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Long-term consequences of radiation therapy

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26 Long-Term Consequences of Radiation Therapy

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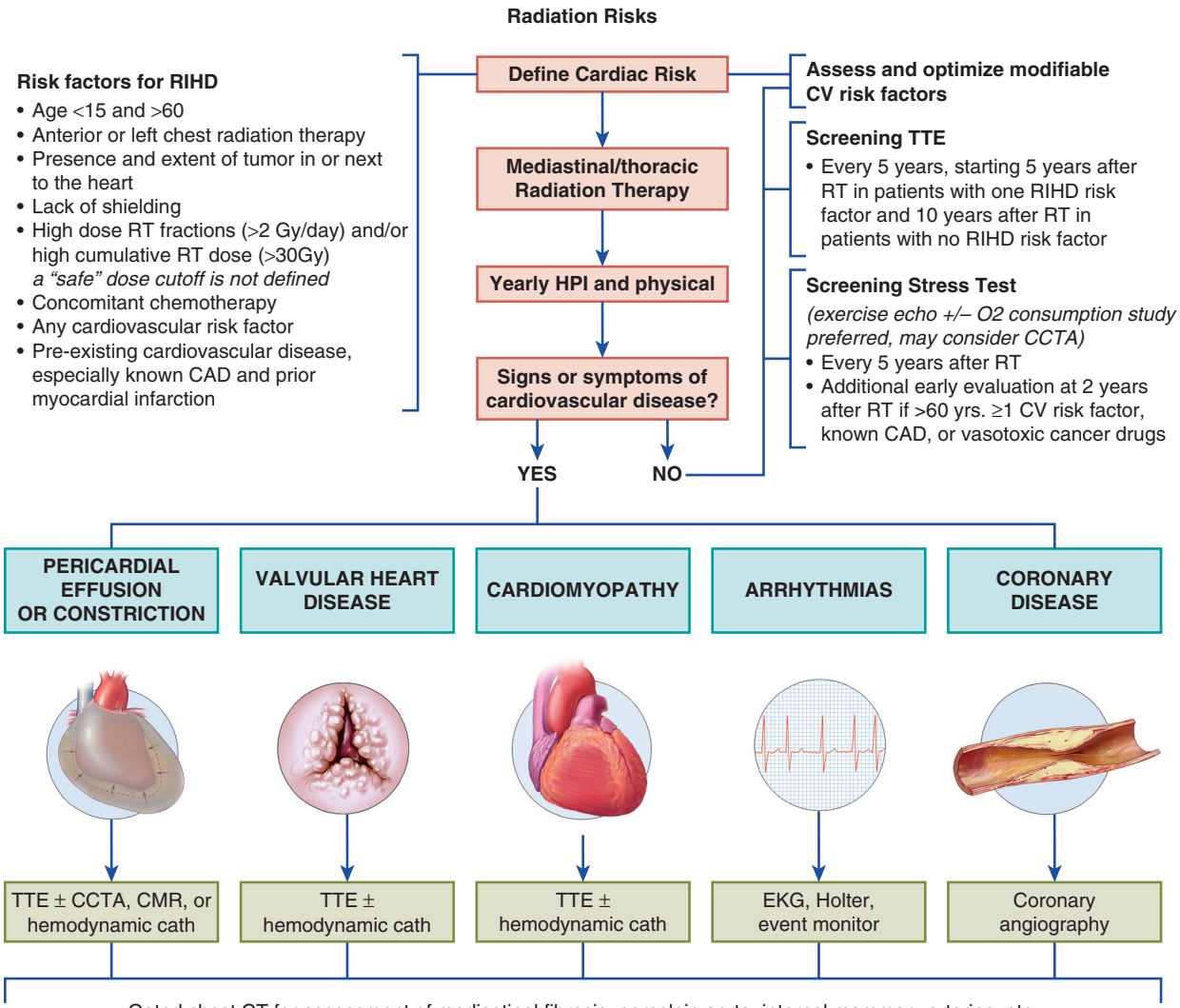

CAD, Coronary artery disease; *CCTA,* coronary computed tomography; *CMR,* cardiac magnetic resonance imaging; *CV,* cardiovascular; *EKG,* electrocardiogram; *Gy,* gray; *HPI,* history of present illness; *RIHD,* radiation-induced heart disease; *RT,* radiation therapy; *TTE,* transthoracic echocardiography.

CHAPTER OUTLINE

KEY POINTS

- Patients with cancer who are exposed to radiation therapy are at increased risk for numerous cardiac complications, including cardiomyopathy, valve disease, pericardial disease, arrhythmias, conduction abnormalities, autonomic dysfunction, and coronary artery disease that usually occur years, if not decades, following therapy.
- Patients with prior mediastinal or thoracic radiation should be screened for signs or symptoms of cardiac disease and modifiable cardiovascular risk factors on an at least annual basis.
- Even in patients with a history of radiation therapy but no signs and symptoms of cardiovascular disease serial screening with a transthoracic echocardiogram and functional/anatomic assessment is recommended; the timing is based on patient- and treatment-specific risk factors.
- If radiation-induced heart disease is diagnosed, treatment is typically the same as that provided for the general population; however, treatment outcomes (i.e., pharmacologic, percutaneous, surgical) may be worse in patients who have had radiation therapy owing to common involvement of multiple heart structures and thus the presence of multiple heart disease processes at once as well as multiple other complications and comorbid conditions acquired during cancer treatment.

Radiation therapy (RT) as a component of cancer treatment is a significant cause of cardiac complications during survivorship. It is most commonly reported after external beam RT (EBRT) for breast cancer or Hodgkin lymphoma (HL) but may also be seen with RT for gastric, esophageal, or lung cancer. All structures of the heart can be affected, including pericardium, myocardium, heart valves, coronary arteries, and conduction system. Accordingly, the spectrum of radiation-induced heart disease (RIHD) is quite broad and includes acute and constrictive pericarditis, (typically restrictive) cardiomyopathy, valvular heart disease (VHD), coronary artery and microvascular disease, heart block, and autonomic dysfunction. A number of these disease processes can ultimately present in heart failure (HF) as the final common pathway (Fig. 26.1). The individual disease elements of RIHD and their treatment will be reviewed herein first, followed by an outline of general screening efforts and preventive recommendations.

