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CONTEMPORARY REVIEW

Radiation-Induced Cardiovascular Disease: Review of an Underrecognized Pathology

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ABSTRACT: Radiation therapy demonstrates a clear survival benefit in the treatment of several malignancies. However, cancer survivors can develop a wide array of cardiotoxic complications related to radiation. This pathology is often underrecognized by clinicians and there is little known on how to manage this population. Radiation causes fibrosis of all components of the heart and significantly increases the risk of coronary artery disease, cardiomyopathy, valvulopathy, arrhythmias, and pericardial disease. Physicians should treat other cardiovascular risk factors aggressively in this population and guidelines suggest obtaining regular imaging once symptomatology is established. Patients with radiation-induced cardiovascular disease tend to do worse than their traditional counterparts for the same interventions. However, there is a trend toward fewer complications and lower mortality with catheter-based rather than surgical approaches, likely because radiation makes these patients poor surgical candidates. When appropriate, these patients should be referred for percutaneous management of valvulopathy and coronary disease.

Key Words: cancer survivors ■ cardiomyopathies ■ cardiotoxicity ■ cardiovascular diseases ■ coronary artery disease ■ fibrosis ■ heart disease risk factors

Radiation-induced cardiovascular disease, although well described in the literature, is an underrecognized phenomenon clinically. Radiation therapy is still widely used in the treatment of numerous cancers despite a nonnegligible risk of complications—the consensus being that the benefits of radiation outweigh its risks in selected cases. At sufficient doses, radiation of the mediastinum can damage virtually any component of the heart—the myocardium, pericardium, valves, coronaries, and conduction system.[1] An increasing number of cancer survivors are seen with premature heart disease despite having no significant cardiovascular risk factors, often decades after completion of radiation treatments. The first data obtained regarding the effects of radiation on the cardiovascular system stem from the survivors of the Hiroshima and Nagasaki atomic bombings, which showed that nearly 10% of the observed group died of heart disease.[2] Nowadays, among survivors of cancer, an increase of 1.7- to 2-fold in cardiovascular death is seen in patients who have undergone radiotherapy. An increase of 7.2-fold in cardiovascular death has been demonstrated in patients having received former radiation techniques before the 1970s.[3] These patients present a therapeutic challenge as there is a paucity of data regarding the specific considerations in their management. In this article, we review the most important clinical effects of radiation therapy on the cardiovascular system, with a focus on recent data regarding its treatment.

RISK FACTORS

A number of risk factors have been linked to radiation-induced cardiovascular disease. The total dose of mediastinal radiation received is a major risk factor for subsequent development of cardiovascular disease. Although complications can be seen with any dose, there is a linear increase in risk of valvular heart disease with total dose of radiation above 30 Gy/m^2.[4] Trials show that dose-escalation of radiation therapy for lung cancer is associated with an increased risk

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Nonstandard Abbreviations and Acronyms

SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement

of subsequent cardiac events (acute coronary syndromes, arrhythmias, pericardial disease).[5] A relative increase of 7.4% in risk of coronary events for each Gy of radiation to the heart has been demonstrated in women with previous breast cancer having received radiation.[6]

Other risk factors for development of cardiovascular disease after radiation include the dose of radiation per fraction, the volume of heart irradiated, and the extent to which the coronary arteries are included in the radiation field.[7] Complications are more commonly seen in patients with left-sided rather than right-sided breast cancer as a larger portion of the heart is included in the radiation field.[6] Concomitant use of cardiotoxic chemotherapy agents, typically anthracyclines, trastuzumab, and fluorouracil further increase the risk of heart disease.[8] Preexisting cardiovascular disease,[6] younger age at the time of radiation and presence of other cardiac risk factors such as hypertension, dyslipidemia, diabetes, family history of coronary artery disease (CAD), active smoking, and inactivity also increase the risk of radiation-induced cardiovascular disease.[7]

Radiation-associated cardiotoxicity appears to be delayed—typically 10 to 30 years following treatment. In patients with prior Hodgkin's lymphoma having undergone radiation therapy, the median time from diagnosis of malignancy to cardiac complications was 19 years.[8] The risk of inducible ischemia on myocardial perfusion scans increases from 5% at 10 years postradiation, to 20% at 20 years postradiation.[9] Finally, for reasons that are still unclear, women tend to have more cardiovascular events and mortality compared with men with radiation-induced cardiovascular disease.[10] However, these findings could be explained by the fact that at least half of the women in these studies were postmenopausal and therefore lacked the cardiovascular protective effect of estrogen.

