Modern Radiotherapy and Risk of Cardiotoxicity

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Abstract

Despite the advancements of modern radiotherapy, radiation-induced heart disease remains a common cause of morbidity and mortality amongst cancer survivors. This review outlines the basic mechanism, clinical presentation, risk stratification, early detection, possible mitigation, and treatment of this condition.

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mias have all been independently linked to chest radiation [2–5]. Advancements in cancer therapy have led to improved survival, which in turn has led to increased recognition and prevalence of RIHD [6, 7]. Despite improved RT techniques and modalities that decrease the total administered radiation dose, RIHD remains a common cause of morbidity and mortality among cancer survivors [8–10]. Therefore, prevention, early identification, and prompt treatment are essential in the management of RIHD. In this review article, we focus on risk factors, basic pathophysiological mechanisms, clinical manifestations, methods for early detection, possible mitigation, prevention and treatment of RIHD.

Introduction

Radiation therapy (RT) is currently administered to about half of the patients with cancer either as a neoadjuvant or adjuvant treatment [1]. Radiation-induced heart disease (RIHD) is a unifying term used to describe all cardiac complications related to RT. Pericardial disease, ischemic heart disease, nonischemic cardiomyopathy, valvular disease, conduction abnormalities, and arrhyth-

Risk Factors

Risk factors contributing to the development of RIHD can be grouped into radiation specific and patient specific (Table 1).

Radiation-Specific Risk Factors

Radiation-specific risk factors include total dose of radiation, mean cardiac dose, volume of the heart irradi-

Table 1. Risks factors associated with the development of RIHD

Radiation specific	Patient specific
Total dose of radiation Mean cardiac dose	Treatment at a young age Traditional cardiovascular risk factors (hypertension, diabetes, obesity, smoking, and hyperlipidemia)
Frequency of radiation treatments Proximity of the tumor to the heart Volume of heart muscle exposed Cardiac avoidance technique	Prior history of cardiovascular disease Genetic susceptibility Concurrent cardiotoxic chemotherapy
RIHD, radiation-induced heart disease.	

ated, proximity of the primary radiated tumor to the heart, fractions of radiation treatments, and lack of cardiac avoidance techniques [4, 11]. The radiobiologic equivalent dose and the linear energy transfer describe the ionization potential of the radiation and therefore the potential for injury to normal tissue [12]. Both higher radiobiologic equivalent dose (which is determined by the dose and fractions delivered) and linear energy transfer (based on whether it is photons or particles being used) will determine the extent of damage [12]. In general, thoracic RT that exceeds 30 Gy is considered a high dose that leads to high mean cardiac dose and places patients at increased risk for RIHD [4, 13]. In a retrospective study of 2,232 patients with Hodgkin's lymphoma who received RT, it was found that total doses of >30 Gy resulted in a 3.5-fold higher risk for cardiac death compared to a matched general population [4]. In addition to the total RT dose, mean heart dose and volume are also independent risk factors for RIHD [4, 14]. A pooled analysis of 6 trials found that patients with non-small cell lung cancer, who developed symptomatic cardiotoxicity, had received a mean cardiac dose of 20.4 Gy, as opposed to 10.0 Gy received by those who did not develop cardiotoxicity [14]. Mean heart doses of <10 Gy, 10–20 Gy, and >20 Gy were associated with 2-year risk-adjusted cardiac event rates of 4, 7, and 21%, respectively [14]. In addition, LV volume receiving >5 Gy was significantly associated with cardiac events including symptomatic pericardial effusion, pericarditis, myocardial infarction, unstable angina, and heart failure [14]. Furthermore, the location and laterality of the radiated tumor in terms of radiation delivery is of significant clinical consequences. A meta-analysis of patients with breast cancer receiving left-sided RT demonstrated a relative risk of 1.29 (95% CI: 1.13–1.48) for coronary artery disease (CAD) and 1.22 (95% CI: 1.08–1.37) for car-

diac death compared to those receiving right-sided RT [15]. Typically, radiation doses are fractionated into smaller daily doses of <2 Gy as it has been found that fractions of >3 Gy are associated with increased cardiotoxicity, particularly pericardial effusions [16]. Cardiac shielding techniques have also been developed over the years from initial subcarinal blocking that was effective in limiting cardiac RT dose [4] to newer cardiac avoidance techniques such as deep inspiratory breath-holds [17] and intensity-modulated RT using multileaf collimator modification [18, 19].