CORONARY ARTERY DISEASE

Coronary atherosclerosis in RIHD typically matches radiation dose exposure in location and severity. With RT for HL, ostial disease of both the right and left coronary arteries are the most classic lesions, whereas after RT for left-sided breast cancer the mid (and distal) left anterior descending coronary artery (LAD) is most commonly involved.[1,2] The clinical presentation of radiation-induced coronary atherosclerosis is similar to that of conventional coronary artery disease (CAD), presenting with stable angina or acute coronary syndrome.[3] For diagnosis, single photon emission computerized tomography myocardial perfusion imaging (SPECT MPI) has indicated perfusion defects in as many as 70% of patients 5 years after RT for breast cancer.[4] However, limited data exist regarding the sensitivity or specificity of SPECT MPI in this specific population and cited data are reflective of other radiation techniques. Positron emission tomography (PET) MPI may be a reasonable alternative to SPECT, given the ability to quantify myocardial blood flow. In comparison with nuclear MPI, stress echocardiography has lower sensitivity but higher specificity the diagnosis of radiation-induced CAD (Table 26.1).[5]

Coronary artery calcium scoring, and coronary computed tomography angiography (CCTA) are gaining increasing interest and may play a larger role for the diagnosis of CAD after RT in the future.

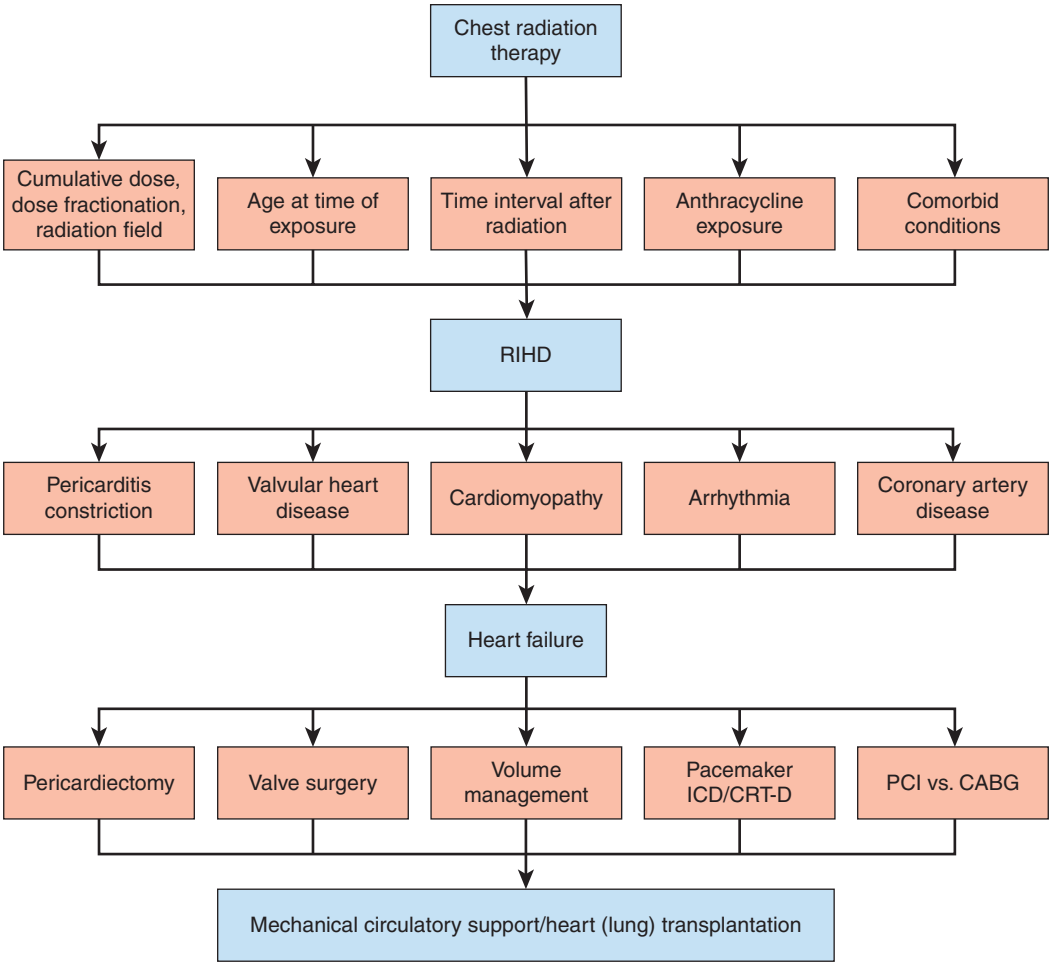

FIG. 26.1 The spectrum of radiation-induced heart disease (*RIHD*), which can culminate in the "common final pathway" of heart failure (HF) presentation. Treatment modalities are directed toward the disease aspects. *CABG,* Coronary artery bypass grafting; *CRT-D,* cardiac resynchronization therapy defibrillator; *ICD,* implantable cardioverter defibrillator; *PCI,* percutaneous coronary intervention. (From Finch W, Lee MS, Yang EH. Radiation-induced heart disease: long-term manifestations, diagnosis, and management. In: Herrmann J, ed. *Clinical Cardiooncology.* 1st ed. Elsevier; 2016.)

In a small cohort study, coronary artery calcium score following mediastinal RT for HL was higher in those with than in those without obstructive CAD (median score of 439 vs. 68), and a score of 0 had a negative predictive value for symptomatic CAD of 100%.[6] Using CTA, another study found a 24% prevalence of CAD in 119 patients who had undergone mediastinal RT as children.[7] Both calcified and noncalcified plaques were seen, primarily in the proximal coronary arteries (57% included the proximal LAD) and mostly non-obstructive. Coronary CTA has thus been attributed a higher sensitivity and negative predictive value for CAD than stress testing. As in general practice, however, catheter-based coronary angiography remains the gold standard for the detection of CAD.