CORONARY ARTERY DISEASE

Epidemiology

CAD is the most common manifestation of radiation-induced cardiovascular disease, with an incidence of up to 85%.[1] Patients with Hodgkin's lymphoma who have undergone thoracic radiation have been shown to have an increased risk of fatal myocardial infarction by 2.5-fold compared with the general population.[11] Fatal myocardial infarction has been reported in children as young as 15 years old after mediastinal radiation in autopsy studies.[12] A study of 79 lymphoma survivors found an incidence of 59% of CAD on computed tomography angiography.[13]

Pathophysiology

Many potential mechanisms have been hypothesized to explain the development of radiation-induced coronary disease. Radiation leads to the formation of free radicals, which can cause molecular damage. Tissue malfunction ultimately occurs when the cell's ability to repair itself is overwhelmed.[14] Radiation initially causes an endothelial injury in the coronaries that leads to a proinflammatory state, which eventually damages blood vessels via oxidative stress, generation of reactive oxygen species, and cytokine release that disrupts DNA strands integrity.[15] This inflammatory cascade leads to ruptured vessel walls, platelet aggregation, thrombosis, and replacement of the damaged coronary intima cells by myofibroblasts (Figure 1),[16,17] These changes ultimately accelerate vessel stenosis and atherosclerosis development, leading to CAD in unusually young patients.

Clinical Presentation

Radiation-induced CAD exists on a wide spectrum from asymptomatic coronary stenosis to angina, acute coronary syndrome, and fatal myocardial infarction. These patients may present with silent myocardial infarction more often than the general population because of damage to nerve endings from radiation.[18] Distribution of the affected coronary arteries depends on the distribution of the radiation dose. For example, mediastinal radiation is usually associated with left anterior descending and right coronary artery involvement, whereas left-sided breast radiation is mostly associated with left anterior descending coronary artery involvement.[13] The arterial narrowing seen with radiation is very proximal and involves the coronary ostia. Compared with nonirradiated controls, patients who have previously received radiotherapy tend to have greater severity and larger extent of lesions.[13]

Management

It is important to highlight some particular considerations in the management of CAD induced by radiation. Although coronary artery bypass graft (CABG) may seem appropriate for patients in whom it is usually indicated, certain difficulties may be faced. First, the arterial and venous conduits can be fibrotic, scarred, or stenosed from prior radiation, preventing them from being viable grafts, as shown by a retrospective review of patients who underwent CABG after mediastinal radiation.[19] In this review, the arterial grafts

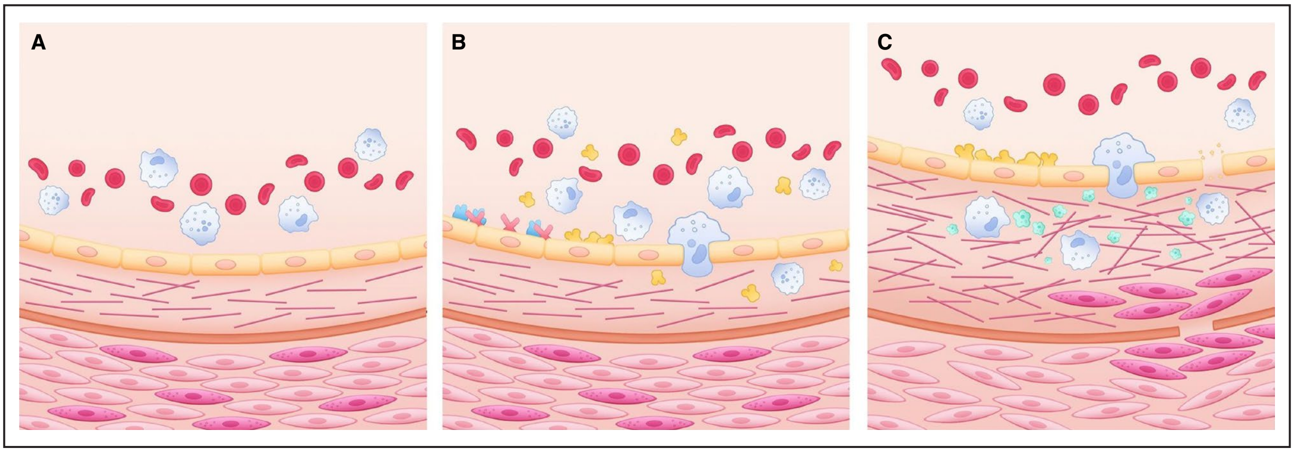

Figure 1. Mechanism of radiation-induced coronary artery disease.
A, Normal blood vessel with circulating red cells and white cells with a normal, thin intima. **B**, Acute changes after radiation with inflammatory cytokines and white cells entering the vessel through endothelial disruption and injury. **C**, Chronic changes after radiation where large quantities of collagen have been produced leading to vessel stenosis and intimal fibrosis. Modified with permission from Cuomo et al[17] ©2018, BMJ Publishing Group Ltd.

were not routinely assessed for patency and 34 out of 113 patients could not receive a left internal mammary artery graft for the aforementioned reasons. Second, these patients are usually deemed high risk for surgery, often labeled as having a hostile chest, with skin damage and friable thoracic vessels leading to poor wound healing and significant bleeding.[20] These patients often have concomitant radiation-induced interstitial lung disease and worsening pulmonary fibrosis has been linked with increased mortality postoperatively.[21] Finally, there is often significant calcification of the thoracic aorta, which precludes safe aortic clamping for cardiopulmonary bypass – if surgery is pursued, there is an increased risk of stroke and mortality.[22] These findings should be reviewed before the choice of intervention as they make these patients high risk for surgery.

