patients between 1980 and 1990) (14)	>3 yrs after treatment, 32% of XRT patients and 37% of XRT+chemothreapy patients had FVC values <80% of predicted, and 7% of patients had a DLCO <80%. Mantle XRT was predictive of FVC and DLCO reduction.			

BC = breast cancer; CI = confidence interval; CIED = cardiovascular implantable electronic device; CV = cardiovascular; DLCO = diffusion lung capacity; EF = ejection fraction; FVC = forced vital capacity; HF = heart failure; HL = Hodgkins lymphoma; IRR = incidence rate ratio; LV = left ventricle; RACD = radiation-associated cardiac disease; RR = relative risk; XRT = mediastinal radiotherapy.

TABLE 2 Risk Factors and Long-Term Manifestations of Chest and Mediastinal Radiotherapy

Risk factors for developing RACD and RAPD
• Younger age at the time of XRT (<50 yrs) • Presence of cardiovascular risk factors or established cardiopulmonary disease • Lack of shielding or cobalt as a source of radiation • High cumulative dose(>30 Gy) or high dose of radiation fractions (>2 Gy/day) • Tumor in or next to the heart • Anterior or left chest radiation • Concomitant chemotherapy (e.g., anthracyclines)
Potential manifestations of chest and mediastinal XRT
Pericardium • Constrictive pericarditis due to extensive fibrous thickening, adhesions, chronic constriction and can be associated with chronic pericardial effusion. Associated with significantly higher surgical mortality
Cardiac muscle • Diffuse subclinical myocardial fibrosis with associated progressive systolic and diastolic dysfunction • Nonischemic cardiomyopathy can occur as an advanced stage of the disease due to extensive fibrosis with severe diastolic dysfunction and signs and symptoms of heart failure (heart failure with preserved ejection fraction more common than reduced ejection fraction) • Ischemic cardiomyopathy can occur due to advanced CAD
Valves • Valve apparatus and leaflet thickening, fibrosis, shortening, and calcification predominant on left-sided valves • Thickening and calcification of aortomitral curtain very commonly seen • Valve regurgitation more common than stenosis • Aortic valve stenosis most common stenotic lesion
Coronary artery disease • Accelerated CAD often seen at a much younger age • Concomitant atherosclerotic risk factors further enhance development of CAD • Can occur ≤5 yrs after exposure • Coronary ostia and proximal segments are typically involved • CAD significantly increases the risk of myocardial infarction and death
Carotid artery disease • Radiotherapy induced lesions are more extensive, involving longer segments and atypical areas of carotid segments
Other vascular disease • Calcification of the ascending aorta and aortic arch (porcelain aorta) • Lesions of any other vascular segments present within the radiation field
Conduction system disease • Ectopy, tachyarrhythmia, baseline sinus tachycardia and autonomic dysfunction commonly seen • Increased risk of pacemaker implantation due to conduction system disease
Lungs • Progressive pulmonary fibrosis • Recurrent pleural effusions

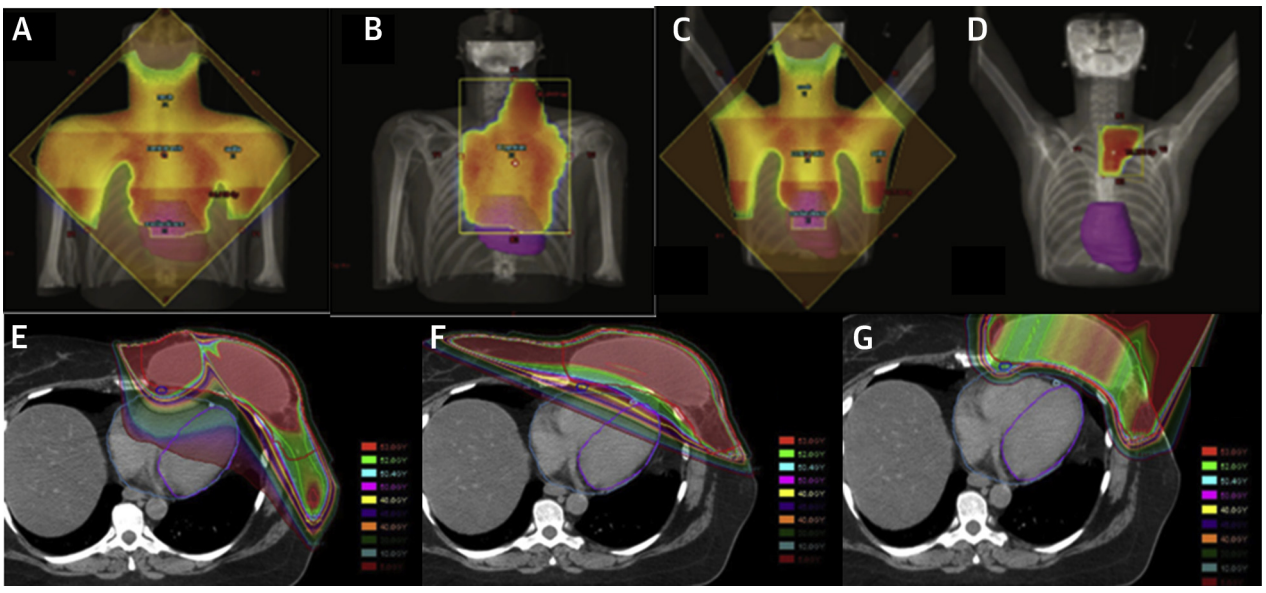
CAD = coronary artery disease; RACD = radiation-associated cardiac disease; RAPD = radiation-associated pulmonary disease; XRT = radiotherapy.

meaningful when IMN chain is included in the target volume (34). Encouraging early outcomes with proton therapy have demonstrated similar acute toxicity, local control, and very low mean heart doses (35,36). For left-sided cases with IMN-RT, the mean heart dose with proton therapy is typically around 1 Gy versus 4-5 Gy with photon therapy. Based on this, a phase 3 national randomized trial (RADCOMP [Radiotherapy Comparative Effectiveness]/RTOG [Radiation Therapy Oncology Group] 3510) to determine whether proton therapy can reduce the rate of 10-year major cardiac events by 40% is ongoing.

LUNG CANCER. As the population of patients receiving XRT for lung cancer is older with multiple cardiovascular risk factors, the emphasis is to intensify therapy to improve survival. However, a meta-analysis has demonstrated worse survival in patients receiving XRT versus surgery alone (37). For many years, 3-dimensional conformal radiation was the standard approach for lung XRT, with significant portions of the heart receiving 60 Gy (mean 30 to 40 Gy). Renewed interest in RACD has developed after reports of worse overall survival (28.7 months) in the high-dose versus standard arm (21.7 months) (38), with volume of the heart receiving >35 Gy independently predicting poor survival. Phase 2 trials have shown improved survival using proton therapy and chemotherapy compared with photon therapy (39). Based on this, a phase 3 randomized trial (Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer [RTOG 13-08]; NCT01993810) comparing proton versus photon therapy in patients receiving definitive chemoradiation for stage 2 to 3 non-small cell lung cancer is ongoing. Also, target volumes vary greatly based on tumor location. In a patient with an upper lobe primary tumor and upper paratracheal lymph nodes, cardiac exposure is close to zero versus a patient with a left lower lobe tumor and subcarinal lymph node involvement (>50 Gy). Thus, when estimating a patient's cardiac risk, it is essential to review the actual treatment plan.

FUTURE OUTLOOK. Patients treated in 2019 will undoubtedly have lower rates of RACD than previously treated patients due to efforts in reducing cardiac exposure. Although significant progress has been made in minimizing unwanted cardiac exposure, the following questions remain unanswered (40). Is there a cardiac dose that is sufficiently safe? Are there certain cardiac parts can tolerate XRT versus others? Is it more dangerous to deliver a high XRT dose to a small cardiac area versus low dose to a large area? Do new chemotherapy agents also have potential additive detrimental effects? In many cases, we are forced to decide between optimizing target coverage and cardiac exposure. The treatment planning requires the radiation oncologist to pick among a variety of radiation techniques. In doing so, they must pick the optimal particle, angles, energy, delivery system, target coverage, and because there are so many unanswered questions about the relationship between dose, volume and cardiac substructures, there is significant practice variation when it comes to XRT delivery.

FIGURE 1 Evolution of XRT Techniques



In a patient with lymphoma, significantly higher cardiac exposure occurred with mantle radiation **(A and C)** versus involved node XRT (**B** suggests large and **D** suggests smaller nodal involvement). In a patient with left breast cancer, comparison plans suggest a significantly higher amount of cardiac involvement with partially wide tangent field **(E)** and **(F)** photons/electrons versus proton therapy **(G)**. Adapted with permission from Maraldo et al. (20) and MacDonald et al. (32). XRT = radiotherapy.

