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Radiation Toxicity to the Cardiovascular System

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Abstract Radiation therapy is an important component of cancer treatment, and today, it is applied to approximately 50 % of malignancies, including valvular, myocardial, pericardial, coronary or peripheral vascular disease, and arrhythmias. An increased clinical suspicion and knowledge of those mechanisms is important to initiate appropriate screening for the optimal diagnosis and treatment. As the number of cancer survivors has been steadily increasing over the last decades, cardio-oncology, an evolving subspecialty of cardiology, will soon play a pivotal role in raising awareness of the increased cardiovascular risk and formulate strategies to optimally manage patients in this unique population.

Keywords Radiation-induced cardiovascular toxicity · Valvular pericardial heart disease

Introduction

Radiation therapy is an important component of cancer treatment. The indications for radiation therapy have expanded from breast cancer and lymphoma to a variety of malignancies and are now applied to approximately 50 % of malignancies. While important benefits toward survival have been observed in cancer patients, an increased awareness of potential cardiotoxicities has emerged and is an area of clinical interest within the growing multidisciplinary field of cardio-oncology. The development of the new subspecialty of cardio-oncology has been recognized by the American College of Cardiology (ACC) as one of the "top cardiology stories for 2014." One of the scopes of the cardio-oncology specialty is the prevention, screening, diagnosis, and management of radiation-induced heart disease.

Mechanisms and Types of Radiation Treatment

The first radiation-induced cardiovascular effects were observed in atomic bomb survivors [1]. During radiation therapy, cancer and non-cancerous cells are affected, especially the ones with rapid proliferation. Radiation-induced DNA damage results in cell cycle arrest and apoptosis [2]. Moreover,

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radiolysis of water molecules leads to oxidative stress which promotes endothelial dysfunction and thrombotic and inflammatory changes [3].

Most data for the cardiovascular effects of radiation comes from studies on breast cancer, Hodgkin's lymphoma, and other thoracic malignancies such as esophageal cancer and lung cancer. Older radiation therapy techniques involved exposure to a large surface of the chest wall with higher doses of radiation.

Newer techniques have been able to reduce both the irradiated myocardial volume and the total delivered radiation dose which have been related to cardiotoxicity. Modern radiation oncology utilizes novel techniques, like intensity-modulated radiotherapy therapy (IMRT) combined with functional imaging (i.e., CT, MRI, and PET), provide both precise radiation target delivery and reduced radiation doses [4]. During the course of cancer therapy, the dose and location of radiation may be altered based on the progression of the malignancy and the effectiveness of previous radiation or chemotherapy effects.

While incidental radiation has been minimized, there does not seem to be a minimal dose of radiation which can assure absence of cardiovascular effects, and prospective studies in the modern era have yet to determine their long-term impact on cardiovascular health. Case studies have found that approximately 2 Gy averaged across the heart results in an increased risk of developing cardiovascular disease [5].

Manifestations of Radiation-Induced Cardiac Toxicity

Valvular diseases, along with angina pectoris and myocardial infarction, are the most common cardiovascular abnormalities found in survivors of Hodgkin's lymphoma (HL). Although studies have varied significantly due to differences in controls and inherent bias, anywhere from 2 to 37 % of HL patients who have previously received mediastinal irradiation have developed valve disease of varying severities [6]. Typically, valvular diseases develop over time, with various studies documenting moderate to severe valvular regurgitation and/or stenosis after 20 years of treatment, with signs of mild dysfunction as early as 10 years post-radiotherapy [6–8]. Left-sided valves are more commonly affected, with the pulmonic valve rarely affected (Fig. 1). A study of 1852 5-year survivors of HL treated between 1965 and 1995 demonstrated that for doses to the affected valve(s) of less than or equal to 30, 31–35, 36–40, and more than 40 Gy, valvular heart disease (VHD) rates increased by factors of 1.4, 3.1, 5.4, and 11.8, respectively, (P trend <.001), and the approximate 30-year cumulative risks were 3.0, 6.4, 9.3, and 12.4 % [9]. The mitral and aortic valves