Despite these complications, clinical outcomes from studies of these patients undergoing CABG seem conflicting. A prospective cohort study found that patients undergoing cardiac surgery who had received more extensive radiation had more complications and decreased survival at 4-year follow-up.[23] However, another study found similar long-term mortality after CABG in patients having previously received radiation compared with controls, at a mean follow-up of 5.4 years.[24] Given that poor outcomes have been documented with CABG in these patients, interest has increased for catheter-based correction of CAD. Nonetheless, outcomes after percutaneous coronary intervention (PCI) have also shown mixed results in this population. A retrospective cohort study of 116 patients showed similar rates of procedural complications and long-term mortality after PCI in patients who had previously received radiation therapy, compared with patients who did not.[25] However, other studies have identified prior radiation therapy as an independent predictor of mortality after PCI (hazard ratio [HR], 1.85; P=0.004)[26] and higher doses of radiation have been associated with poorer survival after PCI (HR, 1.02; P=0.009).[24] Thus, these patients probably tend to do worse than their traditional counterparts for the same interventions, such as PCI and CABG.

To our knowledge, there has been no direct comparison between PCI and CABG in radiation-induced CAD. This would be an important avenue for future research to clearly define which intervention has the best outcomes in this particular population. For now, it seems reasonable to refer these patients for either surgical or catheter-based treatment depending on patient characteristics, with a Heart Team evaluation. If surgery is selected, calcification and patency of thoracic vessels should be assessed. In high-risk patients, catheter-based approaches are likely safer.

VALVULAR DISEASE

Epidemiology

Thoracic radiation has been linked to a significantly increased risk of valvulopathy. The prevalence of valvulopathy is up to 26% at 10 years and 60% at 20 years after radiation.[1] The median interval between the diagnosis of cancer and valvular disease is 23 years, with prevalence and severity of valvulopathy proportional to the dose of radiation received.[4] In comparison with nonirradiated subjects, these patients have a 9.2-fold increased risk of requiring surgery for their valvulopathy.[27]

Pathophysiology

With radiation, valve cusps and leaflets undergo fibrotic changes and thickening, with or without calcification. Mediastinal radiation typically affects the left-sided valves, regardless of the dose distribution,[28] suggesting that higher pressures in the systemic circulation further damage an already fragile valve. Aortic insufficiency is the most commonly seen pathology, followed by aortic stenosis.[29] The aortic valve is usually the closest to the radiation field, increasing the risk for subsequent disease. Mitral and tricuspid pathology has also been reported. As opposed to rheumatic heart disease, mitral valve commissures and leaflet tips are typically spared with radiation.[30] There are typically aortomitral continuity calcifications[31] which can be seen on echocardiogram (Figure 2).

A pathology study assessed by immunochemistry the excised aortic valves of patients who had undergone transcatheter aortic valve replacement (TAVR), comparing previous radiation subjects with controls.[32] The valves of patients with previous lymphoma were found to have decreased density, increased collagen content, and less calcified tissue than the other groups (Figure 3). These changes were attributed to the high doses of radiation received at a young age in these patients, suggesting a different mechanism of valvulopathy than that of traditional disease.[32]

Management

There has been an increasing interest for percutaneous approaches for the correction of valvulopathy in patients with prior mediastinal radiation, as they bypass many potential surgical complications in these patients with a hostile chest. Although aortic regurgitation is the most commonly seen pathology, aortic stenosis is the pathology that most often requires correction, hence will be the focus of this discussion.

Regarding the prognosis after TAVR in patients with a history of radiation compared with controls, the data remain controversial. Multiple studies have shown no difference in mortality at 30 days, 1 year, and 6 months, with similar implantation rates and 30-day safety end point,[33,34] However, there has been demonstration of a nonsignificant increase in 5-year mortality for patients undergoing TAVR with prior radiation exposure.[35] Another study found an increase in all-cause mortality (29% versus 15%, $P<0.01$) and major adverse cardiac event (57% versus 27%, $P<0.01$) at 17 months follow-up after TAVR. Patients with previous radiation had a significantly higher incidence of atrial fibrillation and high-grade heart block requiring pacemaker insertion.[36]

Another retrospective study found a 20% death rate at a median 2.3 years follow-up after TAVR in patients with a history of prior radiation.[37] An imaging study found that improvement in longitudinal strain on echocardiogram post-TAVR was significant only in patients without prior radiation and that a history of chest radiation was associated with more paravalvular aortic regurgitation, stroke, and delirium postprocedure.[38]