PATHOPHYSIOLOGY

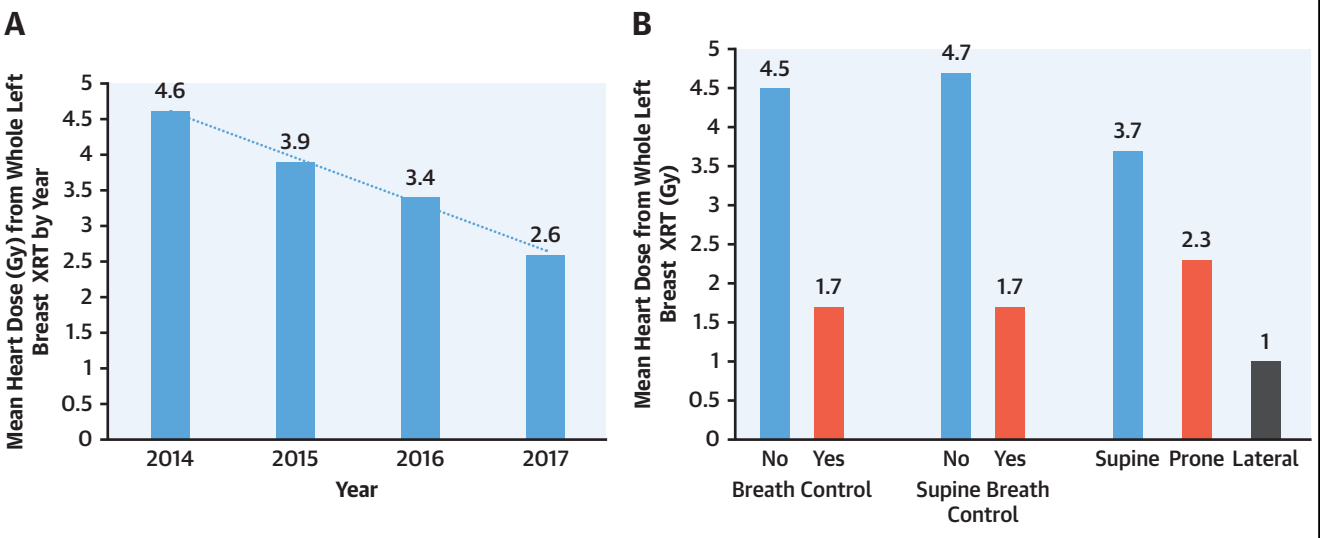
Our current knowledge about deleterious effects of XRT is mainly derived from older animal experiments, which do not necessarily reflect contemporary XRT. Also, the factors associated with progression from acute injury to chronic RACD are still not fully understood. Early events in the post-radiation cascade are loss of endothelial cells with subsequent inflammatory responses, driving vascular damage. For chronic RACD, fibrosis appears to be the key process through which damage ensues (**Figure 3**). A central event promoting pathological fibrosis is the long-term differentiation of fibroblasts into activated myofibroblasts, a process strongly driven by transforming growth factor-beta (41). Activated myofibroblasts, in turn, produce collagenous extracellular matrix components, increasing tissue stiffness, and thus impairing structure elasticity and function. Ionizing radiation can also influence deoxyribonucleic acid methylation profiles of cells, thus modifying gene expression, and of noncoding ribonucleic acids, some of which can modulate key factors in the development of fibrosis.

MANIFESTATIONS

RACD is a spectrum of deleterious effects, ranging from preclinical findings to symptomatic disease (**Table 1, Central Illustration**). Late effects manifest decades after treatment, resulting in a variety of complications including: myocardial fibrosis/dysfunction, congestive heart failure, valvular heart disease, vasculopathy including CAD, pericardial disease, and conduction abnormalities. Clinically, there is substantial overlap resulting in management challenges, as many patients have additional radiation damage to lung parenchyma, and present with nonspecific dyspnea or fatigue, which can be difficult to differentiate from cardiac disease and may further impact cardiac surgical risk.

MYOCARDIAL DISEASE AND HEART FAILURE. As a result of prior XRT, there is evidence of myocardial dysfunction (likely related to diffuse fibrosis) with resultant impairment in functional capacity without heart failure (shown in breast cancer survivors) and heart failure with preserved ejection fraction (in both lymphoma and breast cancer survivors) appears more prevalent than systolic dysfunction (1,2,42). The

FIGURE 2 Evolution of XRT Dosage



Reduction in mean heart radiation doses for left breast cancer by **(A)** year and **(B)** different techniques. Adapted with permission from Drost et al. (25).
XRT = radiotherapy.

anterior position of the right ventricle makes it susceptible to damage, although this is often underrecognized due to suboptimal visualization. Biventricular radiation fibrosis tends to follow a nonischemic pattern. However, coexistent radiation induced micro- and macrovascular disease can result in ischemia/infarction and regional fibrosis. The detrimental effects of radiation to myocardial function can be compounded by chemotherapy, particularly anthracyclines (43), and HER-2/neu receptor antagonist trastuzumab. Recent data suggest that trastuzumab may have a radio-sensitizing effect on breast cancer cells, although it remains unclear whether similar effects occur on normal healthy cells (44).

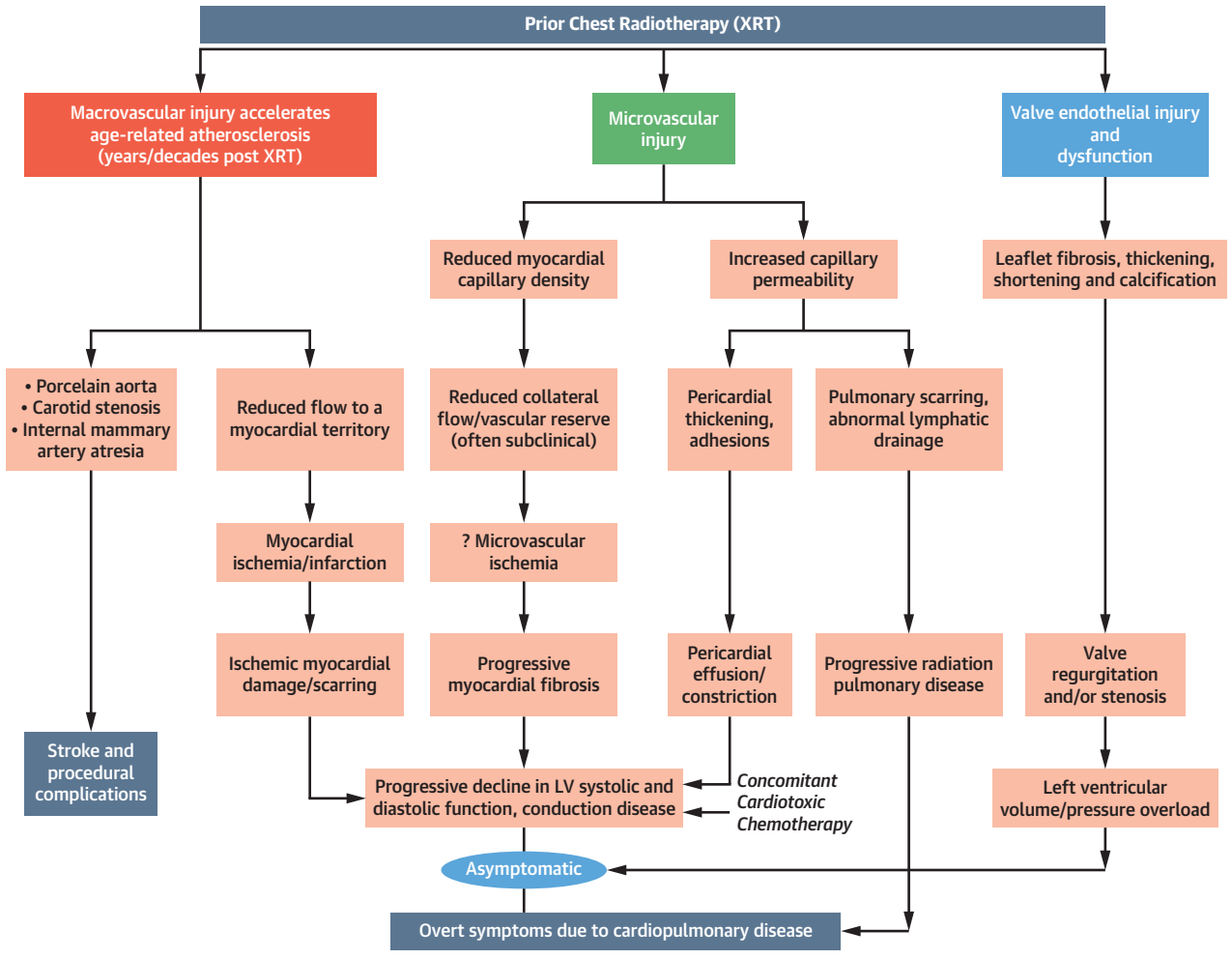
VALVULAR HEART DISEASE. This usually manifests as progressive valve thickening and calcification, resulting in valve restriction presenting as stenosis or regurgitation. Patients usually become symptomatic later than coronary disease, and awareness of this latency is important, given that asymptomatic survivors treated over 20 years ago have increased risk of aortic regurgitation (60% vs. 4%), tricuspid regurgitation (4% vs. 0%), and aortic stenosis (AS) (16% vs. 0%) compared with patients treated within 10 years (45). Radiation-associated valvular thickening and calcification are more extensive, often involving surrounding structures such as the annulus, subvalvular apparatus, and aortomitral curtain, often resulting in a mixed picture of stenosis/regurgitation in multiple valves. Left-sided valves are more often involved versus right-sided. Aortomitral curtain thickening/calcification is a hallmark of previous heart irradiation and its extent is associated with mortality (46).