Patient-Specific Risk Factors

Patient-specific risk factors include treatment at a younger age, hypertension, diabetes, smoking history, obesity, dyslipidemia, and prior history of cardiac disease [2, 3, 20]. Younger patients are at increased risk for developing RIHD. In a retrospective cohort of 2,524 Dutch patients treated for Hodgkin's lymphoma, it was found that patients younger than 25 years had a 4.6- to 7.5-fold increased risk of CAD [3]. While traditional cardiac risk factors such as hypertension, dyslipidemia, and diabetes are known to increase the risk of RIHD [21], smoking, in particular when added to RT, conferred a 3 times higher hazard for myocardial infarction [22]. Additionally, experimental data suggest that genetic variations, including mutations in genes involved in DNA repair pathways, increase cellular radio sensitivity [23]. Concurrent use of cardiotoxic chemotherapeutic agents, particularly anthracyclines, is another risk-enhancing factor for the development of RIHD [2, 3, 24, 25]. Establishment of models for early risk stratification will allow identification of high-risk patients who would potentially benefit from modification of RT or from preventive treatment.

Fig. 1. The pathophysiologic cascade of RIHD. RIHD, radiation-induced heart disease.

Pathophysiology

The initial key pathophysiologic step for development of RIHD is endothelial cell senescence from DNA damage and oxidative stress caused by radiation [26–29]. Senescent endothelial cells release proteins and proinflammatory cytokines, which activate a milieu of subsequent pathways [29]. Increased levels of IL-1, IL-6, IL-8, and TNF- α as well as reactive oxygen species (superoxide and peroxynitrite) have all been implicated as mediators of the subsequent processes [29–31]. Proinflammatory cell recruitment and adhesion follows, mediated by elevated levels of selectins, integrins, and immunoglobulin superfamily members [32]. Elevated circulating levels of vWF as well as downregulation of thrombomodulin, which leads to an increase in free thrombin and activation of platelets, are associated with the development of a prothrombotic state [29]. Finally, metabolic and immunologic alterations including increased glycolysis, altered mitochondrial oxidation and lipid metabolism, and immune system activation mediated by toll-like receptors and the chemokine receptor CXCL6 contribute to the disease [33, 34]. The product of the above pathways is accelerated atherosclerosis, fibrin deposition, intimal thickening, lipid accumulation, inflammation, and thrombosis. The spectrum of CAD, cardiomyopathy, pericardial disease, valvular disease, and conduction abnormalities is collectively described as RIHD. Figure 1 illustrates the pathophysiologic cascade of RIHD.

Clinical Manifestations

Radiation can affect all layers of cardiac tissue and cause a wide range of clinical manifestations [35–37]. Acute inflammation of the pericardium or myocardium can occur during or shortly after radiotherapy [35, 36, 38, 39]. The incidence of acute pericarditis and myocarditis though is rare with modern radiation techniques and lower fractions of RT. They usually manifest with symptoms of chest pain with pleuritic features or dyspnea. Myocardial inflammation can also induce arrhythmias, which may manifest as syncope or palpitations. Late cardiac effects, such as CAD, valvular disease, and conduction abnormalities, can present years or decades after radiotherapy [35, 36, 39]. Overlap of more than one pathologies is common (Table 2).