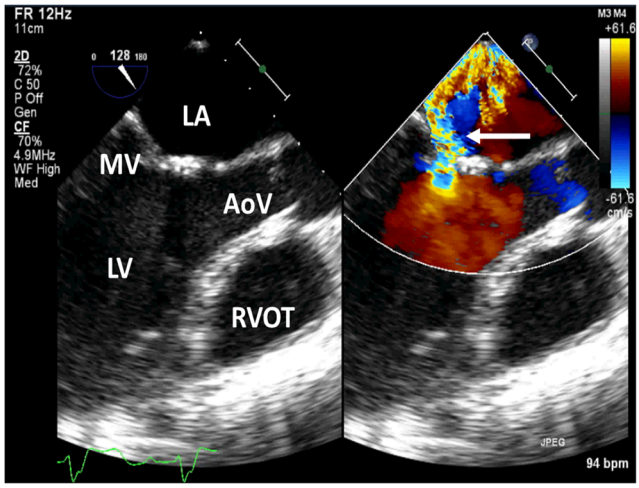

Fig. 1 2-D transesophageal echocardiography, three-chamber midesophageal view of a 36-year-old female with a history of Hodgkin's lymphoma at the age of 18 with a history of mediastinal radiation therapy and chemotherapy presenting with dyspnea. Findings are consistent with radiation-induced valvulopathy with combined mitral valve regurgitation and stenosis. The mitral valve appears thickened with restrictive leaflet motion. On the *right panel*, color Doppler across the mitral valve demonstrates severe mitral regurgitation is noted (*arrow*), along with mitral stenosis with a mitral valve area of 1.4 cm^2. *LA* left atrium, *LV* left ventricle, *MV* mitral valve, *AoV* aortic valve, *RVOT* right ventricular outflow tract

were the most commonly affected. Twenty-three years was the average time of onset for the development of valvular disease. Postmortem studies have shown diffuse or focal leaflet fibrosis and valvular thickening, along with calcification [10, 11]. While mechanistic causes of radiation-induced valvular disease are not well understood, radiation is known to active fibrogenic growth factors (i.e., tissue growth factor β1, myofibroblasts) which can stimulate collagen synthesis in other tissues [12]. A study of isolated human aortic valve interstitial cells exposed to 10 Gy of radiation resulted in an osteogenic phenotypic response, showing significant increases of osteogenic factors such as bone morphogenetic protein, osteopontin, alkaline phosphatase, and transcription factor Runx2, yielding some insight into the accelerated calcification process noted in radiation survivors [13].

A major manifestation of cardiac disease in cancer patients undergoing radiation therapy is accelerated coronary artery disease (CAD) [14]. This incidence is further increased by the traditional cardiovascular risk factors, including smoking, hyperlipidemia, and hypertension. Higher rates of CAD have been found in patients undergoing radiation therapy for breast cancer, Hodgkin's lymphoma, and other cancers requiring mediastinal irradiation. An increased incidence of myocardial infarction (MI) is another manifestation of radiation-induced cardiovascular complications. Studies have demonstrated a 2.2–7.6-fold greater risk of MI in Hodgkin's lymphoma patients [15, 16]. The rate of death from MI also was significantly

higher compared to the general population. The prevalence and severity of MI in Hodgkin's lymphoma patients were higher when treated with anthracycline-containing chemotherapy. The use of anthracyclines in treatment was a strong indicator of increased MI. Radiation dose can also be lowered if increased levels of anthracyclines are needed in order to best counteract the hazardous cardiovascular effects precipitated by anthracycline-based therapy [17]. Myocardial infarction related to radiation therapy is also influenced by the presence of traditional risk factors for CAD. Smoking cessation, lowering of lipid levels, and hypertension can potentially lower the risk of radiation therapy (RT)-induced heart disease, although a prospective trial looking at such interventions is lacking. A comprehensive treatment plan with a physician to identify these risk factors in patients undergoing radiation therapy is crucial toward reducing possible cardiovascular toxicity related to radiation therapy. The coronary location of CAD depends on the irradiated region. Left breast radiation is associated with disease development in the mid-distal left anterior descending artery (LAD) and associated diagonal branches [18], whereas mediastinal radiation, which is used more frequent in Hodgkin's lymphoma, can be associated with ostial coronary lesions [19].

Radiation of the ventricular myocardium can result in systolic and diastolic dysfunction [17, 20]. The mechanism of radiation-induced myocardial dysfunction is unclear. A combination of myocardial fibrosis, microvascular and endothelial dysfunction, and coronary atherosclerosis are possible mechanisms.