PERICARDIAL DISEASE. Although acute pericarditis following XRT tends to be self-limiting, some patients progress to chronic pericardial involvement. In Hodgkin's patients, 20% had pericarditis observed with irradiation of the entire pericardium (11). Chronic pericardial inflammation results in a thickened, rigid, and often calcified pericardial sac. Loss of distensibility can result in ventricular interdependence and constrictive physiology. Given that most RACD patients have some restrictive physiology, it can be difficult to distinguish between restriction (due to underlying myocardial fibrosis) and constriction.

VASCULOPATHY. XRT-associated vasculopathy manifests as both micro- and macrovascular disease and is typically progressive, manifesting years after initial exposure.

Radiation-associated coronary vasculopathy, typically affects the ostia or proximal coronary arteries; however, the proximal right coronary artery, mid-left anterior descending coronary artery, and mid-diagonal branches are particularly involved among patients with breast cancer and left-sided XRT (23). The predilection for the ostial left main and right coronary artery likely relates to coronary artery position within the anterior radiation field and perhaps a greater propensity for intimal proliferation. The

FIGURE 3 Pathophysiology of RACD

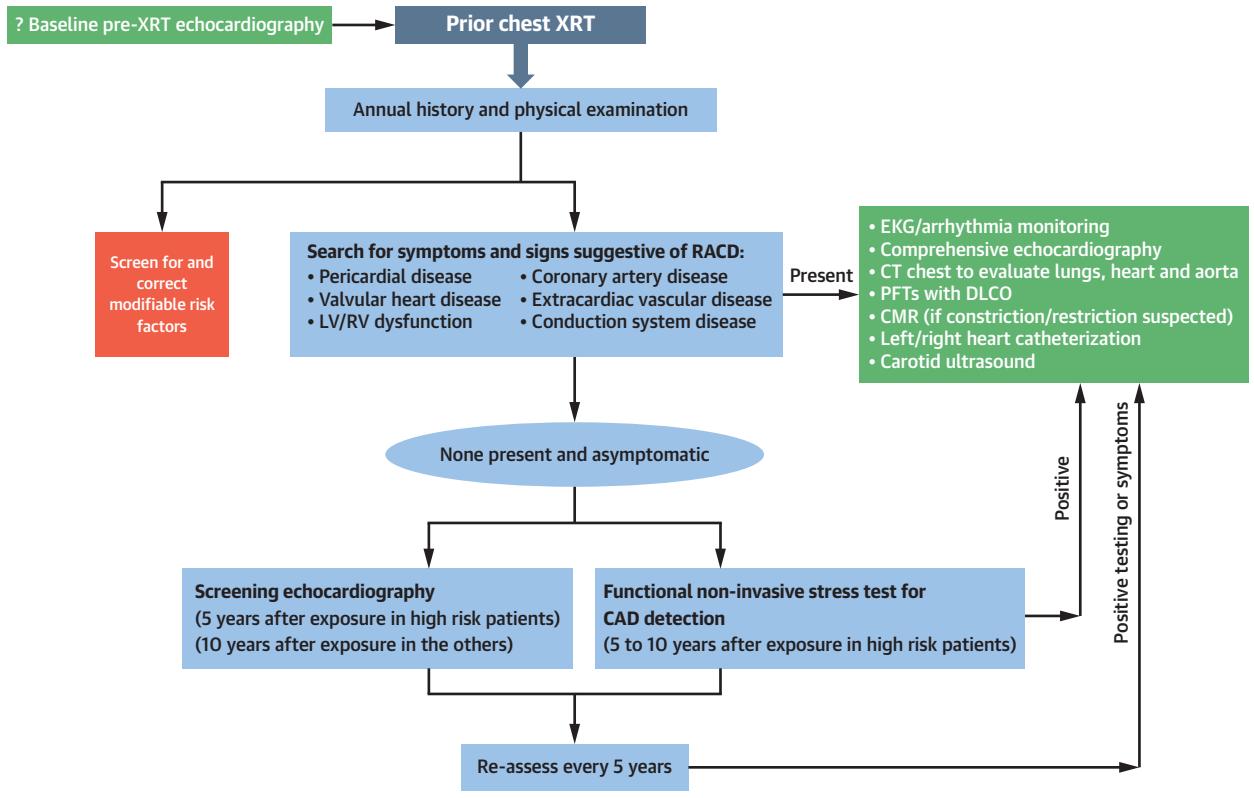


Effect of XRT on various organs. LV = left ventricular; RACD = radiation-associated cardiac disease; XRT = radiotherapy.

lesions tend to be longer, tubular, and concentric and are often noncalcific. Myocardial ischemia can compound concurrent myocardial dysfunction. The risk of myocardial infarction proportionally increases with duration from radiation exposure and is highest in those who received treatment when aged <20 years (47). Microvascular disease is less well studied, although it appears to contribute to myocardial dysfunction via ischemia and resultant fibrosis. Large vessel vasculopathy often involves the thoracic aorta and arch branch vessels, manifesting as atherosclerotic disease, although regional thrombosis leading to vessel occlusion or embolic stroke can also occur. This can assume added significance because it may preclude percutaneous intervention or surgical access (porcelain aorta) (48).

CONDUCTION SYSTEM DYSFUNCTION. XRT results in fibrosis of conduction pathways and subsequent abnormalities, including atrioventricular block, sick sinus syndrome, atrial fibrillation, and ventricular tachyarrhythmias, that can occur years later (49,50). Infranodal and right bundle branch blocks are common, with the anteriorly located right bundle being particularly susceptible. There is a higher proportion of RACD patients who require pacemaker postoperatively (51). However, in a recent study of breast cancer survivors, there was no increased risk of ventricular tachyarrhythmias or conduction abnormalities due to XRT (52). Autonomic dysfunction has been poorly studied, although inappropriate sinus tachycardia has been recognized as a sign of extensive RACD and can result in reduced exercise capacity

FIGURE 4 Imaging in RACD



Suggested screening and diagnostic algorithm for RACD. CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; DLCO = diffusion lung capacity; PFT = pulmonary function test; RV = right ventricular; other abbreviations as in Figure 3.

and potentially increase the risk of tachycardia-mediated cardiomyopathy (10,53).

PULMONARY DISEASE. RAPD occurs as a longer-term consequence of the repair process resulting in pulmonary fibrosis, leading to symptoms due to reduction in forced vital and diffusing capacity, RAPD should be particularly considered when determining suitability for cardiac surgery, because pulmonary complications are a major source of perioperative morbidity and mortality (54). This is especially problematic after repeat cardiac surgery, where recurrent pleural effusions, severely reduced lung volumes, and ventilation impairment are commonly observed (55).

MULTIMODALITY RISK STRATIFICATION, SCREENING, AND DIAGNOSIS

Patients should be educated about the risk of long-term RACD before treatment, and consideration could be given to a cardiology consultation, especially in those with additional risk factors (Table 2). Given the long latency and poor outcomes of RACD, serial screening of cancer survivors is recommended (56) (Figure 4). Transition from pediatric to adult services is also important to ensure adequate follow-up. Typically, screening for CAD should commence <5 years and valvular heart disease ~10 years after XRT, with subsequent imaging then performed at 5-year intervals (56). For patients with conventional risk factors, screening echocardiography is recommended in the fifth year after treatment, and noninvasive stress testing is recommended ≤5 years after treatment and at 5-year intervals, with a preference for stress (dobutamine or exercise) echocardiography (57). Traditional risk factors should be aggressively managed as they act synergistically with radiation exposure, to increase the risk for major coronary events from 2 to 7% (5). Biomarkers such as brain natriuretic peptide and troponin can also be potentially used to identify asymptomatic patients at risk of future events (58). The role of various imaging

TABLE 3 Utility of Various Diagnostic Tests in RACD

	ECG	Echo (+/− Contrast, Strain)	Stress Echo	Stress Nuclear	MDCT	CMR	LHC	RHC	Extravascular Ultrasound
Pericardial diseases									
Effusion	+	++++	−	−	+	+	−	−	−
Pericarditis	++	++	−	−	+	+++	−	−	−
Constriction	+	++++	+	−	++	++++	−	++	−
Cardiac muscle disease									
Subclinical myocardial fibrosis	?	?	−	−	−	+++	−	?	−
Nonischemic	++	++	+	+	++	++++	++++	++	−
Ischemic	++++	++++	++++	+++	+++	++++	++++	++	−
Heart failure with preserved ejection fraction	++	++++	+++	?	++	++	++++	++	−
Valvular disease	?	++++	++++	?	+++	+++	+	++	−
Conduction system disease	++++	+++	++	?	++	++	−	−	−
Coronary artery disease	+++	+++	+++	++++	+++	++	++++	++	−
Extracardiac vascular disease	−	−	−	−	++++	−	−	−	++++

CMR = cardiac magnetic resonance; ECG = electrocardiogram; LHC = left heart catheterization; MDCT = multidetector computed tomography; RACD = radiation-associated cardiac disease; RHC = right heart catheterization.

modalities in RACD is discussed in the following text (Table 3).