Pericardial Disease

The most common cardiac manifestation of RIHD is pericardial disease, which may manifest early, as acute pericarditis (Fig. 2), or late, in the form of pericardial effusion and/or constrictive pericarditis (Fig. 3) [40]. In a study of 294 asymptomatic patients with Hodgkin's lymphoma, who received an RT dose of at least 35 Gy, pericardial thickening by echocardiography was found in 21%, compared to only 2% of patients in the Framingham Heart Study, who were used as controls [41]. In this study, the protocol included a left ventricular block after 15 Gy and a subcarinal block that excluded most of the heart

Fig. 2. A 12-lead ECG showing pericarditis with PR segment depression and generalized concave ST elevation in all leads except aVR which shows ST depression. ECG, electrocardiogram.

Table 2. Clinical manifestations of RIHD

Key characteristics
Pericardial disease
Pericarditis
Constrictive pericarditis
Asymptomatic thickening and small pericardial effusion
Large pericardial effusion and cardiac tamponade
Coronary vasculopathy
Both large epicardial arteries and arterioles are affected
Coronary lesions predominantly in the proximal parts of the epicardial arteries
Acute coronary syndromes or stable ischemic heart disease and ischemic cardiomyopathy
Nonischemic cardiomyopathy
Diffuse fibrosis that does not follow any coronary distribution pattern
Diastolic and in late stages systolic left ventricular dysfunction
Conduction abnormalities
Fibrosis affects the conduction system
Infranodal and right bundle branch blocks are most common due to anterior position of the right bundle
Valvular disease
Thickening and calcification
Typically aortic and mitral valves
Manifests either as stenosis or regurgitation
Annulus of the valve, subvalvular apparatus, and aortomitral curtain might be involved
RIHD, radiation-induced heart disease.

after 30 Gy [41]. In a study, in which RT was given in a dose of 1.8–2.0 Gy per day, for a total of 60 Gy over 6 weeks, among 214 patients with esophageal cancer treated with concurrent chemoradiation therapy, 36% developed pericardial effusion between 2 and 40 months after RT, while 8.4% developed symptomatic pericardial effusion [42]. Patients who develop pericardial effusion following RT should be monitored closely since it may progress to large effusion and cardiac tamponade [43].

Figure 2 shows a 12-lead electrocardiogram demonstrating acute pericarditis related to RT. The patient is a 58-year-old woman with lung cancer who presented 2 weeks after RT with classic symptoms of pericarditis. She was treated with nonsteroidal anti-inflammatory drug (ibuprofen), colchicine, and steroid with full recovery and no recurrence.

Figure 3 shows an echocardiogram showing pericardial effusion related to RT. The patient had lung cancer

Fig. 3. a A moderate to large pericardial effusion. **b, c** No reaccumulation of pericardial fluid.

with disease progression in the mediastinum, for which he was treated with a cumulative dose of 66 Gy RT. Routine chest computed tomography scan a year later showed a large pericardial effusion for which he underwent pericardiocentesis. Pericardial fluid analysis showed only reactive mesothelial cells in a background of acute and chronic inflammation with no evidence of malignancy. Follow-up echocardiograms showed no recurrence of pericardial effusion.

Ischemic Heart Disease

Radiation-induced CAD and accelerated atherosclerosis can present as either angina, acute coronary syndrome, or ischemic cardiomyopathy and heart failure. The coronary lesions are predominantly located in the ostia or the proximal portions of the epicardial vessels [40, 44]. In particular, the anterior part of the heart is more commonly affected by RT, thus resulting in high radiation doses to the left anterior descending artery [45]. In addition to the large epicardial vessels, the small arteries are also affected. The majority of the patients may remain asymptomatic for years [41, 46]. In a large population-based study of breast cancer patients, it was found that the rate of major coronary events increased by 7.4% (95% CI: 2.9–14.5, $p < 0.001$) for each increase of 1 Gy in the mean radiation dose delivered to the heart [47]. The risk started to increase within the first 5 years and extended to at least 20 years following exposure [47]. In this study, virtual simulation and CT planning were used for the reconstruction of radiotherapy fields on a CT scan,

and radiation doses to the structures of interest were then estimated [47].