Management of CAD in cases of radiation therapy is not specifically addressed in United States guidelines on management of acute coronary syndrome and stable ischemic heart disease, however, the same principles apply. Revascularization using either percutaneous coronary intervention or coronary artery bypass graft surgery may be necessary when critical stenoses are present; the need for concomitant valve or pericardial surgery may influence the decision.[8] A noteworthy concern is limited usability of the internal mammary arteries after chest radiation; however, a study of 125 patients

TABLE 26.1 Differential applicability of Imaging Techniques for the Detection and Follow Up of Radiation-Induced Heart Disease

	ECHOCARDIOGRAPHY	CARDIAC CMR	CARDIAC CT	STRESS ECHOCARDIOGRAPHY	ERNA/SPECT PERFUSION
Pericardial Disease					
Effusion—screening and positive diagnosis	++++	++	+	−	−
Effusion—follow up	++++	+	−	−	−
Constriction—screening and positive diagnosis	++++	++++	++	−	−
Myocardial Disease					
LV systolic dysfunction	++++ (1st line, contrast echocardiography if poor acoustic window)	++++	+	++++ (contractile reserve assessment)	++++/++++ (if analysis of function and perfusion needed)
LV diastolic dysfunction	++++	+	−	+	++/+
LV dysfunction—follow up	++++ (1st line, contrast echocardiography if poor acoustic window)	+	−	++ (contractile reserve assessment)	++/++
Myocardial fibrosis	−	++++	+	−	−
Valve Disease					
Positive diagnosis and severity assessment	++++	++	++	++	−
Follow up	++++	+	−	++	−
Coronary Artery Disease					
Positive diagnosis	+ (if resting wall-motion abnormalities)	++++ (stress CMR[b])	++++ (CT angio[a])	++++ (exercise or dobutamine[b])	+/++++
Follow up	+	+	++	++++ (1st line)	+/++

[a]For anatomic evaluation, an excellent negative predictive value.
[b]For functional evaluation.
Angio, Angiography; *CMR,* cardiac magnetic resonance; *CT,* computed tomography; *ERNA,* equilibrium radionuclide angiocardiography; *SPECT,* single-photon emission CT; *LV,* left ventricular.
++++: highly valuable; ++: valuable; +: of interest; −: of limited interest.

who had undergone mediastinal irradiation did not identify vessel fibrosis or significant histologic damage.[9,10] Still, there might be merit in evaluating the internal mammary arteries by conventional or CT angiography before cardiac surgery.

VALVULAR HEART DISEASE

Cardiac valvular abnormalities are common following mediastinal RT (Fig. 26.2 and 28.3), with significant valve disease (defined as mild or greater aortic regurgitation; or moderate or greater mitral or tricuspid regurgitation; or aortic stenosis) in 29% of asymptomatic patients starting 2 years after RT, compared with 4% of age- and gender-matched controls.[11] This rate increases significantly over time to 42% at 14 years and over 60% after 20 years postirradiation in high exposure cohorts, such as patients with lymphoma. Moderate or greater valvular disease is most commonly observed of the aortic and mitral valves, and regurgitation occurs more often than stenosis of these valves. The risk of radiation-induced valvular disease is greatest when the radiation dose exceeds 25 Gy.[12,13]

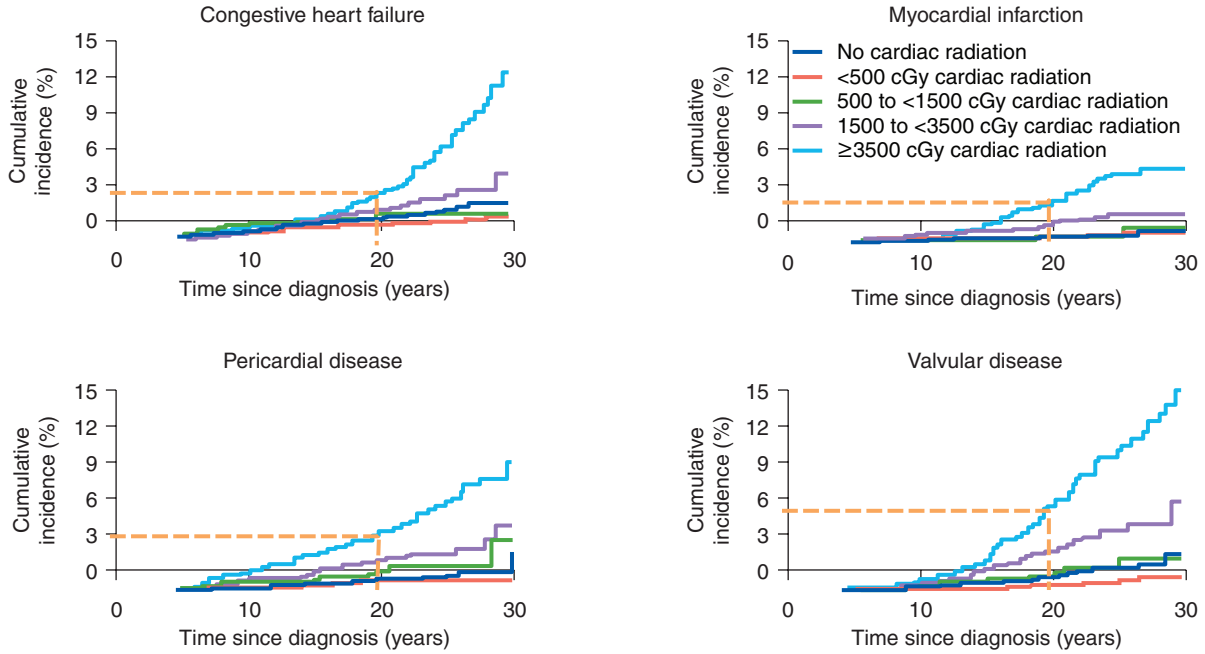

FIG. 26.2 Cumulative incidence of the various aspects of radiation-induced heart disease in childhood cancer survivors. Notice the dose dependency and timeline of 15 years from diagnosis for clinical appearance. (From Mulrooney DA, Yeazel MW, Mertens AC, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606, with permission.)