Throughout the early history of radiation therapy, pericarditis was historically a common cardiovascular complication in patients [21, 22]. Acute pericarditis following radiation therapy, pericardial effusion, delayed pericardial thickening, constrictive pericarditis, and pancarditis has been described in cancer patients who have received radiation therapy. Patients with Hodgkin's lymphoma were especially susceptible to pericarditis after radiation therapy. However, more recent techniques limiting the amount of incidental radiation to the cardiac field and minimizing the dose of radiation have greatly reduced the occurrence.

Finally, radiation therapy can potentially affect the cardiac conduction system, leading to a whole spectrum of arrhythmias [23, 24]. Fibrosis of the conductive system or the myocardium and coronary artery disease are believed to be the prevalent mechanisms. Various degrees of heart block, right bundle branch block (RBBB), non-specific ST-T changes, low voltage, corrected QT segment (QTc) prolongation, supraventricular premature complexes, supraventricular tachycardia (SVT), premature ventricular complexes (PVCs), couplets, and ventricular tachycardia (VT) have been described in patients who received radiation therapy (Table 1).

Table 1 Manifestations of radiation-induced cardiovascular disease

Type of cardiovascular disease	Common manifestations
Valvular heart disease	Valvular dysfunction (aortic and mitral valve most commonly)
Coronary artery disease	Ostial lesions, mid and distal LAD
Myocardial disease	Systolic and diastolic dysfunction, myocardial fibrosis
Pericardial disease	Acute pericarditis, pericardial effusion, delayed pericardial thickening, constrictive pericarditis, and pancarditis
Conduction abnormalities	AV block, RBBB, non-specific ST-T changes, low voltage, QTc prolongation, supraventricular premature complexes, SVT, PVCs, ventricular couplets, and VT

Radiation-Induced Heart Disease: Outcomes

Hodgkin's Disease

Hodgkin's lymphoma serves as a model for radiation-induced heart disease (RIHD) as higher radiation doses to the mediastinum are used compared to other cancers. Cardiovascular mortality is the third most common death in patients who are followed after mediastinal RT, after Hodgkin's disease death and death due to other cancers [25, 26]. Childhood Hodgkin's disease survivors develop cardiovascular disease more often than with any other childhood cancer. An analysis of the Childhood Cancer Survivor Study (CCSS), a multi-institutional retrospectively which obtained cohort of adults who survived at least 5 years after treatment of childhood cancer between 1970 and 1986, revealed that the risk of developing moderate to severe chronic illnesses, including cardiovascular disease and stroke, where overall significantly elevated in any patients who received chest radiation (relative risk 10.6, 95 % confidence interval (CI) 8.8–12.7) and with adjunct anthracycline exposure (relative risk (RR) 13.0, 95 % CI 10.4–16.3) when compared to sibling controls [27].

In patients treated between 1960 and 1995, cardiovascular disease accounted for 9–16 % of mortality [25, 27]. Following radiation therapy for Hodgkin's disease between 1960 and 1998, 11 % of asymptomatic patients who are screened with echocardiography or stress testing are found to have cardiovascular disease, while 96 % of asymptomatic patients had cardiovascular disease when also screening with multigated acquisition scans and cardiac catheterization [28–30]. One study found that 10 % had clinically apparent coronary artery disease at a median of 9 years post-RT, while 6.2 % developed clinically significant valvular dysfunction by 22 years post-RT [28]. Constrictive pericarditis (both asymptomatic and overt) was found in 23 % of patients in another longitudinal study [29]. Compared to the general population, the risk of needing

percutaneous coronary intervention, coronary artery bypass grafting, or valve replacement is also elevated.

One of the most comprehensive studies of the historical course of cardiovascular disease in Hodgkin's lymphoma survivors followed 2524 patients in Dutch hospitals who received treatment between 1965 and 1995, with a median follow-up of 20 years [31]. Data was obtained through retrospective analysis of hospital records, whereas prior studies relied on questionnaires within a cohort, such as the CCSS. Mediastinal radiotherapy was associated with a hazard ratio of 3.6 (95 % CI 2.8–4.6) for cardiovascular disease, with the highest risk being for valvular heart disease (hazard ratio (HR) 6.6, 95 % CI 4.0–10.8), followed by coronary artery disease (HR 2.7, 95 % CI 2.0–3.7), and CHF (HR 2.7, 95 % CI 1.6–4.8). Forty years after treatment with RT alone, the cumulative incidence of any cardiovascular disease was 54.6 %.