The relative risk of death from myocardial infarction is estimated to be double in patients exposed to chest RT compared to the general population. In a cohort of 7,033 patients with Hodgkin's lymphoma treated with RT, the standardized mortality ratio from myocardial infarction was 2.5 (95% CI = 2.1 to 2.9) with an absolute excess risk of 125.8 per 100,000 person-years compared to the general population of England and Wales [48].

Treatment of radiation-induced CAD with common revascularization techniques is challenging. When compared to CAD in nonradiated patients, the mortality is higher in RT-induced CAD, regardless of whether the patients are treated with percutaneous or surgical revascularization [49]. In an observational study of 314 patients treated at Cleveland Clinic, mortality after percutaneous coronary intervention (PCI) for radiation-induced CAD was higher compared to mortality after PCI for typical atherosclerotic CAD [49]. Independent predictors of mortality included balloon angioplasty or bare-metal stent placement, SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score of ≥ 11 , New York Heart Association functional class ≥ 3 , history of smoking, and age ≥ 65 years [49].

Compared to general population, patients with prior chest RT who undergo cardiac surgery, including coronary artery bypass grafting, have worse outcomes. In a case-control study of patients with RIHD, mortality rates after any cardiac surgery were 72% at 7.6 years in RT-

Fig. 4. Myocardial perfusion study showing small- to moderate-sized reversible perfusion abnormality in the anterior wall. The arrow points to the perfusion defects.

exposed patients versus 45% in controls ($p < 0.001$), while mortality rates after coronary artery bypass grafting, specifically, were 46 versus 28%, respectively [50]. Furthermore, graft patency failure and surgical complications including sternal dehiscence and infection rates are in-

creased in patients with prior RT compared to the general population [51]. Due to the above challenges, as well as the frequent presence of concomitant valvular and pericardial disease, any revascularization attempts in patients with prior RT should be planned very carefully. A

Fig. 5. a Echocardiogram shows severely calcified aortic and mitral valves causing aortic and mitral stenosis. **b** Doppler across aortic valve shows severe aortic stenosis and aortic regurgitations. The red arrow points towards the aortic valve and the white arrow shows the mitral valve.

personalized treatment approach involving the heart team model and a multidisciplinary team with experience in managing these patients is crucial.

Figure 4 shows the myocardial perfusion scan showing ischemia in the anterior wall, in a 41-year-old man presenting with chest pain 5 years after completion of RT for Hodgkin's lymphoma.

Nonischemic Cardiomyopathy

RT causes myocardial damage with resultant fibrosis and development of diastolic dysfunction, which may ultimately lead to restrictive cardiomyopathy or progress to systolic dysfunction [39, 52]. Myocardial fibrosis is usually diffuse and does not follow any coronary distribution pattern although fibrosis related to concurrent CAD is also present [5, 46]. Survivors of Hodgkin's disease who had previously received RT were found to have an increased incidence of heart failure compared to the general population (standardized incidence ratio of 4.9) translating to 25.6 excess cases of heart failure per 10,000 patients/year [25]. In this study, the radiotherapy techniques used were different over the years; for example, in the 1960s, patients were treated with cobalt-60 or orthovoltage therapy, whereas from the 1970s onward, linear accelerators were used (usually 8-MV photons), but the vast majority of patients had received a classical mediastinal field radiation [25].

Patients can present with dyspnea, fatigue, edema, orthopnea, and/or paroxysmal nocturnal dyspnea. In a study of relatively young patients with Hodgkin's disease (only 33% of the patients in this study were >50 years of age), who were treated with mediastinal irradiation, the

prevalence of diastolic dysfunction was several-fold greater than in community studies [53].

Heart failure in patients with previous RT could be multifactorial with a combination of primary myocardial damage, constrictive pericarditis, and ischemic heart disease. Therefore, clinical evaluation and appropriate investigations are needed to differentiate the possible causes of heart failure in these patients.