When valve disease is symptomatic or other indications for replacement are present, surgical management is indicated, according to standard valve guidelines (see Chapter 28).[14,15] Patients with RIHD undergoing valve surgery have a relatively high rate of morbidity and mortality after valve surgery (30-day mortality of 12%).[14,15] Because mediastinal RT can result in comorbidities that can result in prohibitively high surgical risk (e.g., frozen mediastinum or porcelain aorta), percutaneous valve therapies may be preferable in many cases.[13] Of note, the Society of Thoracic Surgeons (STS) risk score as a standard tool for surgical risk assessment in patients with aortic stenosis underestimates the risk of surgical aortic valve replacement (SAVR) in this population. Transcatheter aortic valve replacements have been used successfully in patients with severe aortic stenosis whose radiation-induced mediastinal and pulmonary fibrosis precluded surgery. In several nonrandomized analyses, patients who underwent transcatheter aortic valve replacement had a higher survival rate after valve replacement compared with patients who underwent surgical aortic valve replacement.[16] More recently, percutaneous edge-to-edge mitral valve repair, with technologies such as MitraClip (Abbott Medical, Abbott Park, IL), has been used for radiation-induced mitral regurgitatio.[17] One potential concern after MitraClip for RT-induced mitral regurgitation is that if there is ongoing reactive damage to the mitral apparatus, delayed mitral stenosis may occur; however, at 6 months postprocedure there was nearly a 90% rate of improved New York Heart Association (NYHA) functional class.[17]

CARDIOMYOPATHY

Direct damage to the myocardium from radiotherapy may result in cardiomyopathy even in the absence of significant epicardial CAD or VHD. Prior thoracic radiation exposure increases the risk of HF substantially (hazard ratio [HR], 2.7 to 7.4 for HL and HR, 1.5 to 2.4 for breast cancer).[18] Radiation-induced cardiomyopathy (RICM) more commonly presents as HF with preserved ejection fraction.[18] For patients with breast cancer receiving radiotherapy, the odds ratio of developing HF per log of mean cardiac radiation dose is 16.9 (3.9 to 73.7) for HF

with preserved ejection fraction (EF), and 3.17 (0.8 to 13.0) for HF with reduced EF.[19] Studies measuring diastolic function in long-term survivors of HL who received RT have, however, shown inconsistent results and many have found none or only mild changes in diastolic parameters.[18]

Patients who develop RICM present similar to those with HF from any other causes. The effects of radiation are synergistic with anthracycline chemotherapy, resulting in doubling of the risk of heart failure compared with RT alone.[20–22] Myocardial fibrosis, which is a hallmark of RICM, can be seen in a patchy or diffuse distribution on cardiac magnetic resonance (see Table 26.1).[23] Echocardiography, including strain imaging using speckle tracking, can be helpful in identifying radiation-induced myocardial dysfunction.[24] Global longitudinal strain may become abnormal before the ejection fraction declines, which is typically reduced compared with controls, but still in the normal range. Fibrosis within the myocardium and endocardium may additionally result in diastolic dysfunction.[25] When HF with reduced ejection fraction is present, therapy for cardiomyopathy does not differ from that of nonradiation-induced cardiomyopathies. In patients with advanced RICM, orthotopic heart transplantation is a last resort; however, it should be noted that mediastinal fibrosis may increase the operative risk significantly.[26] Last but not least, all patients presenting with HF after chest RT should be evaluated for all possible radiation toxicities, including CAD, VHD, and pericardial disease, which can present as or at least contribute to HF in these patients.

PERICARDIAL DISEASE

In the early era of mantle radiation for HL high radiation doses resulted not infrequently in acute pericarditis (up to 60% incidence in early studies) often with pericardial effusions and risk of cardiac tamponade.[27] Pericardiocentesis or surgical approaches may be required in the latter case, and nonsteroidal antiinflammatory drugs take center stage in the management of the acute inflammation and pericardial irritation. Long-term complications may include pericardial fibrosis resulting in constrictive pericarditis (CP), which may be delayed to more than 20 years after RT.[28–30] CP caused by mediastinal RT has similar symptoms and physical examination findings; diagnostic evaluation and management is likewise similar to CP owing to other causes.[29] The most notable distinction from other etiologies is that RT-induced CP has been associated with a significantly higher long-term mortality.[31] This is exemplified in patients undergoing pericardiectomy: 5-year mortality is 2.5 times higher in patients who have RT versus those who have not (90% vs. 36%).[31,32] When CP is present along with valvular disease, perioperative mortality is increased to as high as 40% at 30 days.[14,15] Thus, if symptomatic CP is present in patients with cancer after RT, candidacy for pericardiectomy needs to be carefully considered, and not too early and not too late, owing to considerable perioperative mortality.

PERIPHERAL ARTERY DISEASE

Thoracic radiation or RT for head and neck cancers may include the carotid or subclavian arteries in the radiation field.[33] In patients with RT for HL, 7% of patients were found to have carotid or subclavian atherosclerosis causing at least 40% stenosis after 20 years. Additionally, 4% developed transient ischemic attack or stroke only 5.6 years (median) after RT. The median radiation dose to the low-cervical region in patients who developed carotid or subclavian stenosis was 44 Gy. In patients with head and neck cancers even higher doses may be encountered (approaching 56 Gy in one study).[34] In these patients, carotid stenosis rates are as high as 79% at a median of 9.2 years after RT, compared with a reference of 21%. The (relative) risk of stroke after neck RT for either HL or head and neck cancer is five to six times higher than that seen in siblings or the general population.[35] The risk of stroke is increased regardless of whether the head and neck cancer type is associated with smoking.[35] In this population, carotid or subclavian artery stenting, carotid endarterectomy, and subclavian artery bypass grafting are all potential therapies.[33] In patients with RT exposure for breast cancer treatment, there is an increase in arterial stiffness (measured by the augmentation index and carotid-radial pulse-wave velocity) in the arm ipsilateral to the radiation site compared with the contralateral arm, suggesting direct and localized vascular damage as a result of RT.[36]

ARRHYTHMIAS AND AUTONOMIC DYSFUNCTION

Fibrosis of the conduction system, including the bundle branches, His bundle, and the atrioventricular node, may occur after thoracic RT.[11] Other factors associated with conduction disease in these patients include right coronary artery disease and calcification of the aortomitral curtain.[37–39] When complete heart block occurs, syncope is the most common clinical presentation in symptomatic patients and it may require pacemaker implantation. Patients after chest radiation may also be at higher risk of atrial fibrillation.