ECHOCARDIOGRAPHY. Echocardiography is the first imaging technique to screen, diagnose, and monitor RACD (56). Detection of any structural abnormality, measurement of ventricular performance, and evaluation of valvular heart disease severity (calcification, fibrosis/rigidity, retraction, stenosis, regurgitation) are the key echocardiographic findings in RACD. For both constrictive (e.g., prominent respirophasic diastolic bounce of the septum, significant inspiratory variation of mitral E-wave velocity, hepatic vein expiratory diastolic flow reversal, annulus reversus) and effusive pericardial pathophysiology (i.e., features of cardiac tamponade), echocardiography is the modality of choice, whereas it is less useful for diagnosing pericardial thickening and calcifications (56). Although left ventricular (LV) ejection fraction (LVEF) is the most common tool in global systolic function assessment, subtle changes may be missed due to dynamic changes in loading conditions or measurement variability (59). RACD-related cardiac dysfunction is defined as a >10% decrease in LVEF to a value <50% to 53%, confirmed by repeated imaging 2 to 3 weeks after the baseline diagnostic study (60). Three-dimensional echocardiography-measured LVEF appears more useful and is more reproducible for serial assessment (61). Contrast echocardiography, though it improves delineation of the LV endocardial borders, remains less accurate than 3-dimensional echocardiography (61). Also, because the majority of patients have preserved LVEF, diagnosis is challenging (2). Reductions in systolic myocardial deformation are detected immediately and 2 months after XRT, in the absence of detectable reductions in LVEF. Strain echocardiography demonstrated abnormal global longitudinal strain (GLS) and global circumferential strain in 33% and 21.7%, respectively, whereas depressed LVEF was detected in only 5.7% of patients (62). Abnormal GLS was also correlated with reduced quality of life and lower mean 6-min walk distances. The lower observer variability of GLS allows for easier recognition of the change in systolic function when compared with LVEF (63). Thus, whereas reduced EF is a late finding in RACD, abnormal strain may herald early-onset disease and is increasingly being incorporated into screening. In RACD patients with preserved LVEF undergoing cardiac surgery, LV-GLS <−14.5% was associated with higher mortality, versus with normal LV-GLS (64). However, thresholds for GLS abnormality in such patients remain unknown.

Echocardiography is highly sensitive in detecting valvular disease (56,65). The earliest change relates to progressive valvular retractions accompanied by regurgitation occurring within the first 10 years. The progression to fibrotic thickening and calcification occurs much later, with stenosis often appearing 20 years after XRT (56,65). Mitral and aortic valve regurgitations are the most common defects, and when stenosis occurs, it most commonly affects the aortic valve. Progressive thickening and calcification of the aortomitral curtain is a characteristic finding (46). Though transthoracic echocardiography is often sufficient for diagnosis, transesophageal echocardiography is occasionally performed for further diagnostic refinement. However, given the possibility of XRT-associated esophageal injury, care should be taken to minimize procedural time.

The value of rest echocardiography in CAD is limited to the assessment of the presence and extent of regional wall motion abnormalities. Stress-induced wall motion abnormality is a reliable indicator of myocardial ischemia, which is highly sensitive and specific (>80%) for angiographically assessed epicardial CAD (22,30).

MULTIDETECTOR CARDIAC COMPUTERIZED TOMOGRAPHY. Multidetector computed tomography (MDCT) is commonly employed for evaluation of aortic, valvular, myocardial, and pericardial calcification on either contrast or noncontrast imaging. Preoperative assessment for aortic calcification is important to determine suitability for aortic cross-clamping and cannulation in patients undergoing cardiac surgery. Significant valvular and/or annular calcification may preclude valvular repair. For transcatheter valve therapies, 4-dimensional MDCT is crucial for pre-procedural planning, including assessment of annular shape and size (aortic, mitral, and tricuspid) and ileofemoral vasculature (66). MDCT is also useful to evaluate extracardiac structures for surgical planning in redo surgeries (67). Extensive mediastinal fibrosis or lack of a safety margin between the sternum and adjacent structures may necessitate a nonsternotomy/transcatheter strategy. Pulmonary fibrosis has an adverse impact on survival in RACD and should be evaluated (54). Pericardial calcification, thickening, venacaval enlargement, and ventricular conical deformity are suggestive of pericardial constriction (68). Also, coronary calcium scoring and computed tomography (CT) angiography can be useful in RACD for its negative predictive value, with no atherosclerosis suggesting a very low risk. However, many patients have severe noncalcific stenoses rendering calcium scoring less useful, and in cases with extensive coronary calcification, assessment for luminal stenosis on CT angiography becomes difficult due to blooming artifact.

NUCLEAR SCINTIGRAPHY. Single-photon emission CT and positron emission tomography can assess myocardial ischemia in RACD. Studies are limited by small numbers, but show that 12% of asymptomatic patients have stress induced perfusion defects; and in patients receiving both XRT and chemotherapy, a high proportion of new perfusion defects (69,70).

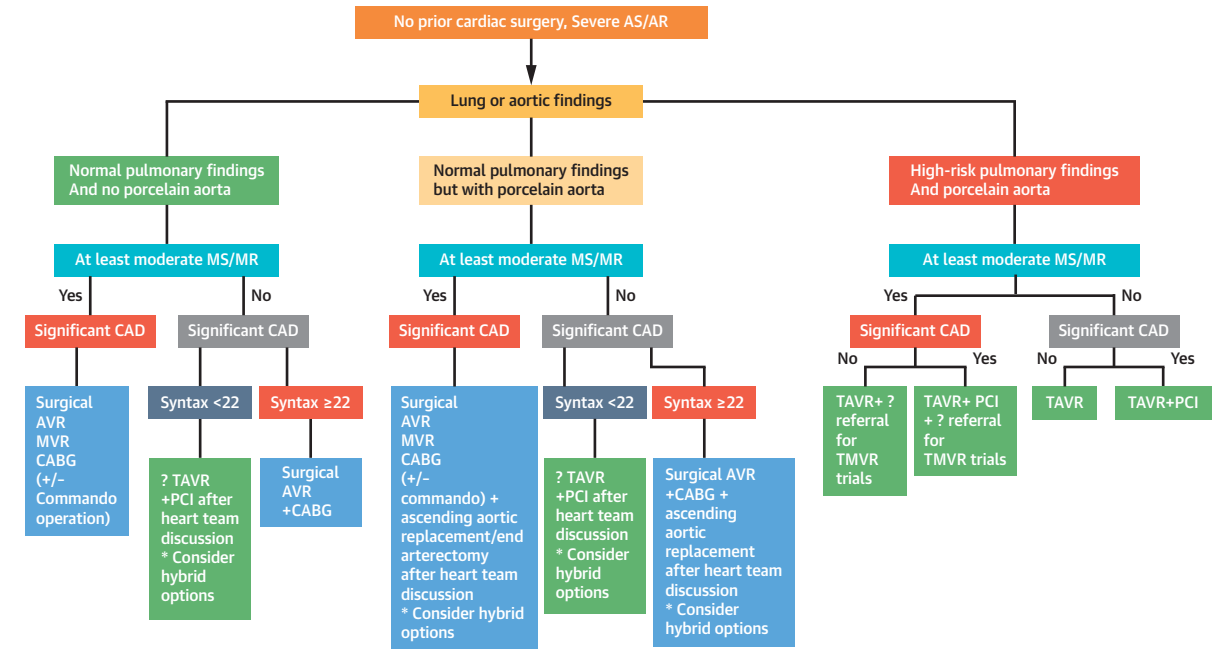
CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance (CMR) can provide useful simultaneous functional and structural data, enabling detection of coronary, valvular, and pericardial disease. Cine imaging allows assessment of ventricular mass, volumes, function, and regional wall motion abnormalities, which can then be correlated with late gadolinium enhancement to establish regions of viability, scar, and nonischemic fibrosis. Valvular function can be assessed by calculation of transvalvular gradients and regurgitant volumes. Radiation-induced pericardial thickening, effusions, and features of constrictive physiology are suggested by ventricular conical deformity, diastolic septal bounce, diastolic chamber restraint, inferior venacaval enlargement, and respirophasic septal shift, whereas increased pericardial signal intensity on edema weighted T2 imaging and late gadolinium enhancement suggests pericardial inflammation (71). First-pass perfusion imaging (using pharmacological stressors) can identify underlying myocardial ischemia. T1 mapping may prove useful for RACD, but requires further investigation. CMR is not routinely recommended, but can be useful for assessment of ischemic/nonischemic myocardial fibrosis, assessment of pericardial constriction, and as an adjunct to echocardiography in technically difficult subjects.