Radiation protection blocks covering the left ventricle and reduced fraction size have resulted in decreased cardiac radiation dose when compared to the historical mantle field [25, 32, 33]. Despite these changes to radiation treatment, van Nimwegen et al. found that incidence of cardiovascular disease in patients who were irradiated between 1965 and 1974 did not differ significantly from those who received RT between 1985 and 1995. Involved-node radiation therapy (INRT) for radiation therapy for Hodgkin's disease has replaced mantle field radiation in recent years, resulting in further reductions in radiation dose to the heart [34]. Development of RIHD is projected to decrease as a result of INRT; however, long-term follow-up of these patients is needed to further quantify the risk.

In regards to cerebrovascular outcomes, in patients who received mantle radiation for Hodgkin's disease as a child (median dose 40 Gy) in the CCSS, the relative risk of stroke was 4.32 (95 % CI 2.01–9.29) compared to siblings [35]. Another study found that patients who had received mantle radiation as adults had an incidence ratio for stroke and TIA of 2.2 (95 % CI 1.7–2.8) and 3.1 (95 % CI 2.2–4.2), respectively, when compared to the incidence of the general population [36]. A retrospective study of 415 patients with a history of mantle field radiation for Hodgkin's disease found a 7 % incidence of non-coronary atherosclerotic disease at 20 years post-treatment [28]. This included transient ischemic attack and stroke as well as subclavian or carotid artery stenosis. The median age of radiation therapy was 51 years in patients who suffered a TIA or stroke, and the median latency post-treatment was 5.6 years. In patients who had carotid or subclavian artery stenosis without stroke, the latency post-treatment to diagnosis was much longer (median 21 years) while the median age was much younger (20 years). Patients who developed carotid or subclavian atherosclerosis received a median low cervical-radiation dose of 38 and 44 Gy, respectively.

A literature review done by the Children's Oncology Group (COG) demonstrated that in adult survivors of childhood Hodgkin's disease treated with mantle radiotherapy (which involves irradiation of major lymph nodes above the diaphragm from the inferior portion of the mandible to the insertion of the diaphragm), compared to sibling controls, there was a 5.6-fold increased risk for stroke (95 % CI 2.6–12.3) after adjusting for age, race, and gender. At a mean age of 33.8 ± 7.1 years, the rate of late-occurring stroke was 109.8 per 100,000 person-years (95 % CI 70.8–161.0). The authors surmised that instead of direct effects of radiation of the cerebrovascular system, thromboembolic disease from either cardiac, aortic, or valvular disease, and premature atherosclerosis may have been mechanisms leading to this finding [37].

Breast Cancer

Breast cancer is commonly treated with adjunctive radiation therapy [38]. Among the patients with early breast cancer in the Surveillance Epidemiology, and End Results (SEER) registry, 37 % received radiation treatment. Multiple studies have revealed an increased rate of cardiovascular mortality among patients who receive RT for breast cancer [38, 39]. Irradiation to the left breast in patients diagnosed with breast cancer between 1973 and 1982 was associated with a cardiovascular mortality laterality ratio (compared to right breast irradiation) of 1.42 (95 % CI 1.11–1.82) [38]. Major coronary events increased by 7.4 % per 1 Gy of mean radiation dose received by the heart in patients treated between 1958 and 2001 [40]. The mean cardiac radiation dose was 6.6 Gy for left breast irradiation and 2.9 Gy for right breast irradiation. Ischemic heart disease and acute myocardial infarction are the primary causes of excess cardiovascular mortality in patients who receive breast irradiation, due to the coronary arteries' (especially the left anterior descending artery) presence within the radiation fields.

Contemporary radiation therapy regimens for breast cancer have improved cardiovascular morbidity. New developments in breast cancer radiation treatment include tangential radiation fields (as opposed to anterior fields) [41] and computed tomography radiation planning. Since these developments, the laterality of coronary artery disease after radiation treatment for breast cancer has steadily declined. In patients in the SEER registry who were treated from 1983 to 1992, the hazard ratio for ischemic heart disease for left breast compared to right breast irradiation was 0.79 (95 % CI 0.52–1.18) [38, 42]. Early randomized trials for RT in breast cancer patients also found that the RT arms had higher rates of coronary artery disease than the controls [41]. However, the more recent Danish Breast Cancer Cooperative Group trials included the use of radiation treatment planning and radiation protection blocks for the heart [43, 44]. In these trials, there was no increased risk of ischemic heart disease in those randomized

to RT. Although irradiation of the internal mammary lymph nodes in early stage breast cancer increases the radiation dose to the heart, recent trials have demonstrated benefits in breast cancer recurrence and breast cancer mortality [45, 46]. No differences in cardiovascular disease were found after 10 years of follow-up; however, if regional lymph node irradiation gains in prominence, these data may need to be re-examined after long-term follow-up.