Surgical aortic valve replacement (SAVR) has also shown to have worse outcomes in patient with a history of previous mediastinal radiation. A matched cohort study found that mediastinal radiation was associated with statistically significant increased 6-year mortality (48% versus 7%, $P<0.001$).[39] However, it has been underlined that a significant proportion of patients undergoing SAVR were undergoing concomitant procedures like CABG. Isolated SAVR had improved 5-year survival compared with combined procedure.[40]

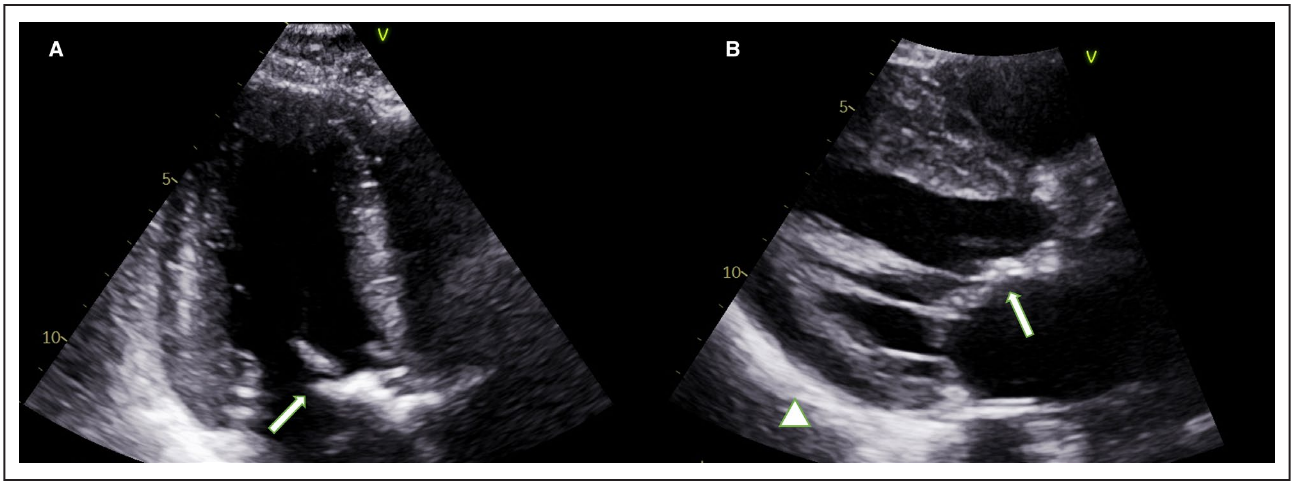

Figure 2. Echocardiographic findings of radiation-induced heart disease.
A, 3-chamber view showing a heavily calcified and stenotic aortic valve (arrow) in a patient with radiation-induced cardiotoxicity. **B**, Classic findings of aortomitral continuity calcifications caused by radiation (arrow) and pericardial thickening and calcifications (arrowhead)