Autonomic dysfunction with a reduction in parasympathetic tone and an increase in sympathetic tone may be observed after mediastinal RT,[40] translating into higher resting heart rates and heart rate variability and reduced baroreflex sensitivity. For instance, patients who had received RT (median dose of 38 Gy at a median follow-up time of 19 years) for HL are noted to have a higher resting heart rate than HL patients without RT and a higher rate of abnormal heart rate recovery (31.9% vs. 9.3%) at one minute of recovery after Bruce protocol stress testing. Abnormal heart rate response in this study was noted to be associated with a higher risk of all-cause mortality (HR, 4.60; 95% CI, 1.62 to 13.02). Additionally, RT for nasopharyngeal carcinoma has been associated with reduced heart rate response to deep breathing or the Valsalva manuever.[41] The authors hypothesize this may be related to fibrosis of the carotid artery walls with resultant stiffening of baroreceptors. Although fibrotic changes are less likely to revert, aerobic exercise may reduce autonomic imbalance by various mechanisms, last but not least by reconditioning.[42]

PREVENTION AND SCREENING FOR RIHD

Although dose reduction efforts including radiation protection blocks, advanced planning techniques, and involved field radiation have had a significant impact on reducing the risk, RIHD remains a concern and warrants screening efforts. Even more, practices nowadays will still have to care for patients exposed to high-dose chest RT in the past.

Patients who have had RT should be seen annually as part of a survivorship plan regardless of the presence of symptoms (Table 26.2). Biomarkers and cardiac enzymes have limited use at this time, primarily owing to a lack of data as to how they should be applied.[43] Screening efforts for RIHD thus remain primarily imaging-based. The American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI), the Society for Cardiac Angiography and Intervention (SCAI), and the International Cardio-Oncology Society (IC-OS) have released screening guidelines for RIHD (Central Illustration).[44,5] The guiding principles are to screen for asymptomatic coronary artery and VHD, CP, and cardiomyopathy in patients who are at high risk for RIHD, especially those who have received at least 30 Gy of radiation (plus or minus additional risk factors). Recommendations include echocardiography and stress test starting 5 to 10 years after RT, then every 2 to 5 years, depending on risk (see Table 26.2).

The ASE/EACVI guidelines do not specify the choice of noninvasive stress tests, whereas SCAI recommends exercise echocardiogram as the preferred test.[44,5] When stress echocardiography is used, consideration should be given to a concomitant oxygen consumption study because it tests the cardiopulmonary axis, given the potential involvement of the lung fields and related changes after chest radiation. Another alternative mentioned by the SCAI guidelines is coronary CTA for screening, assessing the overall burden of CAD. This aspect is given further attention in the IC-OS guidelines, which recommend the use of CAC and CCTA for (earlier) visualization of evolving CAD in patients after RT.[5] If the screening tests identify evidence of cardiovascular disease, then additional diagnostic imaging should be pursued, including diagnostic catheterization, coronary angiography, cardiac magnetic resonance (CMR), or computed tomography, as appropriate.[44] CMR may be an important diagnostic tool for the detection of RIHD. In one study where CMR was performed in HL survivors at a median time of 24 years following RT, 70% of patients had significant abnormalities. These abnormalities included valvular dysfunction, reduction in left ventricular EF, late myocardial enhancement, and perfusion deficits[45] Contrast-enhanced MRI is excellent for the diagnosis of acute pericarditis by demonstrating pericardial enhancement.

Deformation imaging with strain is a sensitive way to detect myocardial dysfunction; it is widely used in the assessment of oncology patients,

TABLE 26.2 Screening Recommendation for Asymptomatic Patients With Cardiac Radiation Exposure (for the SCAI algorithm, please see Central Illustration)

Screening for CAD
European Society of Medical Oncology consensus statement • evaluation for CAD/ ischemia, even if asymptomatic, starting at 5 years post-treatment and then at least every 3-5 years thereafter
EACVI/ASE consensus statement • Functional noninvasive stress test • Screening recommended in high-risk patients* • Starting 5 to 10 years after radiation exposure • Reassess every 5 years • Annual cardiovascular history and examination
International Cardio-Oncology Society consensus statement • Comprehensive cardiovascular history and physical exam annually • Review available CT imaging for atherosclerotic calcifications as available • Screening for CAD with coronary artery calcium, coronary CT angiography, or functional stress testing in patients without documented atherosclerosis on prior evaluations • Starting 5 years after radiation exposure • Repeat screening at 5 year intervals, depending on the patient's overall cardiovascular risk
Screening for noncoronary atherosclerotic disease
EACVI/ASE consensus statement • carotid artery ultrasonography in patients with neurologic signs or symptoms
International Cardio-Oncology Society consensus statement *After head and/or neck radiation* • Auscultation for carotid bruits during their routine physical examination • Screening for signs and symptoms of dysautonomia on follow-up physical examinations (including orthostatic vital signs) • Review of available CT scans for carotid calcifications to aid in identification of asymptomatic atherosclerosis • Carotid ultrasound to screen for development of asymptomatic atherosclerotic plaque • Initial evaluation as early as 1 y post-radiation in higher risk patients (determined by radiation dose and CV risk) • Follow-up every 3 to 5 y can be useful to guide preventive therapy *After abdominal or pelvic radiation* • Review of available CT scans for aortic and iliofemoral calcifications to identify atherosclerosis can be useful • Evaluation for radiation nephropathy and/or renal artery stenosis in patients with worsening renal function and/or systemic hypertension can be useful
Screening for valvular disease
European Society of Medical Oncology consensus statement • evaluation for valvular disease, even if asymptomatic, starting at 5 years post-treatment and then at least every 3-5 years thereafter
EACVI/ASE consensus statement • Echocardiogram • Starting 5 years after radiation in high-risk patients* • Starting 10 years after radiation in all others • Reassess every 5 years • Annual cardiovascular history and examination
International Cardio-Oncology Society consensus statement • Comprehensive cardiovascular history and physical exam annually • Screening recommended for patients who received RT with the heart in the radiation field • Starting at 5 years post RT • Reassess every 3-5 years
Screening for cardiac dysfunction/cardiomyopathy
American Society of Clinical Oncology Clinical Practice Guideline • Echocardiogram • Screening recommended for high-dose radiotherapy (≥ 30 Gy) where the heart is in the treatment field or lower-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600mg/m^2) in combination with lower-dose RT (< 30 Gy) where the heart is in the treatment field • Starting during and/or 6 to 12 months after completion of cancer-directed therapy • Regular evaluation of cardiovascular risk factors including smoking, hypertension, diabetes, dyslipidemia, and obesity