LEFT AND RIGHT HEART CATHETERIZATION. Invasive catheterization provides complementary and confirmatory information to noninvasive imaging. Left heart catheterization allows assessment of coronary stenosis severity. Right heart catheterization is useful for calculation of intracardiac and pulmonary pressures. Simultaneous left and right heart measurements allow for evaluation of constrictive physiology and cardiac index, with a low index prompting evaluation for restrictive cardiomyopathy. Because proximal CAD may be underappreciated, especially if ostial in location, there should be a low threshold for utilizing intravascular ultrasound, particularly in the setting of pressure damping or contrast reflux.

EXTRACARDIAC VASCULAR ULTRASOUND. Many instances of extensive radiotherapy involve the carotid and subclavian arteries. As a result, the clinical threshold to perform ultrasound of these vessels should be low. Additionally, pre-operative internal mammary artery (72) and vein mapping allows for assessment of the quality and availability of coronary bypass conduits.

RADIATION-ASSOCIATED PULMONARY DISEASE. Subjects with a history of thoracic radiation should be screened for RAPD, as it is associated with reduced survival in RACD (54). Typically, this manifests as pulmonary fibrosis with traction bronchiectasis in severe cases. Clinical examination, chest x-ray, pulmonary function testing (lung volumes and diffusion lung capacity), and dedicated high-resolution CT chest is generally recommended.

FIGURE 5 Treatment of RACD



All evaluation and management should be performed at an experienced center with a heart team of cardiologists and cardiac surgeons experienced in management of RACD. Many treatment decisions might have to be individualized, especially in the setting of cardiac reoperation.

Suggested management algorithm of patient with RACD. AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MR = mitral regurgitation; MS = mitral stenosis; MVR = mitral valve replacement; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement; TMVR = transcatheter mitral valve replacement; other abbreviations as in Figures 3 and 4.

MANAGEMENT

All patients with a prior cancer history should be questioned about radiation or cardiotoxic chemotherapy. Often, radiation exposure is only realized when cardiac testing suggests a more extensive calcific or fibrotic process than typical for age. An experienced team of cardiologists, imaging specialists, interventionalists, and cardiothoracic surgeons is recommended to guide therapeutic strategies (73). Physicians treating complex patients with RACD have an important task of resetting patient expectations and educating regarding the poorer outcomes in RACD. A suggested approach to patients with complex symptomatic RACD, based on our experience, is discussed in the following text and shown in Figure 5.

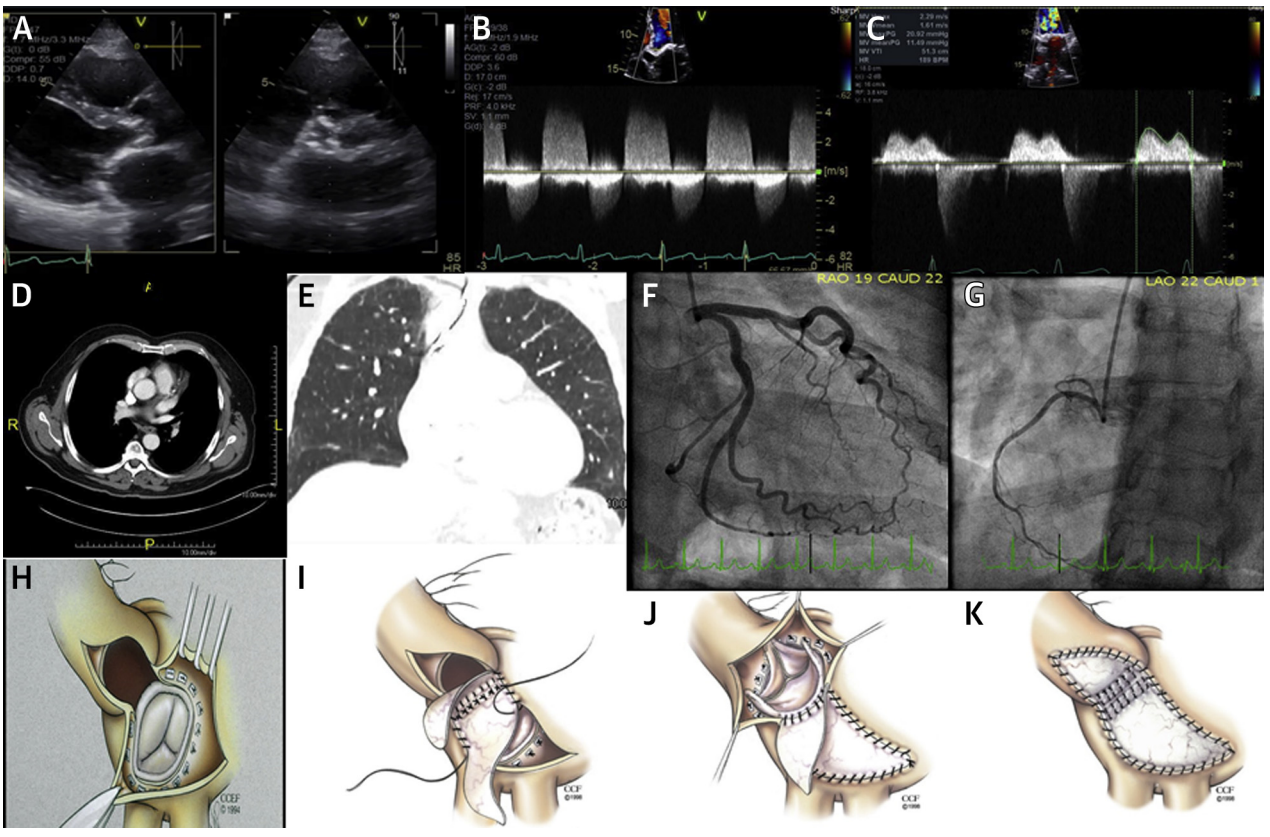
MEDICAL THERAPY

Medical therapy is typically undertaken according to standard guidelines. Pericardial constriction may warrant a trial of anti-inflammatory therapy, in case of reversibility (74). The benefit of heart failure pharmacotherapy in subclinical myocardial dysfunction remains unknown. Although no drug is currently approved for treatment of RACD, some studies highlight the potential therapies studied in animal models (75). Statins might have benefits on radiation-induced fibrosis (76). Prior reports have showed that treating experimental animals with angiotensin-converting enzyme inhibitors or angiotensin receptor blocker reduces radiation-induced injury of normal tissue (77). Intraperitoneal melatonin injection before XRT decreased vascular damage, cardiac fibrosis, and myocyte necrosis observed after 6 months (78). Recombinant human neuregulin-1β prevented mitochondrial dysfunction early after cardiac irradiation. At a later stage, it also decreased fibrosis and cardiomyocyte hypertrophy (79). However, well-conducted prospective studies are lacking. As a result of no definitive medical therapies for RACD, most symptomatic patients require invasive therapies to relieve significant lesions.

CARDIAC SURGERY

The surgical approach to RACD must take into account all the possible manifestations of RACD

FIGURE 6 A Patient With RACD Who Underwent Cardiac Surgery



Echo revealing significant mixed (stenotic and regurgitant) aortic and mitral valve disease and calcification of aortomitral curtain **(A to C)** Computed tomography revealing no porcelain aorta or pulmonary **(D and E)** no obstructive coronary artery disease **(F and G)** schematic representation of Commando operation (aortic and mitral valve replacement with reconstruction of aortomitral curtain) **(H to K)**. RACD = radiation-associated cardiac disease.

(**Figure 6, Central Illustration**). Whether the primary indication for surgery is CAD or valvular heart disease, it should be assumed that there would be radiation injury to the aorta, ventricles, pericardium, lungs, and chest wall. As a result, pre-operative evaluation should include echocardiography, coronary angiography, MDCT, and pulmonary function testing. Strong consideration should be given to CMR and combined left and right heart catheterization with simultaneous pressure measurements if there is concern for constrictive pericarditis versus restriction.

Many RACD patients have some degree of restrictive lung disease with decreased lung volumes. Although there are no strict cutoffs, forced expiratory volume at 1 min <1 l and diffusion lung capacity <40% should raise concerns that post-operative ventilator weaning may be difficult. It is also important to recognize that these patients often have undrained pleural effusions that contribute to poor pre-operative study metrics, some or all of which may improve with correction of the valve and coronary lesions. The combination of very poor pulmonary function numbers and pulmonary fibrosis on MDCT should raise concerns of significant RAPD.