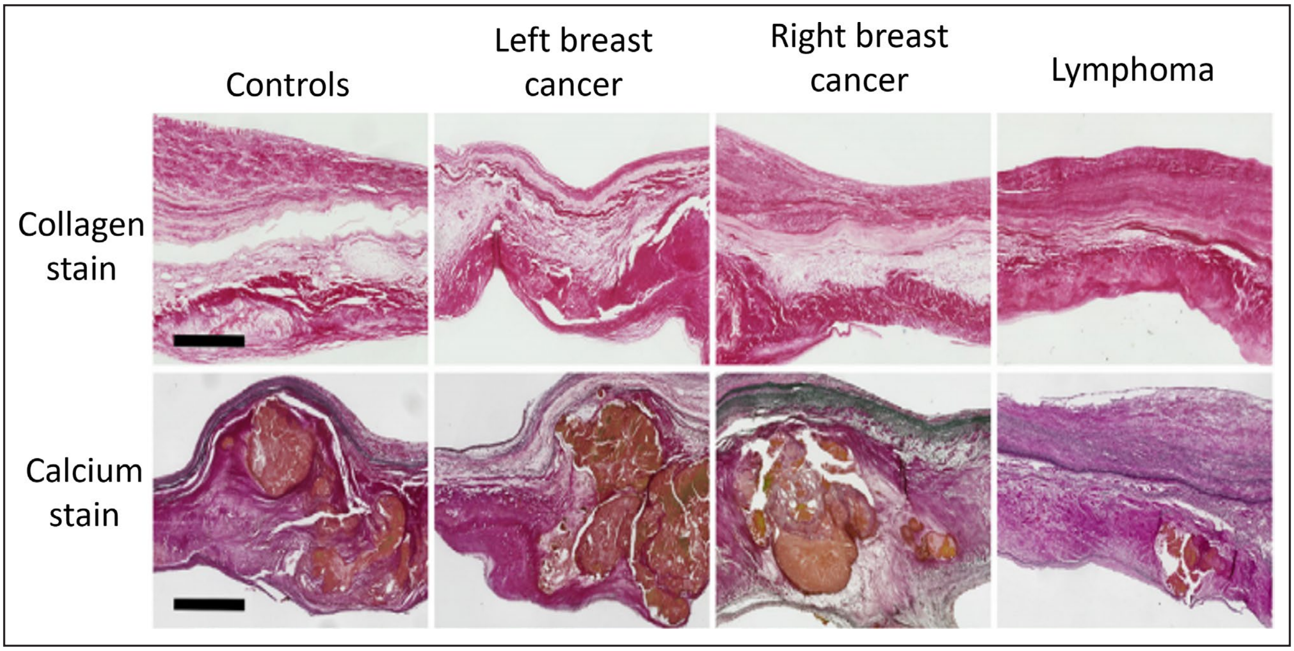

Figure 3. Immunohistochemistry staining of aortic valves after TAVR with staining for collagen, and calcium.
Hodgkin's lymphoma patients who have received high-dose radiation at a young age have a different pathology for aortic stenosis where their valves are more fibrotic with collagen deposits, as opposed to calcified. Left-sided breast cancer is believed to lead to more heart disease than right-sided breast cancer because radiation to the left breast is in more direct line with the heart. However, this study found similar composition of calcium and collagen in both entities. This is perhaps explained by that radiation to the breast is angulated toward the apex of the heart as opposed to the base, where the valves are found. Modified with permission from van Rijswijk et al[32] ©2020, Elsevier. TAVR indicates transcatheter aortic valve replacement.

Similar outcomes have been demonstrated in mitral valve surgery in patients having previously undergone radiotherapy compared with controls, showing a 55% 5-year survival compared with usual survival rates of 80% to 95% for traditional cases.[41]

Only 1 study so far has directly compared outcomes after TAVR and SAVR in this population. A retrospective review was done of all patients with severe aortic stenosis at the Mayo Clinic from 2011 to 2018 who underwent TAVR or SAVR with a history of mediastinal radiation.[42] TAVR patients had a higher Society of Thoracic Surgeons score than surgical patients and there was a significant postoperative decrease in atrial fibrillation rates and hospital stay in TAVR patients. In addition, 30-day mortality was lower with TAVR (1.8% versus 9.1%, P=0.21), as was the ratio of observed-to-expected 30-day mortality. However, there was an increase in readmission rates, mostly because of heart failure.

In summary, TAVR seems to be a promising avenue for treatment of radiation-induced aortic stenosis with lower mortality than SAVR, especially in patients at high risk of surgery with high Society of Thoracic Surgeons score. Both SAVR and TAVR show higher mortality and complications in patients who have previously received radiation therapy compared with controls. Aortic regurgitation is the most common valvulopathy seen with radiation, yet there is still little known on how to manage this condition.

CARDIOMYOPATHY

Epidemiology

Thoracic radiation has been linked with a significantly increased risk of nonischemic cardiomyopathy of several etiologies (direct fibrosis of the myocardium, hypertrophy secondary to valve disease, and restrictive cardiomyopathy from constrictive pericarditis). In patients with Hodgkin's lymphoma having received 35 Gy or more of mediastinal radiation, 14% had evidence of diastolic dysfunction on echocardiogram.[11] Recent reviews estimate the prevalence of radiation-induced cardiomyopathy at more than 10%.[1] A case-control study found a median interval of 3.6 years from diagnosis of cardiomyopathy related to radiation to death.[43] Finally, a recent case-control study looking at women having received contemporary (1998–2013) radiation for breast cancer has shown that 64% of women developed heart failure with preserved ejection fraction.[44]

Pathophysiology

Radiation leads to fibrosis of the myocardium and epicardium. As described in the coronary disease section, endothelial injury results in narrowing of the capillaries, leading to a decreased ratio of effective blood vessels to myocytes, ultimately leading to myocardial cell death.[11] The presence of inflammatory cytokines and inflammatory cells seems to promote the differentiation of smooth muscle cells into myofibroblasts, which generate large amounts of collagen.[45] Radiation predominantly causes restrictive cardiomyopathy with diastolic dysfunction, with stiffening of the myocardium secondary to replacement of the interstitium and dead myocytes by collagen and fibrotic tissue.[11] The right ventricle is more often affected than the left ventricle given it is more anterior and closer to the radiation beam.[1]