TABLE 26.2 Screening Recommendation for Asymptomatic Patients With Cardiac Radiation Exposure (for the SCAI algorithm, please see Central Illustration)—cont'd

International Late Effects of Childhood Cancer Guideline Harmonization Group
• Screening recommended for individuals treated with ≥ 35 Gy of chest radiation or anthracycline ≥ 100mg/m2 + ≥ 15 Gy of radiation, and screening may be reasonable for moderate doses (15 Gy to 35 Gy)
• Echocardiogram, cardiac MRI, radionuclide angiography
• Starting no later than 2 years after completion of cardiotoxic therapy for high-risk survivors
• Repeat at 5 years after diagnosis
• Reassess every 5 years (can consider more frequent surveillance for high-risk individuals)
• Screening for modifiable cardiovascular risk factors
International Cardio-Oncology Society consensus statement
• Echocardiogram (or cardiac MRI) screening recommended for patients at risk of cardiomyopathy
• Starting as early as 6-12 months after radiation therapy in high-risk patients**
• In all patients in whom the heart is in the radiation field, an echocardiogram within 5 years post RT is recommended
• Reassessment every 5 years by echocardiogram and NT-proBNP levels can be useful

Table 5. Screening recommendation for asymptomatic patients with cardiac radiation exposure. *High-risk patients were defined as having had anterior or left chest irradiation as well as one of the following risk factors: dose greater than 30 Gy, dose fraction greater than 2 Gy, age less than 50 years, lack of shielding, concomitant anthracyclines, cardiovascular risk factors, or known cardiac disease.
**Patients at high-risk for radiation-associated cardiac disease defined as those with: 1) mediastinal radiotherapy ≥30 Gy with the heart in the treatment field; 2) lower dose radiotherapy (<30 Gy) with anthracycline exposure; 3) patients aged <50 years and longer time since RT; 4) high dose of radiation fractions (>2 Gy/d); 5) presence and extent of tumor in or next to the heart; 6) presence of CV risk factors; and 7) pre-existing CV disease
CT, Computed tomography; *EACVI/ASE,* European Association of Cardiovascular Imaging/American Society of Echocardiography.
van Leeuwen-Segarceanu EM, Bos W-JW, Dorresteijn LD, et al. Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. *Cancer Treat Rev.* 2011:37(5):391–403.

particularly those undergoing treatment with anthracyclines.[46] Evidence indicates that strain is abnormal in patients with cancer who have had radiation exposure. One study measured strain values in those patients with breast cancer receiving either right- or left-sided chest radiotherapy prior to, immediately after, and 2 months following therapy. Regional strain changes were noted immediately and at the 2 month follow up in patients with left-sided breast cancer; however, this was not seen in patients with right-sided breast cancer.[47]

The right ventricle (RV) is also affected as a result of RT in patients with cancer; however, few studies have evaluated the extent and mechanism of these changes. It is likely that the same mechanisms of myocardial fibrosis, endothelial dysfunction, and oxidative stress known to contribute to left ventricular dysfunction, valve disease, pericardial diseases, and CAD also affect RV function and structure. RV wall thickness appears reduced in patients who have received chemotherapy alone or a combination of chemotherapy and low- or high-dose RT. The effect of RT on RV systolic function remains unclear, with some studies showing a decrease whereas others show no significant change.[48]

PREVENTIVE DRUG THERAPIES

Evidence regarding the prevention of cardiotoxicity owing to radiation exposure is limited and no agents are approved for the prevention or treatment of RIHD. The role of preventive medications, including (high-dose) statins, antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB), is unclear. Indeed, renin-angiotensin aldosterone system inhibitors (both ACEi and ARBs) and HMG-CoA reductase inhibitors (statins) have been shown to prevent both cardiac fibrosis and damage to other organs after radiation in experimental studies though not universally.[49,50] Importantly, there is paucity of data in humans, but a study evaluating the effects of statin therapy on arterial endothelial function in acute lymphoblastic leukemia or non-Hodgkin lymphoma survivors is on-going. Certainly, cardiovascular risk factors amplify the burden of radiation in terms of risk of ischemic heart disease and acute coronary events (Fig. 26.3) as well as HF and even VHD (see Chapter 24, Fig. 24.1). Pristine control of controllable risk factors is therefore paramount, including the use of ACEi/ARBs and statins, when indicated, and in keeping with their positive effect on vascular health and atherosclerosis.