Once the decision has been made a patient is potentially a surgical candidate, MDCT is crucial for surgical planning (67). Even in primary surgery, radiation-induced scarring (54) can result in the innominate vein and other vascular structures being in close sternal proximity, making sternotomy hazardous. A careful 3-dimensional MDCT will allow for a full understanding of aortic, valvular, and intravalvular calcium, and in particular the location and extent of mitral annular calcification. Severe circumferential mitral annular calcification merits

pre-planning for an aggressive resection with anterior annular debridement and reconstruction of the intervalvular fibrosa, the "Commando" operation.

TIMING OF SURGERY. Many RACD patients have complex disease involving multiple valves, coronaries, conduction system, and a degree of ventricular systolic and diastolic dysfunction. In our experience, due to radiation injury to lungs and pleura with resultant lymphatic dysfunction, RACD patients are prone to complications relating to intrathoracic fluid retention after surgery, with a major impact on recovery and quality of life after surgery. In light of this, the normal criteria for surgical timing, especially in valve disease, should be adjusted for patients with RACD. Surgery should, in general, be considered later in the course of disease than normal. This is especially important in patients with multivalve disease where one valve may have severe dysfunction and another mild or moderate. Redo surgery in RACD carries a significant elevation in operative risk and morbidity compared with non-RACD surgery, such that every attempt should be made to address all of the issues at the first operation (55). Managing patient expectations is critical, as recovery after surgery cannot be expected to confer near normal quality of life in all cases.

PRE-OPERATIVE PLANNING AND INTRAOPERATIVE STRATEGIES. Pre-surgical evaluation should be systematic. Planning for cannulation, aortic cross clamping, and managing valvular calcium and calcification of the cardiac fibrous skeleton are important (80). Calcification, which appears thin and patchy on MDCT, will allow for safe aortic clamping. More dense and circumferential calcification should merit planning for circulatory arrest and replacement of the ascending aorta. With all but the most straightforward-appearing aortic calcification on CT, the surgeon should be comfortable planning to remove or work around all the areas of calcification. Therefore, a flexible perfusion and myocardial protection strategy would include: routine cannulation of the right axillary artery with a side graft, routine bicaval cannulation, and routine direct cannulation of the ostium of the coronary sinus for retrograde cardioplegia. This approach allows for flexibility in dealing with unexpected reconstruction problems in what are often long, multicomponent operations.

SURGICAL PROCEDURES FOR RACD

CORONARY ARTERY BYPASS GRAFTING. Conduit and available targets define options for coronary bypass as in non-RACD patients. Internal thoracic arteries can potentially lie within the radiation field in many patients; however, these arteries can be used successfully after ascertaining their patency. Those that appear small and fibrotic are best avoided; however, the majority should be amenable. Vein mapping before surgery is useful to define the quality of venous conduits because last minute decisions are best avoided. Radial artery conduits can be used with similar criteria to non-RACD bypass surgery. Coronary targets are likely to be diffusely calcified, although less so than in patients with severe diabetes or renal insufficiency. Diffuse disease may limit the effectiveness of bypass despite a severe proximal lesion; however, finding an adequate touchdown site for a graft is usually not a problem.

AORTIC AND MITRAL VALVE REPLACEMENT. Serious consideration should be given to replacing both aortic and mitral valves even if 1 is moderately diseased, because intra-operative options may be limited by areas of calcium that can often span between the 2 valves. A common scenario exists in which the aortic valve disease is severe and mitral valve disease is moderate, often with posterior mitral annular calcification. In this scenario, it is tempting to replace the aortic valve and leave mild-to-moderate mitral regurgitation. Although this result may be initially acceptable, valvular disease in radiation patients may progress rapidly, leaving a patient with a functioning aortic prosthesis and progressively severe mitral valve disease within a few years of surgery. In light of higher risk of reoperative surgery in RACD, every consideration should be made to perform a complete operation at the first surgery (55).

Valve tissue in RACD is not normal, and tends to thicken and scar progressively over time. There is a very real risk in RACD of transforming a regurgitant valve into a stenotic valve with repair, a situation that will likely worsen with progressive fibrosis and calcification. Replacement over repair is favored for these reasons in patients with RACD affecting the mitral valve, if intervention is required (51).

EXTENSIVE RECONSTRUCTION OF THE AORTOMITRAL CURTAIN. Two major findings in RACD patients complicate aortic and mitral valve surgery. The first is confluent calcification extending from the aortic annulus across the aortomitral curtain and involving the anterior leaflet of the mitral valve (46). This can complicate exposure to, and suture placement in, the anterior mitral annulus or make safe replacement impossible. If calcium is effectively debrided, there may be little healthy tissue remaining to allow adequate fixation and sealing of the valve. The

second finding is the small annular size of the aortic and mitral annuli. This may relate to early radiation exposure when the heart is still growing, to progressive fibrosis and scar shrinkage, or a combination. Small aortic root and small mitral annulus are a common finding in this patient population. The combination of severe fibrous skeleton calcification and small annuli make a more aggressive approach to double-valve replacement attractive. Division of the aortomitral curtain and anterior mitral leaflet allows for better exposure of the posterior mitral annulus for debridement of calcification, suture placement, and reconstruction. In the Commando operation, a patch of autologous or bovine pericardium is fashioned to repair and expand the dome of the left atrium, the mitral annulus, aortomitral curtain, aortic annulus, and aortic valve. This approach allows for repair of the defect left by aggressive debridement of calcium, adequate sealing of the 2 prosthetic valves, and in most cases at least 1 valve size increase in both aortic and mitral valves for more physiological hemodynamics. This is especially important if bioprosthetic valves are used with consideration for future valve-in-valve transcatheter interventions.

CHOICE OF PROSTHESIS. Given the increased risk of cardiac reoperation, mechanical prostheses are appealing especially for younger patients undergoing valve replacement in RACD (55). However, consideration should be given to the fact that RACD patients often have other medical comorbidities that may affect their ability to take lifelong anticoagulation. In such patients, placement of bioprostheses and subsequent valve-in-valve transcatheter therapy as a second operation appear attractive. Despite the advances in transcatheter mitral therapy, current technology is limited in the face of prior mitral repair and mitral annular calcification (81). As valve-in-valve transcatheter therapy evolves, double-valve replacement with stented bioprostheses, combined with aortomitral curtain patch and dual annular enlargement, should be considered as a first operation in patients with contraindications to warfarin and no comorbidities.

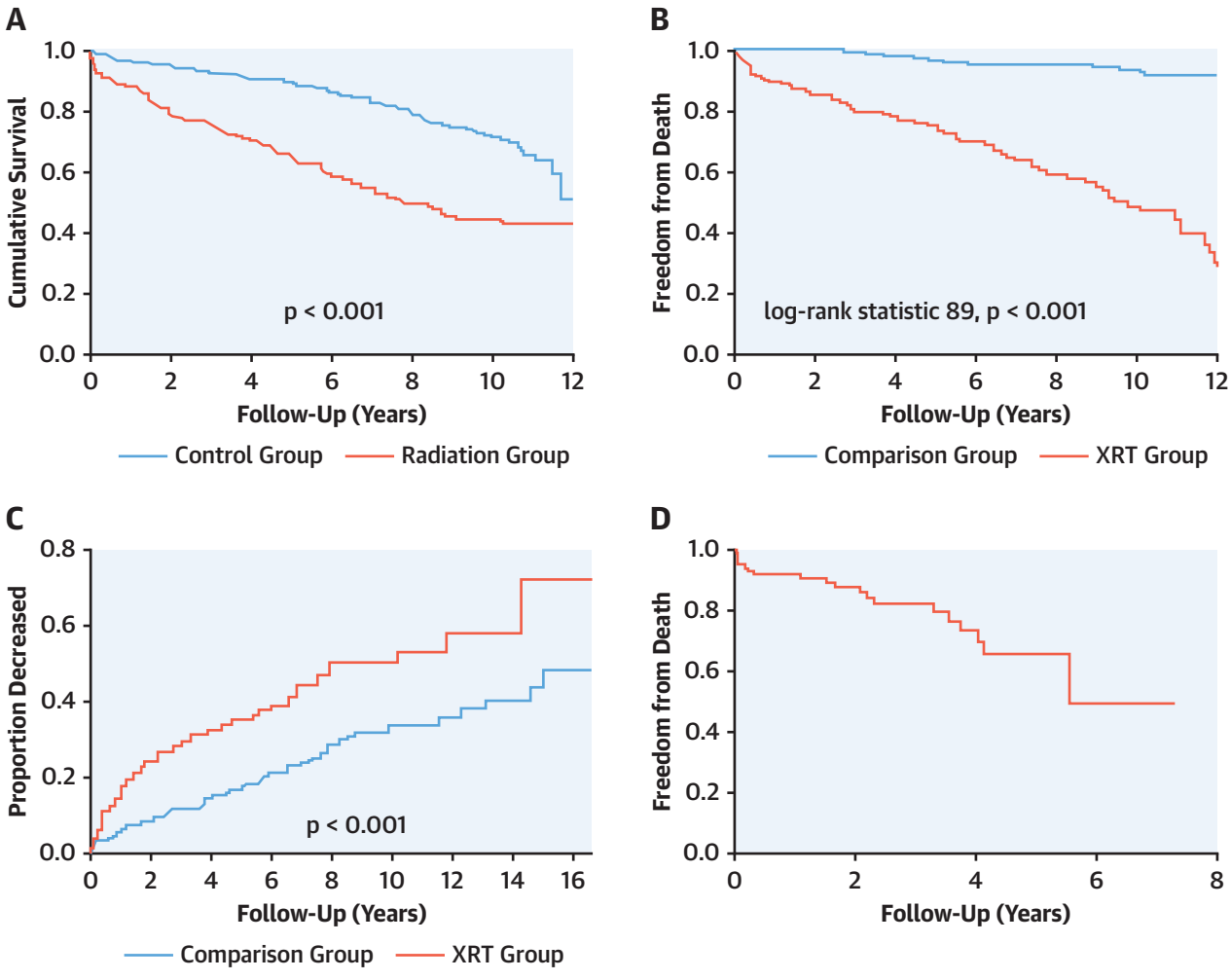
CARDIAC TRANSPLANTATION. A small series has reported acceptable outcomes following cardiac transplantation in RACD patients, but longer-term survival is reduced relative to cardiac transplantation in the nonradiation cohort, in part due to higher risk of recurrent malignancy due to associated immunosuppression (82). Hence, transplant candidacy must be carefully decided on a case-by-case basis in recognition of this increased risk.