Anthracyclines, which are commonly part of the chemotherapy regimen of Hodgkin's lymphoma, are known to cause cardiomyopathy with predominantly systolic dysfunction. The use of anthracyclines is a risk factor for development of cardiomyopathy in patients who also receive radiation. A case-control study of 91 Hodgkin's lymphoma survivors found a 3-fold increase in risk of cardiomyopathy in patients who received both radiation and an anthracycline compared with radiation alone, irrespective of the dose of anthracycline and radiation. There was no synergistic effect between the two.[43]

Management

Heart failure symptoms from radiation are treated with standard medical therapy with beta blockers, angiotensin-converting enzyme inhibitors, and diuretics. However, specific data on radiation-induced cardiomyopathy treatment are lacking and less is known in general about the treatment of diastolic compared with systolic dysfunction.[46] In end-stage radiation-induced cardiomyopathy, cardiac transplant has shown to be an option although 5-year survival was lower in these patients compared with cardiomyopathy of other etiologies (58% versus 73%, P=0.025). This was mostly attributed to early postoperative mortality from sternal wound dehiscence, wound infection, respiratory failure, and kidney injury.[47,48] Death on the waiting list for transplant was not higher in patients having previously received radiation, suggesting that they were not sicker but had a more important operative risk. Although previous radiation therapy is not an absolute contraindication to cardiac transplantation, these patients should be carefully selected and monitored for postoperative complications.

PERICARDIAL DISEASE

Epidemiology

Radiation can cause a wide array of pericardial disease, ranging from asymptomatic pericardial calcifications, thickening and effusions incidentally found on imaging (Figure 2), to progressive heart failure due to chronic constrictive pericarditis, acute pericarditis, and cardiac tamponade. An autopsy study examining patients who had undergone mediastinal radiation showed that 70% had some form of pericardial disease, usually effusion or constriction.[49] In a series of 117 patients treated for esophageal cancer with radiation therapy, 36% had pericardial effusion, occurring at a median of 6 months after treatment.[50]

Clinical Presentation

Acute pericarditis can be seen as a rare, short-term complication of radiation-induced inflammation to the pericardium, usually seen with the high doses of radiation given in Hodgkin's lymphoma.[51] In the long term, collagen and fibrin replace the normal adipose tissue of the heart leading to fibrosis of the pericardium. This can also lead to impaired venous drainage and accumulation of fibrinous exudate in the pericardial space, resulting in pericardial effusion. Calcification, thickening, and stiffening of the pericardium can also lead to constrictive pericarditis, usually decades after radiation treatments.[52]

Management

Symptomatic management of constrictive pericarditis and its heart failure symptoms is achieved with diuretics, although definitive treatment consists of pericardial stripping or pericardiectomy. Among patients undergoing pericardiectomy for constrictive pericarditis, previous radiation therapy has been shown to be the strongest predictor for adverse outcomes. Out of all causes of constrictive pericarditis, radiation was the one associated with the worst survival, with a 5-year survival rate of 12%.[53] This has been attributed to the concomitant effect of radiation on other cardiac structures and poor surgical profiles. Hence, the choice to proceed with surgery for the treatment of radiation-induced constrictive pericarditis should be carefully balanced with the important risks of the procedure. In some cases, symptomatic management of heart failure may be more appropriate.

CONDUCTION ABNORMALITIES

Epidemiology

Conduction abnormalities are a rare complication of radiation therapy for cancer. Up to 4% to 5% of patients having previously received radiation will develop a pathology of their conduction system.[1] Abnormal heart rate recovery times after exercise has been found in 32% of patients having previously undergone radiation therapy compared with 9% in controls.[54] Conduction abnormalities usually appear within 2 months of the end of radiation treatments.[55]

Clinical Manifestation

The conduction system can be directly injured by radiation through an inflammatory process resulting in fibrosis or via fibrosis after ischemia of the myocardium.[18] Radiation is associated with higher prevalence of prolonged QT interval, ventricular tachycardia, sinus node dysfunction, atrioventricular blocks, fascicular blocks, and bundle branch blocks (right bundle most common, because it is anterior and in direct line with the radiation field).[56] Radiation has also been linked to autonomic dysfunction with loss of circadian variability in heart rate, inappropriate chronotropic response to stress and persistent tachycardia, presumed to be secondary to decreased vagal tone.[54]

Management

Radiation-induced arrhythmias warrant the same investigations and interventions as their traditional counterparts including ECG, Holter or telemetry monitoring, antiarrhythmic drug use, and placement of pacemaker or defibrillator when indicated. Subpectoral approach can be considered for pacemaker or defibrillator implantation if there is significant subcutaneous fibrosis secondary to radiation.[1]

PREVENTION AND SCREENING

Many techniques have emerged in order to reduce the incidence of radiation-induced cardiovascular disease. Newer radiation protocols allow for more precise and efficient delivery of smaller doses of radiation and reduce the volume of heart exposed within the field by shielding the heart, with the intent of maintaining cancer-free survival.[57] With major changes since the 1970s, fewer cardiac events are now seen.[58] For example, the incidence of acute pericarditis after radiation has decreased from 20% to 2.5%.[59] Currently, it is not certain whether these strategies reduce the prevalence of complications or simply delay the timing of their onset, but there seems to be a reduction in severity of symptoms. It is still unclear whether there is any safe dose at which no adverse event on the heart is seen. Other strategies to minimize the risk of complications include using the minimal dose of anthracyclines necessary given their potential concomitant toxicity.