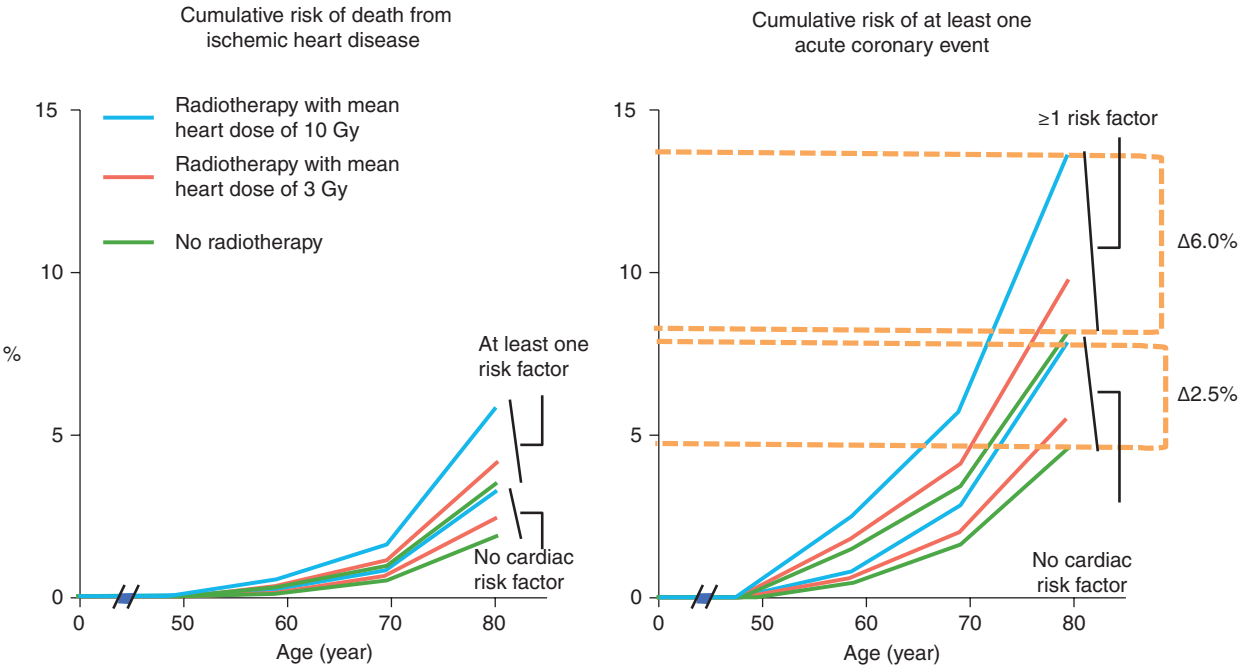

FIG. 26.3 Cumulative risk of death from ischemic heart disease (*left*) and of at least one acute coronary event (*right*) in patients after chest radiation for breast cancer. (From Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med.* 2013;368:977).

FUTURE AVENUES

Although there is a continued focus in the literature on the cardiovascular manifestations of RT, existing studies do not provide much insight into preventative strategies that reduce the development of RIHD. Whereas there are mixed data on the effects of traditional medications for the management of conventional cardiovascular risk factors and diseases, there is a paucity of randomized, controlled clinical trial data in patients who have had radiation. In addition, the precise timing of these therapies in patients having had chest RT, as well as accompanying surveillance strategies for cardiovascular toxicity, remain unknown. Multidisciplinary collaborations between cardiology and oncology are essential to establish registries and clinical trials to assess long-term outcomes and the impact of surveillance and proposed pharmacologic intervention and strategies. Whereas the landscape of cancer treatment continues to evolve, including RT techniques, many questions and challenges remain for the field of cardio-oncology to investigate in order to provide evidence-based care for the detection and treatment of radiation treatment-induced manifestations of cardiovascular disease.

REFERENCES

1. Nilsson G, Holmberg L, Garmo H, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol*. 2012;30:380–386.
2. Cheng YJ, Nie XY, Ji CC, et al. Long-trm cardiovascular risk after radiotherapy in women with breast cancer. *J Am Heart Assoc*. 2017;6(5):e005633.
3. Santoro F, Ferraretti A, Centola A, et al. Early clinical presentation of diffuse, severe, multi-district atherosclerosis after radiation therapy for Hodgkin lymphoma. *Int J Cardiol*. 2013;165:373–374. doi:10.1016/j.ijcard.2012.08.027.
4. Marks LB, Yu X, Prosnitz RG, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys*. 2005;63:214–223.
5. Mitchell JD, Cehic DA, Morgia M, Bergrom C, Toohey J, Guerrero PA, Ferencik M, Kikuchi R, Carver JR, Zaha VG, Alvarez-Cardona JA, Szmit S, Daniele AJ, Lopez-Mattei J, Zhang L, Herrmann J, Nohria A, Lenihan DJ, Dent SF. Cardiovascular Manifestations From Therapeutic Radiation: A Multidisciplinary Expert Consensus Statement From the International Cardio-Oncology Society. JACC CardioOncol. 2021 Sep 21;3(3):360–380. doi: 10.1016/j.jaccao.2021.06.003. PMID: 34604797; PMCID: PMC8463721.
6. Andersen R, Wethal T, Gunther A, et al. Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. *Am J Cardiol*. 2010; 105:149–152.
7. Kupeli S, Hazirolan T, Varan A, et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. *J Clin Oncol*. 2010;28:1025–1030.
8. Handler CE, Livesey S, Lawton PA. Coronary ostial stenosis after radiotherapy: angioplasty or coronary artery surgery? *Br Heart J*. 1989;61:208–211.
9. Gansera B, Schmidtler F, Angelis I, et al. Quality of internal thoracic artery grafts after mediastinal irradiation. *Ann Thorac Surg*. 2007;84:1479–1484.