Conduction Abnormalities and Arrhythmias

Fibrosis can also affect the conduction system leading to the development of arrhythmias and heart block with symptoms of lightheadedness and syncope. Abnormal electrocardiogram is present in up to 75% of long-term survivors who have received mediastinal radiation [54]. In this study, the radiation techniques included 4- or 6-MV radiation source, equal weighting of daily fraction from anterior and posterior portals, <2 Gy daily fraction size, and similar heart and lung blocking [54]. The most common conduction abnormalities are infranodal and right bundle branch blocks. This is due to the anterior position of the right bundle, which makes it more susceptible to damage by RT [55]. There are reports of advanced atrioventricular block including complete heart block requiring permanent pacemaker implantation although this is rare [56]. Both supraventricular and ventricular arrhythmias are more prevalent in children and young adults who have received cardiac radiation [55].

Valvular Disease

Chest RT is associated with thickening and calcification of the cardiac valves, typically involving the aortic

and mitral valves [41]. Radiation-induced valvular disease is usually a late manifestation and presents with symptoms and signs of heart failure due to either valvular stenosis or regurgitation [41]. The most common valvular abnormality is aortic regurgitation with ~60% of asymptomatic patients who have received radiation >20 years prior having at least mild aortic regurgitation [41]. The incidence of aortic stenosis (16 vs. 0%, p value 0.0008) and moderate-to-severe tricuspid regurgitation (4 vs. 0%, p value 0.06) is also more common amongst patients who had received RT >20 years earlier, when compared to those receiving RT within the previous 10 years [41].

Frequently, in addition to the valves, surrounding structures including the annulus of the valve, subvalvular apparatus, and aorto-mitral curtain are involved [40, 41]. Calcification of the aortic valve, mitral valve, or intervalvular fibrosa is found in up to 90% of patients who have been treated with radiation >20 years ago [41]. This increased calcification in the subvalvular and supra-annular structures creates technical difficulties during valve replacement either by percutaneous or surgical methods. In a study of 173 patients with radiation-induced valvular disease who underwent cardiac surgery, aorto-mitral curtain thickness of >0.6 cm independently predicted mortality [57]. In a smaller report of 37 patients who underwent valvular replacement for radiation-induced valvular disease, the rate of in-hospital complications was 59%, in-hospital death was 14%, and 1-year mortality was 24%. Transcatheter intervention is a reasonable alternative to surgery, particularly in case of isolated valve disease, with shorter in-hospital stay (7 vs. 14 days) and lower in-hospital mortality (6 vs. 25%, $p = 0.19$). One-year mortality was similar (18 vs. 25%, $p = 0.4$) [58].

Figure 5 shows valvular heart disease in a 52-year-old man who presented with chest pain and dyspnea 35 years after completion of RT for Hodgkin's lymphoma.

Carotid Disease

Radiotherapy is known to cause both asymptomatic and symptomatic carotid artery disease [59, 60]. An increased risk of transient ischemic attack or stroke has been documented in 5-year survivors of Hodgkin's lymphoma [61]. As extensive area of the neck is usually radiated, RT often produces carotid lesions that are more diffuse, involving long arterial segments than the traditional bifurcation stenosis [60]. Due to extensive fibrosis, these patients may be more suitable for carotid stenting as opposed to surgical carotid endarterectomy. Carotid artery rupture following RT has also been reported [62].

Autonomic Dysfunction

Thoracic RT has also been associated with autonomic dysfunction [54, 63]. In 1 study, ~27% of patients with previous mantle cell radiation had a blunted blood pressure or heart rate response to exercise, suggesting autonomic dysfunction [54]. Another study of Hodgkin's lymphoma survivors demonstrated that resting tachycardia and abnormal heart rate recovery following stress were more common in patients treated with RT compared to controls (odds ratios: 3.96 [95% CI: 2.52–6.23] and 5.32 [95% CI: 2.94–9.65], respectively) [63]. In these patients, presence of autonomic dysfunction was associated with an increased all-cause mortality [63].