Patients who have undergone radiation should be screened and aggressively treated for cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, obesity, inactivity, and smoking. The American

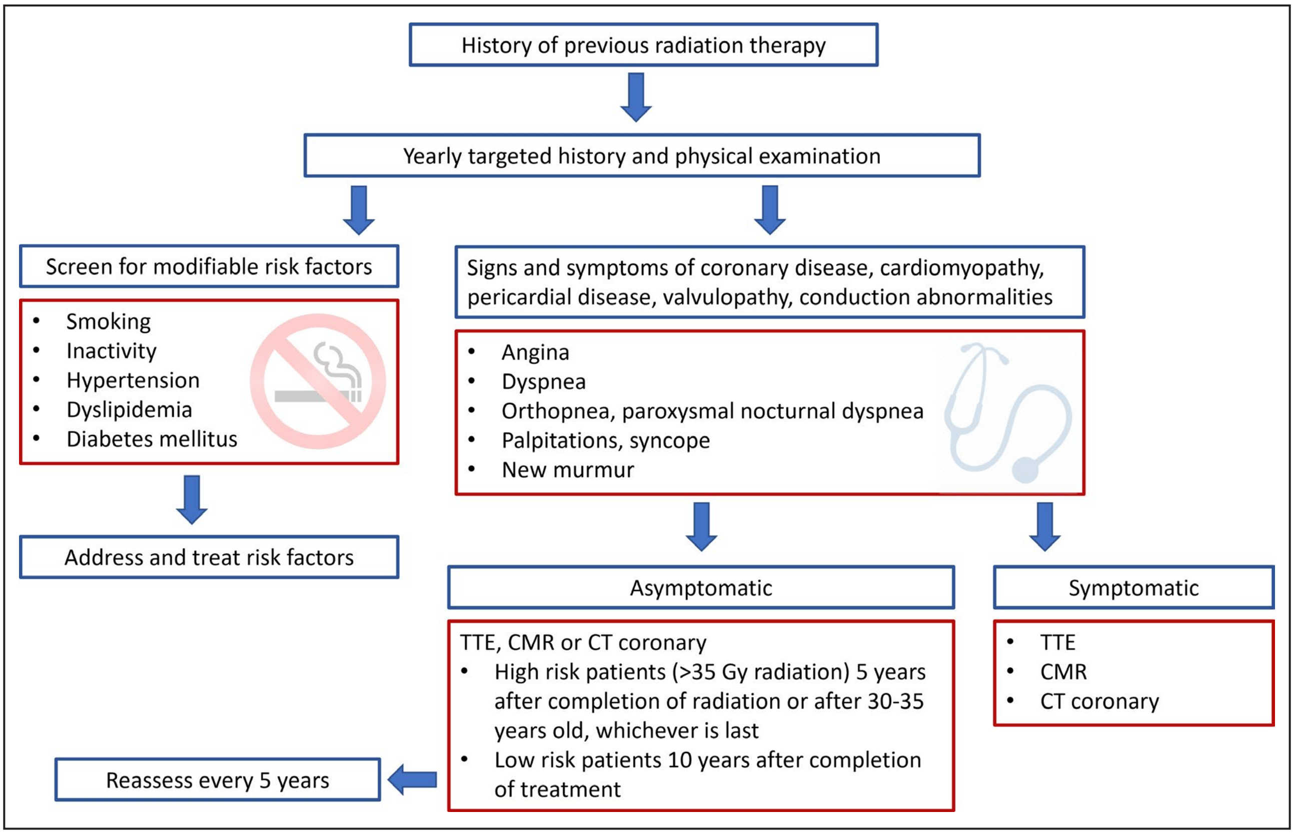

Figure 4. Screening guidelines of radiation-induced cardiovascular disease.
CMR indicates cardiac magnetic resonance; CT, computed tomography; and TTE, transthoracic echocardiogram. Modified with permission from Lancelloti et al[60] ©2013, Elsevier.