10. Khan MH, Ettinger SM. Post mediastinal radiation coronary artery disease and its effects on arterial conduits. *Catheter Cardiovasc Interv*. 2001;52:242–248.
11. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol*. 2003;42:743–749.
12. Cella L, Liuzzi R, Conson M, et al. Dosimetric predictors of asymptomatic heart valvular dysfunction following mediastinal irradiation for Hodgkin's lymphoma. *Radiother Oncol*. 2011;101:316–321.
13. Janelle GM, Mnookin SC, Thomas JJ, et al. Surgical approach for a patient with aortic stenosis and a frozen mediastinum. *J Cardiothorac Vasc Anesth*. 2003;17:770–772.
14. Handa N, McGregor CG, Danielson GK, et al. Valvular heart operation in patients with previous mediastinal radiation therapy. *Ann Thorac Surg*. 2001;71:1880–1884.
15. Crestanello JA, McGregor CG, Danielson GK, et al. Mitral and tricuspid valve repair in patients with previous mediastinal radiation therapy. *Ann Thorac Surg*. 2004;78:826–831.
16. Zhang D, Guo W, Al-Hijji MA, et al. Outcomes of patients with severe symptomatic aortic valve stenosis after chest radiation: transcatheter versus surgical aortic valve replacement. *J Am Heart Assoc*. 2019;8:e012110.
17. Scarfo I, Denti P, Citro R, Buzzatti N, Alfieri O, La Canna G. MitraClip for radiotherapy-related mitral valve regurgitation. *Hellenic J Cardiol*. 2019;60:232–238.
18. Nolan MT, Russell DJ, Marwick TH. Long-term risk of heart failure and myocardial dysfunction after thoracic radiotherapy: a systematic review. *Can J Cardiol*. 2016;32(7):908–920.
19. Saiki H, Petersen IA, Scott CG, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. *Circulation*. 2017;135(15):1388–1396.
20. Billingham ME, Bristow MR, Glatstein E, et al. Adriamycin cardiotoxicity: endomyocardial biopsy evidence of enhancement by irradiation. *Am J Surg Pathol*. 1977;1:17–23.
21. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. 2007;109:1878–1886.
22. Shapiro CL, Hardenbergh PH, Gelman R, et al. Cardiac effects of adjuvant doxorubicin and radiation therapy in breast patients with cancer. *J Clin Oncol*. 1998;16:3493–3501.
23. Umezawa R, Ota H, Takanami K, et al. MRI findings of radiation-induced myocardial damage in patients with oesophageal cancer. *Clin Radiol*. 2014;69:1273–1279.
24. Tsai HR, Gjesdal O, Wethal T, et al. Left ventricular function assessed by two-dimensional speckle tracking echocardiography in long-term survivors of Hodgkin's lymphoma treated by mediastinal radiotherapy with or without anthracycline therapy. *Am J Cardiol*. 2011;107:472–477.
25. Heidenreich PA, Hancock SL, Vagelos RH, et al. Diastolic dysfunction after mediastinal irradiation. *Am Heart J*. 2005;150:977–982.
26. Uriel N, Vainrib A, Jorde UP, et al. Mediastinal radiation and adverse outcomes after heart transplantation. *J Heart Lung Transplant*. 2010;29:378–381.
27. Cohn KE, Stewart JR, Fajardo LF, et al. Heart disease following radiation. *Medicine*. 1967;46:281–298.
28. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. *Circulation*. 1999;100:1380–1386.
29. Greenwood RD, Rosenthal A, Cassady R, et al. Constrictive pericarditis in childhood due to mediastinal irradiation. *Circulation*. 1974;50:1033–1039.
30. Applefeld MM, Cole JF, Pollock SH, et al. The late appearance of chronic pericardial disease in patients treated by radiotherapy for Hodgkin's disease. *Ann Intern Med*. 1981;94:338–341.
31. George TJ, Arnaoutakis GJ, Beaty CA, et al. Contemporary etiologies, risk factors, and outcomes after pericardiectomy. *Ann Thorac Surg*. 2012;94:445–451.
32. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. *J Am Coll Cardiol*. 2004;43(8):1448.
33. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA*. 2003;290:2831–2837.
34. Lam WW, Leung S, So NM, et al. Incidence of carotid stenosis in nasopharyngeal carcinoma patients after radiotherapy. *Cancer*. 2001;92:2357–2363.
35. Dorresteijn LD, Kappelle AC, Boogrd W, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol*. 2001;20:282–288.
36. Vallerio P, Sarno L, Stucchi M, et al. Long-term effects of radiotherapy on arterial stiffness in breast cancer women. *Am J Cardiol*. 2016;118(5):771–776.
37. de Waard DE, Verhorst PM, Visser CA. Exercise-induced syncope as late consequence of radiotherapy. *Int J Cardiol*. 1996;57:289–291.
38. Orzan F, Brusca A, Gaita F, et al. Associated cardiac lesions in patients with radiation-induced complete heart block. *Int J Cardiol*. 1993;39:151–156.
39. Santoro F, Ieva R, Lupo P, et al. Late calcification of the mitral-aortic junction causing transient complete atrio-ventricular block after mediastinal radiation of Hodgkin lymphoma: multimodal visualization. *Int J Cardiol*. 2012;155:e49–e50.
40. Groarke JD, Tanguturi VK, Hainer J, et al. Abnormal exercise response in long-term survivors of Hodgkin lymphoma treated with thoracic irradiation. *J Am Coll Cardiol*. 2015;65:573–583.
41. Huang CC, Huang TL, Hsu HC, et al. Long-term effects of neck irradiation on cardiovascular autonomic function: a study in nasopharyngeal carcinoma patients after radiotherapy. *Muscle Nerve*. 2013;47:344–350.
42. Scott JM, Jones LW, Hornsby WE, et al. Cancer therapy-induced autonomic dysfunction in early breast cancer: implications for aerobic exercise training. *Int J Cardiol*. 2014;171(2):e50–e51.
43. Nellessen U, Zingel M, Hecker H, et al. Effects of radiation therapy on myocardial cell integrity and pump function: which role for cardiac biomarkers? *Chemotherapy*. 2010;56:147–152.
44. Iliescu CA, Grines CL, Herrmann J, et al. SCAI Expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologıa Intervencionista). *Catheter Cardiovasc Interv*. 2016;87:E202–E223.
45. Machann W, Beer M, Breunig M, et al. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 2011;79(4):1117–1123.
46. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27(9):911–939.
47. Erven K, Jurcut R, Weltens C, et al. Acute radiation effects on cardiac function detected by strain rate imaging in breast patients with cancer. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1444–1451.
48. Tadic M, Cuspidi C, Hering D, et al. Radiotherapy-induced right ventricular remodeling: The missing piece of the puzzle. *Arch Cardiovasc Dis*. 2017;110(2):116–123.
49. van der Veen SJ, Ghobadi G, de Boer RA, et al. ACE inhibition attenuates radiation-induced cardiopulmonary damage. *Radiother Oncol*. 2015;114:96–103.
50. Zhang K, He X, Zhou Y, et al. Atorvastatin ameliorates radiation-induced cardiac fibrosis in rats. *Radiat Res*. 2015;184(6):611–620.