Head and Neck Cancers

Peripheral arterial disease (PAD) may develop following radiation therapy for head and neck tumors, including carotid and subclavian artery disease [47]. Radiation-induced carotid artery disease is commonly seen after RT for nasopharyngeal cancer, pleomorphic adenoma, and laryngeal cancer, as well as Hodgkin's disease. Carotid artery plaques in patients who have received head and neck RT have more tendency to ulceration and vulnerable plaques than in conventional carotid artery atherosclerosis [48]. Radiotherapy for head and neck tumors (dose range 50–66 Gy), regardless of the tumor subtype, is associated with an increased risk of ischemic stroke (RR 5.6, 95 % CI 3.1–9.4) [47]. The risk for stroke after 15 years post-treatment was 12 % (95 % CI 6.5–21.4 %). The increased risk of stroke is likely related to the relatively high doses of radiation used for head and neck cancer, which may be as high as 70–80 Gy [49, 50]. However, another study with a lower dose range (40–50 Gy) used in Dorrestejin et al.'s study did not find an increased risk in stroke [51, 52]. In older patients (>65 years) diagnosed with head and neck tumors between 1992 and 2002 that were included in the SEER registry, the 10-year incidence of stroke, stroke death, and carotid revascularization was 34 % in patients treated with RT alone compared to 26 % in patients treated with surgery alone ($p < 0.001$) [53]. Overall, the studies on head and neck tumors show conflicting results, likely attributing to the heterogeneity of cancers study, including factors of varying degrees of surgical intervention along with different radiotherapy protocols, selection bias in regards to patients who survived long term with their malignancy, as well as an older population with pre-existing cardiovascular risk factors that are at baseline already at elevated risk for cerebrovascular disease, with similar outcomes in stroke in both arms. More prospective trials are needed in more homogenous head and neck tumor patient populations and consistent treatment modalities to elucidate the impact of radiotherapy on these patients.

Prevention, Evaluation, and Management of Radiation-Induced Heart Disease

Patients receiving chest radiation have an increased risk to develop CAD and myocardial dysfunction. Aspirin and statin therapy should be encouraged, especially in high-risk patients based on the traditional risk factors for CAD. The preventive role of antiplatelet therapy, statins, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blockers (ARB) I developing or reducing the progression of RIHD is unclear [54, 55].

Cancer patients who received radiation should be screened for cardiac and peripheral vascular disease based on symptomatology, the region and dose of radiation therapy, and the presence of pre-existing risk factors [56]. It is important to note the limitations of stress testing in patients with radiation-induced coronary artery disease (RICAD); other methods of assessment, such as coronary artery calcium (CAC) scoring, may provide evidence of premature atherosclerotic disease and alter primary prevention treatment with earlier initiation of aspirin and statin therapy (Figs. 2 and 3). Coronary CTA may be considered for equivocal/positive functional stress test findings or for patients with suspected cardiac symptoms.

Echocardiography, CT, and MRI may identify most of the manifestations of radiation-induced heart disease and should be selected based on symptoms and clinical examination. The role of cardiac catheterization has been largely replaced by non-invasive testing; however, it should be reserved for cases