Early Detection

Several serum biomarkers and imaging modalities have been proposed for early detection of RIHD. Thus far, the readily available biomarkers, such as troponin and brain natriuretic peptide, have not been validated in predicting the development of RIHD [64–68]. Two other biomarkers, namely, placental growth factor and growth differentiation factor 15, were found to be elevated in patients with lymphoma and lung cancer exposed to a higher mean cardiac dose [64]. Since placental growth factor contributes to angiogenesis and atherogenesis and growth differentiation factor 15 is a cytokine secreted in response to tissue injury, inflammation, and oxidative stress, the above observation provides insights into the pathophysiology of RIHD. Further studies need to confirm their value as predictors of RIHD before its use in clinical practice.

Due to widespread use and cost effectiveness, screening echocardiography has been proposed as the imaging modality of choice for the early detection of asymptomatic RIHD [69]. In a prospective study of patients receiving thoracic radiation, at 1 year after completion of RT, there was an association between the mean and maximum LV dose and a decrease in left ventricular ejection fraction (57.6–56.4%) as well as worsening global longitudinal myocardial strain (–17.6 to –17.3) [70]. Further studies in patients with breast cancer have shown a worsening in left ventricular strain as early as 2 months after RT [71, 72]. Whether these echocardiographic findings correlate with subsequent development of clinical RIHD and the appropriate timing of surveillance echocardiography remain to be determined.

Coronary calcium score (CAC) is a useful tool for detection of preclinical atherosclerosis and independently predicts future cardiovascular events [11, 73]. Since all

patients who receive chest RT undergo CT scans for diagnostic, treatment, or surveillance purposes, CAC may serve as an inexpensive, practical imaging modality for early detection of atherosclerotic RIHD. However, the typical chest CT scans do not have the same number of slices through the heart compared with the dedicated CAC study and may therefore underestimate the calcium score. Furthermore, even though CAC can detect preclinical coronary atherosclerosis, it may not be useful for the detection of the other forms of RIHD (nonischemic cardiomyopathy, valvular disease, conduction abnormalities, and pericardial disease).

Single-photon emission computed tomography myocardial perfusion imaging has been used in some studies as a tool for early detection of myocardial ischemia after RT in asymptomatic individuals. In a small prospective study by Hardenbergh et al. [74], about 60% of women with left-sided breast cancer developed new perfusion defects 6 months after RT. A subsequent larger study from the same institution confirmed the high prevalence of perfusion defects after RT (40% after 2 years) and showed that perfusion defects were correlated with left ventricular wall motion abnormalities [37].

Current recommendation is for screening echocardiogram 5 years after chest radiation in high-risk patients and 10 years in the other patients [69]. Functional noninvasive stress test is recommended 5–10 years after chest radiation in high-risk patients [69].

Although strong evidence and clinical data to guide post-RT cardiac surveillance is lacking and recommendations are based on expert opinions, comprehensive screening and long-term routine follow-up for RIHD, especially of high-risk patients, seem to be prudent, given the high prevalence and long latency period between exposure and onset of the disease [75]. The above is reflected in the consensus statement by the European Association of Cardiovascular Imaging, the American Society of Echocardiography [69], and the guidelines published by the American Society of Clinical Oncology (ASCO), the Canadian Cardiovascular Society, and the European Society of Cardiology (ESC) [13, 76, 77].

Prevention and Mitigation of RIHD

Minimizing cardiac exposure to radiation is essential in reducing the risk of RIHD [14, 78, 79]. Personalized protocols of RT with adjustments in total dose and frequency of therapies based on risk, targeted image-guided RT with reduction in radiation field and volume, respira-

tory motion management, and improvement in conformity with intensity-modulated RT and proton beam therapy are currently used methods for prevention of RIHD [80–83].