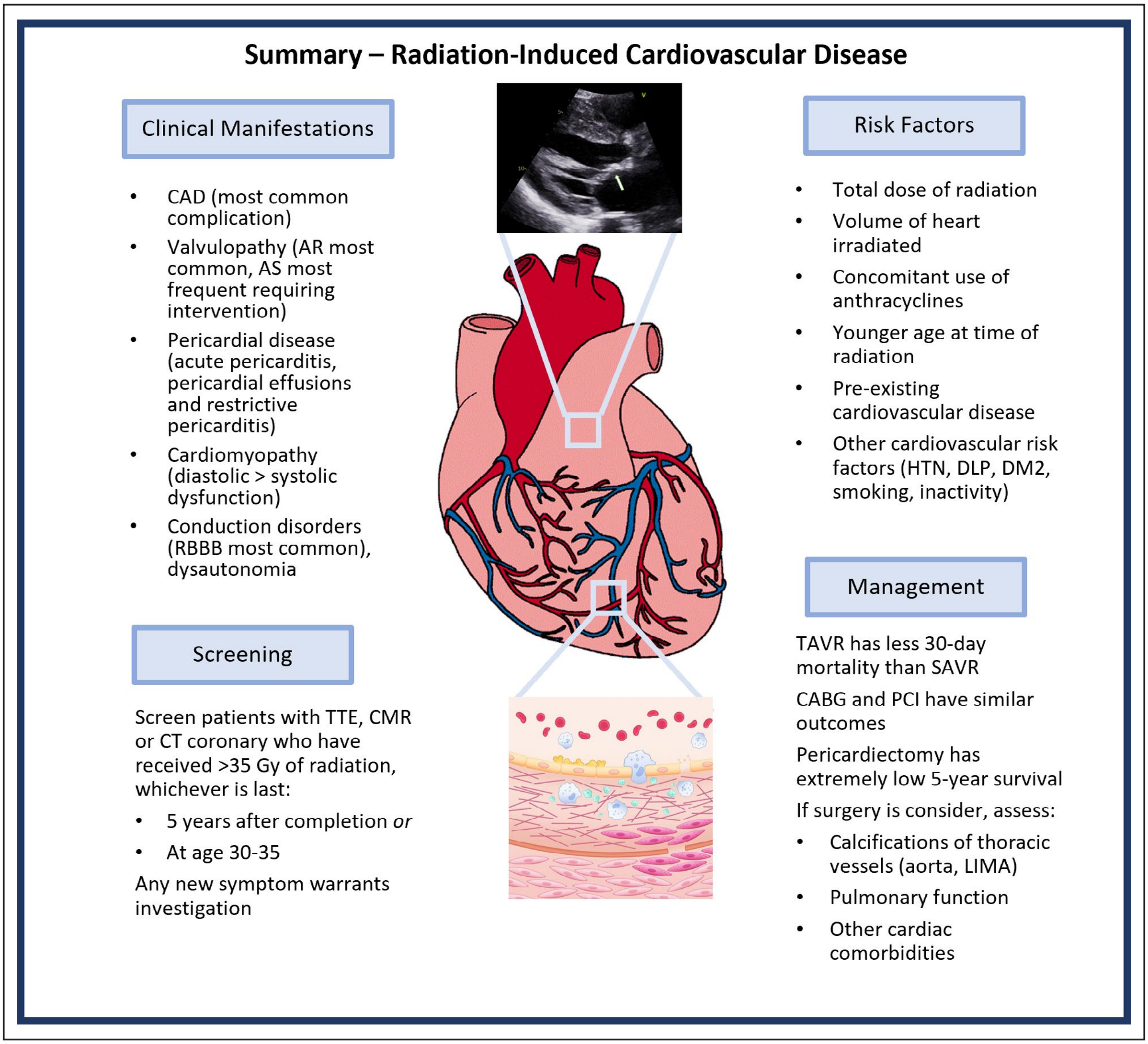

Figure 5. Summary of the findings of radiation-induced cardiovascular disease.
AR indicates aortic regurgitation; AS, aortic stenosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CT, computed tomography; DLP, dyslipidemia; DM2, diabetes type 2; HTN, hypertension; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and TTE, transthoracic echocardiogram.

Society of Echocardiography has proposed guidelines in 2013 for screening of radiation-induced cardiovascular disease, recommending to screen with transthoracic echocardiogram, cardiac magnetic resonance imaging, or coronary computed tomography angiography in patients who have received more than 35 Gy of radiation, either 5 years after completion of therapy or after ages 30 to 35 years old, whichever is last (Figure 4). Any new cardiac symptoms should warrant investigation.[60] Hence, cardiovascular disease should be screened for diligently and according to current guidelines in patients having received radiation.

CONCLUSION

Modern oncology treatments make for an increased number of cancer survivors, leading to an increasing population who presents with the late complications of radiation (summarized in Figure 5). Although this is becoming increasingly rare, especially with newer radiation delivery modalities, physicians should be vigilant in suspecting the development of cardiotoxicity decades after radiation completion. Patients with radiation-induced cardiovascular disease have poorer outcomes after correction of their disease compared with controls as they are poor surgical candidates, and these potential complications may make surgery less appealing. Further research is needed in this field to determine optimal ways to treat these patients.

ARTICLE INFORMATION

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Disclosures

None.

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