POST-OPERATIVE CONSIDERATIONS. Chronic pleural and pericardial effusions are common with RACD patients after surgery. Although in most cases these are adequately treated with prolonged drainage, pleural effusions recurring up to a few weeks after surgery may require longer-term soft drainage catheters. Conduction system disturbances are common, especially with more aggressive reconstruction. Many patients need more than a few days of temporary pacing after surgery. Placement of permanent LV epicardial pacing leads should be considered. Leadless pacemaker might be considered in patients with limited venous access. Management of post-operative diuresis is often difficult due to restrictive ventricles. It should be anticipated that the normal course of post-operative diuresis would be prolonged, often for weeks. Another danger in applying “routine” cardiac surgery management to these patients is over-application of beta-blocker therapy. RACD patients are often rate dependent for cardiac output, because the ventricle is limited by fibrosis and varying stroke volume. Higher pacemaker heart rates should be considered for those patients who are dependent, and nodal blocking agents should be limited.

SURGICAL OUTCOMES

Multiple studies have suggested that although operative mortality for RACD patients in experienced centers may approach that for matched non-RACD patients, long-term outcomes are demonstrably worse, with XRT exposure emerging as an independent risk factor (55,82,83) (**Figure 7**). In a study of 478 patients (173 RACD and 305 matched group without RACD) undergoing cardiac surgery, a significantly higher proportion of patients died in the RACD group versus the comparison group (55% vs. 28%; $p < 0.001$) over 7.6 ± 3 years, despite similar EuroSCOREs (55). Cardiac reoperation in RACD was associated with significantly higher longer-term mortality. Similarly, in patients with severe AS undergoing surgical aortic valve replacement (AVR), patients with prior mediastinal XRT ($n = 173$) had significantly worse longer-term survival versus a matched cohort ($n = 173$) (84). Recently, it has been also shown that in patients with moderate AS, those with prior XRT have a similar rate of progression of AS versus a comparison group. Despite that, the XRT patients had significantly higher longer-term mortality, with prior XRT a major risk factor for longer-term mortality (85). We simply do not understand enough about the variation in myocardial fibrosis, pulmonary disease, and the impact of radiation-induced vasculopathy on outcome to make meaningful predictions about who

FIGURE 7 Outcomes of RACD



Different groups undergoing **(A)** cardiac surgery, **(B)** SAVR, **(C)** PCI, and **(D)** TAVR. Adapted with permission from Wu et al. (55), Donnellan et al. (83,84), and Reed et al. (91). SAVR = surgical aortic valve replacement; other abbreviations as in Figures 3 and 5.

is truly high risk for operative intervention. This complex disease process demands the close attention of a multidisciplinary team and the careful application of less-invasive technologies when appropriate (Figure 8). For those patients in whom the disease has progressed to the point surgery is appropriate, consideration should be given to performing the most complete operation considering safety, valve and coronary disease, fibrous skeleton reconstruction, and aortic reconstruction as necessary to safely arrest the heart. Although long-term outcomes remain less favorable, patients without significant pulmonary (54) or myocardial fibrosis may achieve excellent long-term success with surgery. Future efforts must be directed to determine which patients may benefit the most from surgery.

PERCUTANEOUS CARDIOVASCULAR INTERVENTIONS

Owing to the complexity and multifaceted disease manifestations of RACD as well as lack of evidence from randomized studies, management strategies taking into consideration percutaneous cardiovascular interventions are best developed within a heart team representing broad expertise (66,86–88).

PERCUTANEOUS CORONARY INTERVENTION

INDICATION AND TREATMENT SELECTION. Among patients with RACD manifesting as chronic CAD, the indication should follow the established recommendations (86). Although patients with isolated 1-vessel or 2-vessel CAD preferentially undergo percutaneous coronary intervention (PCI), the treatment selection of patients with multivessel CAD is more nuanced and modified CAD extent, SYNTAX score, diabetic status, and the presence of left main disease (89). Moreover, the decision between PCI and coronary artery bypass grafting should give priority to the ability to achieve complete revascularization (and treatment of concomitant valvular lesions), taking into account pulmonary status and porcelain aorta. Specifically, multivessel CAD (without valvular disease) with SYNTAX score <22 should be preferentially treated by PCI. Similarly, left main disease at the ostium and shaft, as well as left main disease with SYNTAX score <32, should be considered for PCI as long as technically feasible (86).

In patients with RACD presenting with non-ST-segment elevation acute coronary syndrome, the timing of the intervention should follow initial risk stratification with an invasive strategy recommended within 2 h among very high-risk patients, within 24 h among high-risk patients, and within 72 h among intermediate-risk patients (90). Patients with RACD presenting with acute coronary syndromes are preferentially managed by PCI of the culprit lesion. In patients with RACD presenting with ST-segment elevation myocardial infarction, primary PCI constitutes the therapy of choice.

OUTCOMES. Data are conflicting regarding outcomes of patients with RACD undergoing PCI. Reed and et al. (91) (**Figure 7**) reported increased longer-term all-cause and cardiovascular mortality compared with matched controls in an observational cohort of 314 patients that underwent PCI between 2000 and 2012. Multivariable analysis identified previous XRT, SYNTAX score >11, balloon angioplasty and bare-metal stents (BMS) as independent predictors of mortality. Conversely, Fender et al. (92) observed no difference in longer-term all-cause and cardiovascular mortality in 115 patients with previous XRT compared with 450 propensity score-matched control patients undergoing PCI between 1994 and 2013. However, the volume and dose of radiation therapy appeared to modify outcomes, with increasing radiation exposure being associated with poorer long-term outcomes (93). The same group reported a similar risk of repeat revascularization among patients with RACD indicating the absence of a significantly increased risk of target lesion revascularization or stent thrombosis (94).