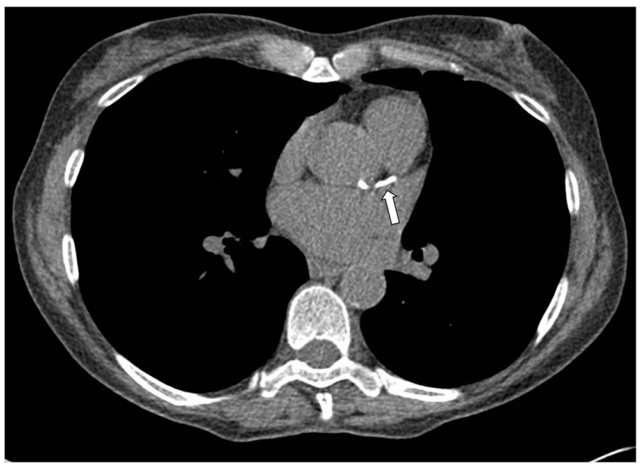

Fig. 2 Coronary artery calcium (CAC) imaging in an asymptomatic 73-year-old Caucasian female with a history of ductal carcinoma in situ of the left breast, who received a total of 60.4 Gy radiation to the left breast with no adjunct chemotherapy at the age of 64. The total CAC score was determined to be 320.2 with the CAC score of each coronary vessel as follows: left main coronary artery = 171.1, left anterior descending artery = 126.1 (*arrow*), left circumflex = 0, and right coronary artery = 22.9. Patient's calcium burden places her in the 83rd percentile of coronary artery calcium burden for age, race, and gender by the Multiethnic Study of Atherosclerosis (MESA) (http://www.mesa-nhlbi.org/Calcium/input.aspx). Her estimated MESA 10-year coronary heart disease (CHD) event rate is estimated to be 5.2 % if the CAC score is put into account and 2.6 % by conventional risk factor assessment (http://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx), showing the influence of the CAC score to increase her absolute risk of CHD events at 10 years by 100 %

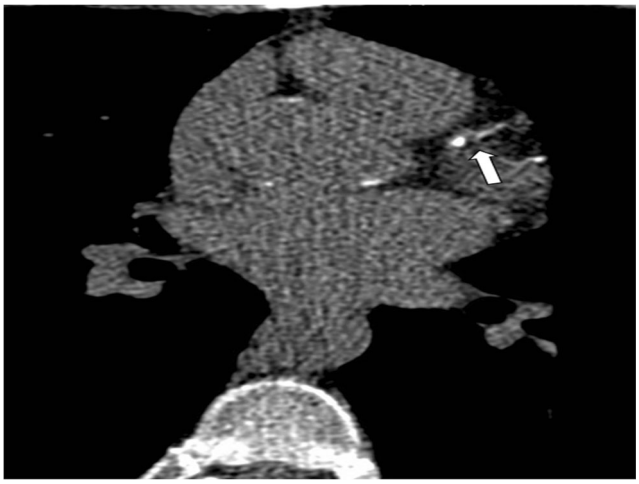

Fig. 3 CAC imaging in an asymptomatic 47-year-old Caucasian male with a history of Hodgkin's lymphoma at the age of 24 who received 40 Gy of mantle radiation with no adjunct chemotherapy. The total CAC score was determined to be 306.6, with the CAC score of each coronary vessel as follows: left main coronary artery = 114, left anterior descending artery = 132 (*arrow*), left circumflex = 8.4, and right coronary artery = 52. Patient's calcium burden puts him at the 98th percentile for his age, race, and gender as per MESA (http://www.mesa-nhlbi.org/calcium/input.aspx). His 10-year atherosclerotic vascular disease risk (ASCVD) was calculated at 2.1 % (http://tools.acc.org/ASCVD-Risk-Estimator/) which would put him traditionally at low risk and does not put into account his CAC score. However, his estimated MESA 10-year CHD event rate is estimated to be 7.2 % if the CAC score is put into account and 2.6 % by conventional risk factor assessment (http://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx), showing the influence of the CAC score to increase his absolute risk of CHD events at 10 years by 176 %

of unclear etiology of ventricular dysfunction or pulmonary hypertension, to accurately assess systolic and diastolic function, constrictive or restrictive physiology, or when endomyocardial biopsy is needed to confirm the diagnosis of anthracycline toxicity or unexplained heart failure [17, 57, 58].

Conclusion

Radiation-induced cardiovascular disease may present with various manifestations including valvular, myocardial, pericardial, coronary or peripheral vascular disease, and arrhythmias. An increased clinical suspicion and knowledge of those mechanisms is important to initiate appropriate screening for the optimal diagnosis and treatment. As the number of cancer survivors has been steadily increasing over the last decades, cardio-oncology, an evolving subspecialty of cardiology, will soon play a pivotal role in the optimal management of those patients. Larger randomized trials on patients receiving radiation therapy is needed to better understand the mechanisms of radiation-induced cardiac toxicity and define the role of its pharmacologic prevention.

Compliance with Ethical Standards

Conflict of Interest Konstantinos Marmagkiolis, William Finch, Despina Tsitlakidou, Tyler Josephs, Cezar Iliescu, John F. Best, and Eric H. Yang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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