Radiation doses have been fractionated into daily doses smaller than 2 Gy since higher doses have been associated with cardiotoxicity. In a multicenter study of 57 patients with esophageal cancer treated with RT, all patients who developed nonmalignant pericardial effusions had received RT with 3.5 Gy daily fractions [16]. Cardiac avoidance techniques have evolved over the years limiting radiation exposure to the heart and decreasing the incidence of RIHD. In a large study of 2,232 patients with Hodgkin's disease followed for 9.5 years, subcarinal blocking reduced the relative risk of cardiac disease, including heart failure, pericarditis or pancarditis, cardiomyopathy, or valvular heart disease from 5.3 (CI: 3.1–7.5) to 1.4 (CI: 0.6–2.9), although it did not decrease the relative risk of acute myocardial infarction (RR: 3.7 vs. 3.4) [4]. Among 89 patients with left-sided breast cancer enrolled in the SAVE-HEART study, the use of deep inspiration breath-hold reduced mean heart radiation doses by 35% (interquartile range: 23–46%) as compared to free breathing, which translated to a greater reduction in expected years of life lost due to RIHD (0.07 vs. 0.11 years, respectively) [17]. In another study, intensity-modulated RT and moderate deep inspiration breath-hold significantly reduced heart V30 from 19.1 to 3.1% ($p < 0.0004$) [19]. In a more recent study of 49 patients with left-sided breast cancer, a multileaf collimator modification technique was tested and resulted in significant reduction in the mean left anterior descending artery (LAD) dose by 7.0 Gy, the mean LAD planning risk volume dose by 5.9 Gy, the maximum LAD dose by 12 Gy, and the mean heart dose by 0.73 Gy, whilst maintaining breast and boost volume dosimetry [18]. Furthermore, a recently published phase IIB randomized clinical trial of 145 patients compared total toxicity burden and progression-free survival between proton beam therapy and intensity-modulated RT for advanced esophageal cancer. The trial was stopped early since in the interim analysis proton beam therapy had a significantly lower mean total toxicity burden compared to intensity-modulated RT while maintaining similar progression-free survival [84]. Although these contemporary techniques appear to have decreased the incidence of cardiac complications related to RT, residual risk remains [78].

In addition to minimizing the exposure of the heart to RT (primary prevention), pharmacologic therapy might also have a role after exposure (secondary prevention).

There is some evidence that metformin may be beneficial in subjects undergoing RT [85, 86]. A retrospective national cohort study based on the Taiwan Cancer Registry, including 6,993 women with early-stage breast cancer who received adjuvant breast RT, showed that metformin use during RT reduced the risk of heart failure and CAD (adjusted hazard ratio: 0.789, 95% CI: 0.645–0.965, $p = 0.021$) [85]. However, large prospective confirmatory studies are needed before advocating its use in clinical practice. Statins may be beneficial as limited evidence from animal studies and retrospective human studies suggest that statins might prevent cardiac fibrosis and reduce cerebrovascular and cardiovascular events when administered after chest RT [87, 88]. A large retrospective study of 5,718 patients treated with RT for thoracic or head and neck cancers reported that statin use after RT was associated with a significant reduction of stroke by 32% (hazard ratio = 0.68, 95% CI: 0.48–0.98, $p = 0.0368$) and a trend of reducing the composite of cerebrovascular (transient ischemic attack and fatal or nonfatal stroke) or cardiovascular events (fatal or nonfatal myocardial infarction) (hazard ratio = 0.85, 95% CI: 0.69–1.04, $p = 0.0811$) [87]. Colchicine has also been proposed as a prophylactic treatment option to mitigate the cardiotoxic effects of RT given its anti-inflammatory properties. However, strong clinical evidence supporting its benefit is lacking [89]. Although there are plausible explanations for the benefit of aspirin, statin, and colchicine in prevention of RIHD, large-scale data on the use of these medications for prevention of RIHD are needed [90]. Finally,

aggressive treatment of traditional cardiovascular risk factors and prior cardiovascular disease is important during and after RT.

Conclusion

Although modern radiation techniques, by reducing the dose delivered to the heart, have decreased the incidence of RIHD, they remain a major cause of morbidity and mortality among cancer survivors. In its early phase, RIHD may remain asymptomatic but can present symptomatically years after completion of RT. Prevention and early recognition is essential in the management of RIHD.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.W.Y. and E.K. conceptualized and wrote the initial draft of the manuscript. N.L.P., A.D., S.H.L., J.A., Z.L., and J.B. reviewed and edited the manuscript. The manuscript has been read and approved by all authors.

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