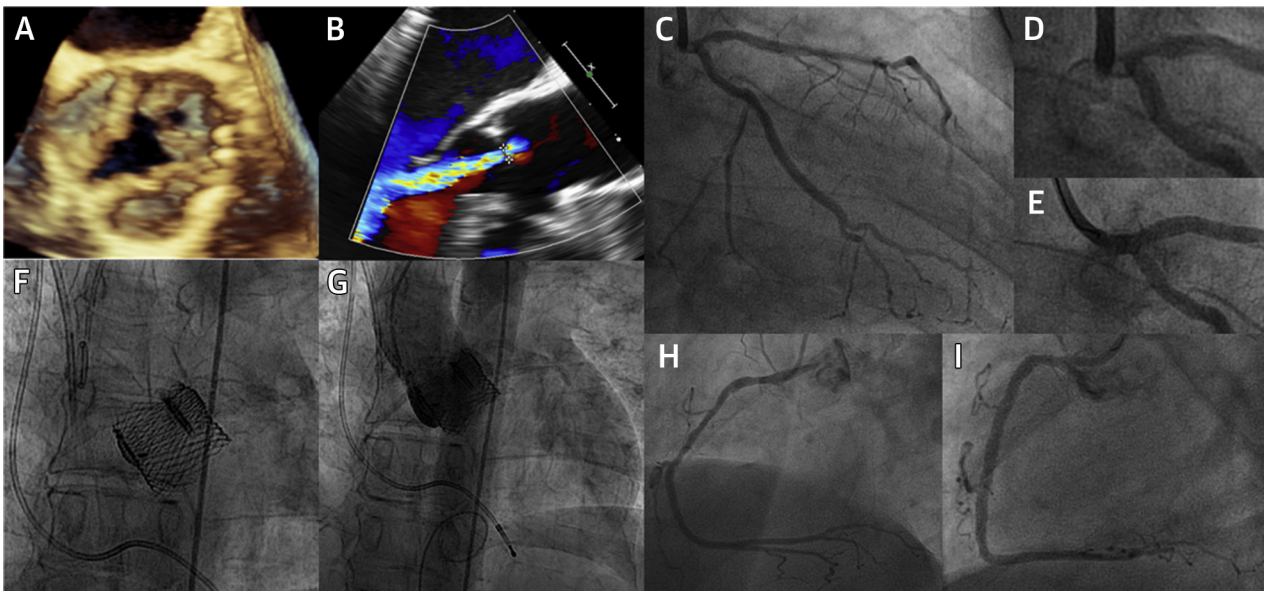
TECHNICAL CONSIDERATIONS. Drug-eluting stents should be the default device (86). Compared with BMS, drug-eluting stents have been shown superior in terms of efficacy (restenosis, target-lesion revascularization, major cardiac events) and at least as safe (95,96). More recent evidence in patients with multivessel and left main CAD indicates substantial improvements in terms of efficacy compared with previous trials comparing coronary bypass and BMS (97–99). In terms of vascular access, the radial approach should be preferred, analogous to patients without RACD (86). However, these findings need to be qualified in terms of operator experience and technical feasibility. Specifically in the setting of patients with RACD, ostial disease of the right coronary artery or left main may be more challenging in terms of guiding catheter selection and position. Intracoronary imaging may be considered to guide and optimize treatment of patients with RACD undergoing PCI (86). Selection of stent dimension (diameter and length), as well as optimization of procedural outcomes, may be guided by intracoronary imaging with use of optical coherence tomography or intravascular ultrasound.

LONG-TERM FOLLOW-UP CARE. Following PCI, the duration of dual antiplatelet therapy in patients with RACD should be governed by the underlying clinical setting (chronic vs. acute coronary syndromes) and bleeding risk (100,101). Among patients with ACS, the default duration of dual antiplatelet therapy is 12 months, which may be shortened to 6 months in case of high bleeding risk or extended to up to 30 months in case of low bleeding but high thrombotic risk (100,101). Patients with RACD should adhere to the same rigorous secondary prevention strategies and lifestyle changes as patients without RACD. After PCI, patients with RACD may be evaluated within 3 months and on annual basis thereafter, with noninvasive functional testing limited to symptomatic patients or high-risk patients such as those with left main disease.

TRANSCATHETER AORTIC VALVE IMPLANTATION

INDICATION AND TREATMENT SELECTION. As compared with patients without RACD, aortic valve disease in patients with RACD is more frequently associated with calcification of the ascending aorta, involvement of coronary ostia, calcification of the aortomitral curtain with extension into the anterior

FIGURE 8 A Patient With RACD Who Underwent TAVR



Echo showing severe aortic stenosis **(A and B)**, no obstructive coronary disease **(C to E, H, and I)**, and TAVR **(F and G)**. Abbreviations as in Figures 3 and 5.

mitral leaflet, a higher prevalence of severe conduction abnormalities, and diastolic and/or systolic dysfunction owing to myocardial fibrosis (46). All these may potentially complicate transcatheter aortic valve implantation (TAVR) owing to the risk of injury to the ascending aorta or cerebral embolization (porcelain aorta), coronary obstruction (ostial disease), annulus rupture, pacemaker implantation, and low-flow, low-gradient physiology, and require careful pre-procedural planning.

TAVR for AS should be performed according to guidelines (66,87). Currently, TAVR is recommended in patients at increased surgical risk; but recent data have suggested its superiority and noninferiority in intermediate- and low-risk patients as compared with surgery (102–104). TAVR should be considered the default strategy among patients with RACD, particularly if transfemoral access can be performed without complicating factors such as advanced CAD, multivalvular disease, or an excessive risk for coronary obstruction or annulus rupture (**Figure 8**).

OUTCOMES. Among patients included into the PARTNER (Placement of Aortic Transcatheter Valve) 1B trial and continued access registry, 85 of 369 patients (23%) were considered inoperable for surgical AVR based on technical ineligibility (105). The most common criteria for surgical inoperability in these patients were porcelain aorta (42%) and previous radiation therapy to the chest (25%). Patients considered technically inoperable had a somewhat shorter hospital stay versus those considered clinically inoperable (5.3 vs. 5.9 days; $p = 0.04$). Clinical event rates among inoperable patients at 30 days were 4.7% for all-cause mortality, 3.6% for stroke, 13% for hemorrhagic complications, and 17.6% for vascular complications. At 2-year follow-up, mortality was lower among inoperable patients versus conservative treatment (23.3% vs. 67.4%; $p < 0.001$), and increasing STS score was an independent predictor of mortality, whereas technical inoperability was found protective (105). A recent study reported outcomes of 98 patients with radiation-associated severe AS undergoing TAVR (**Figure 7**) (84). Post-procedural permanent pacemaker was required in 15% of patients and moderate to severe aortic regurgitation was recorded in 8% of patients. At 2.3 years, the annualized mortality was 8%/year, and multivariable analysis identified reduced LV stroke volume index as a predictor of increased long-term mortality (84).

TECHNICAL CONSIDERATIONS. Compared with surgery, TAVR performed via transfemoral access has consistently been shown to provide similar or superior outcomes in terms of mortality and stroke, as well as risk of renal failure, new-onset atrial fibrillation, and major bleeding (106). As a result, transfemoral access should be the default access in patients

considered for TAVR, including those with RACD as long as the vascular dimensions and anatomy demonstrate feasibility. However, owing to chest radiation exposure, transapical and transaortic access require careful evaluation, and other alternative access routes including transcaval, transaxillary, transsubclavian, and transcarotid may be explored. Precise delineation of the topographic anatomy of the aortic root by means of MDCT is routinely recommended in patients considered for TAVR. Extension of calcium into the ascending aorta and the aortomitral curtain are associated with an increased risk of annular rupture. This risk may be mitigated by avoiding predilation or consideration of self-expanding or mechanically expanding valves over balloon-expandable valves. The use of newer-generation transcatheter valves should minimize the risk of paravalvular regurgitation. Patients with RACD also feature a higher prevalence of AV conduction abnormalities, which needs to be considered in device selection to address the need of permanent pacemaker implantation. Patients with porcelain aorta should also undergo careful evaluation of atheromata of the ascending aorta. The latter may be associated with the risk of embolization during TAVR and may call for cerebral embolic protection devices.

LONG-TERM FOLLOW-UP CARE. After discharge, patients should be followed clinically, as well as by serial transthoracic echocardiographic follow-up, at 1 month, 12 months, and then annually (66,87). Among patients without indication for oral anticoagulation, long-term antiplatelet therapy with either aspirin or thienopyridine is recommended. Whether dual antiplatelet therapy is necessary for a variable period of time following TAVR is subject to debate.

OTHER TRANSCATHETER VALVE THERAPIES. Because data on transcatheter mitral and tricuspid valve therapies are evolving, there is not much experience in the setting of RACD. However, mitral annular calcification, commonly observed in RACD, is associated with significantly increased mortality following transcatheter mitral replacement (81,107). Future refinements in technology should undoubtedly improve these data and increase feasibility in challenging RACD patients. Additionally, many patients present with paravalvular leaks following initial valvular replacements. Management decisions (especially cardiac reoperation [108] or paravalvular leak closure) would have to be individualized in these high-risk patients; and the discussion is beyond the scope of this article.

ELECTROPHYSIOLOGY

RACD-associated conduction abnormalities are managed according to standard recommendations. This may include antiarrhythmic agents, permanent pacemakers or resynchronization therapy, and implanted defibrillators for prevention of sudden cardiac death.

CONCLUSIONS

With increased awareness, incidence of RACD from prior XRT exposure is likely to rise over the next decade. Management of RACD remains challenging due to increased rates of morbidity and mortality. Coordinated management by an experienced team of providers at a center of excellence is strongly advocated. Timing of surgical intervention must be individualized on the basis of the complexity of the disease, comorbidities, and technical difficulty. Percutaneous options are increasingly available, although their use and suitability in RACD is evolving. It is crucial to develop comprehensive multimodality imaging based screening protocols to adequately identify those at risk, plan interventions, and evaluate treatment response. However, the longer-term future should involve developing XRT delivery protocols that minimize the chances of developing RACD in the future.

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