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*Review*

# Radiation-associated Cardiac Injury

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**Abstract.** *Chest radiotherapy continues to play an important role in the treatment of breast cancer, Hodgkin's lymphoma, and other malignancies. Subsequent cardiac injury has been described involving essentially all structures of the heart, with most radiation-induced injury being progressive in nature. Our understanding over the multifactorial etiology and development of radiation-associated cardiac injury has advanced, leading to improved techniques aimed at decreasing cardiac radiation exposure and associated risks. Monitoring after radiotherapy clearly appears to be indicated; however, optimal recommendations regarding cardiac screening remain difficult to establish.*

It is now well-known that chest irradiation for the treatment of malignancies can cause radiation-associated cardiac injury, but late cardiac injury continues to emerge as an important clinical concern as cancer survivors continue aging. Such injury can involve seemingly all structures, including the pericardium, myocardium, conduction systems, valves, and coronary arteries. In the present article, we review radiation-associated cardiac injury, with a discussion of pathogenesis, prevention, and treatment when such information is available.

## Radiation Dose, Fractionation, and Technique

Larger radiation doses appear to increase the risk of cardiovascular morbidity, though there is no minimum dose at which the onset of cardiac injury seems to correlate. In a large population-based case control study evaluating breast cancer patients who received radiotherapy, the radiation dose was proportional to the risk of major coronary events (*e.g.* myocardial infarction, coronary revascularization, or death from ischemic heart disease). The rates of major coronary events increased by 7.4% for each increase of 1 gray (Gy) (1). Similarly, a large retrospective cohort study of more than 14.000 childhood cancer survivor patients revealed that cardiac radiation exposure of >15 Gy increased the relative risk of congestive heart failure (hazard ratio (HR)=5.9), myocardial infarction (HR=5.0), pericardial disease (HR=6.3), and valvular abnormalities (HR=4.8) when compared to non-irradiated survivors (2). Furthermore, when Hodgkin's and non-Hodgkin's lymphoma patients were treated with radiotherapy, all patients showed evidence of damage to various cardiac structures, 10 of which showed evidence of myocardial fibrosis. Out of these 10 patients, only the 7 who had received greater than 30 Gy had moderate to severe fibrosis (3). Comparably, in additional literature, Hodgkin's lymphoma patients receiving mediastinal radiotherapy of 30-35 Gy alone had an increased risk of cardiac morbidity (HR=1.82), though this risk was highest in patients treated with both radiotherapy and anthracycline-based chemotherapy (HR=2.77) (4). There is a three-fold increased risk of cardiac death in Hodgkin's survivors irradiated with 30 Gy or more relative to an age-matched population (relative risk (RR)=3.5), though, interestingly, there was no such increased risk among patients treated with <30 Gy (5). It has been measured that irradiating a left-sided breast tumor, on average, exposes the heart to a radiation dose more than twice as high as when irradiating a right-sided breast tumor (6.3 Gy *vs.* 2.7 Gy). Consistent with this, mortality from ischemic heart disease in left-sided tumor patients is higher than in right-sided tumor patients (mortality ratio left *vs.* right 1.13) (6, 7). The radiation-associated cardiac risk appears to increase with time after exposure. In breast cancer patients irradiated from 1972-1983 and followed for 3 decades, cardiac mortality ratios (left *vs.* right-sided) increased with time, from 1.19 (1.03-1.38) at <10 years to 1.35 (1.05-1.73) at 10-14 years, 1.64 (1.26-2.14) at 15-19 years, and 1.90 (1.52-2.37) at >20 years after irradiation (8).

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With improvements in technique, cardiac radiation exposure has been minimized by both excluding the heart from treatment fields and by lowering daily radiation fraction, thereby decreasing the overall risk of resultant cardiovascular morbidity and mortality. Following nearly 14,000 breast cancer patients receiving left-sided radiotherapy for 15 years after irradiation, mortality from radiation-induced ischemic heart disease was 13.1% in 1973-1979, dropping to 9.4% in 1980-1984 and 5.8% in 1985-1990 (9). Hodgkin's patients treated from 1940-1966 showed an increased relative risk of fatal myocardial infarction when compared to patients treated from 1967-1985 (6.33 *vs*. 1.97) (10). These findings may be partially explained by an increased use of subcarinal blocking to limit radiation exposure to the heart. In Hodgkin's patients treated from 1960-1991, subcarinal blocking was shown to decrease the relative risk of non-myocardial infarction related cardiac deaths from 5.3 to 1.4. The overall occurrence of fatal myocardial infarctions, however, remained without significant change (3.7 to 3.4), implying that subcarinal blocking may not protect the proximal coronary arteries from radiation exposure (5).

Further protective techniques have emerged with the goal of continuing to reduce cardiac injury attributable to chest irradiation. Intensity-modulated radiotherapy (IMRT) reduces the volume of the heart receiving radiation compared to conventional tangent fields (11-13). IMRT was shown to reduce the maximum total radiation dose delivered to the left ventricle by 30.9% (49.14 *vs*. 33.97 Gy) (13). Supporting this, there exist further data reporting a significant reduction in the volume of the heart receiving more than 30 Gy when IMRT was employed (12.5% to 1.7%) (11). It has been calculated that IMRT reduces the excess radiation-induced cardiac death risk from 6.03% to 0.25% (13).

Decreasing the total number of radiotherapy sessions by increasing the dose per session has been used in an attempt to further limit cardiac injury. After 10 years of monitoring, hypofractionated radiotherapy was found to be non-inferior in the treatment of certain breast cancer patients (14). With longer follow-up, a separate cohort of breast cancer patients treated from 1975-1991 was able to provide more information regarding the cardiac mortality of hypofractionated radiotherapy. Patients receiving two 4.3 Gy fractions per week for 10 fractions with a target dose of 43 Gy had an increased risk of ischemic heart disease mortality compared to those receiving five 2.5-Gy fractions per week for 20 fractions with a target dose 50 Gy (HR=2.37), as well as relative to the control group (HR=1.59). The increased risk emerged after 12 to 15 years, hinting at the importance of working towards a better understanding over the long-term surveillance appropriate in these patients (15).

## Coronary Artery Disease and Conduction Disease

Radiation therapy to the chest wall increases the risk of accelerated atherosclerosis, potentially leading to severe coronary artery disease (16). Through analyzing autopsy and pediatric studies, chest irradiation was shown to cause early atherosclerosis, suggesting that cardiac injury in irradiated patients is a result of radiation, independent of degenerative changes from aging (3). Although the pathogenesis of premature coronary artery disease after radiation treatment remains unclear, high dose radiation to the chest wall is thought to cause intimal injury, leading to endothelial disruption and activation of myofibroblasts and platelets. Endothelial injury results in the formation of cholesterol plaques containing infiltrates of macrophages and neutrophils that have been associated with plaque hemorrhage and increased risk of coronary thrombosis (17, 18).

The location of radiotherapy to the chest wall influences the risk of myocardial ischemia. In a study of 199 patients with breast cancer who underwent irradiation, there was an increased risk of coronary stenosis in the mid-left anterior descending artery (LAD) and distal diagonal arteries (odds ratio (OR)=4.38), as well as a higher risk of high-grade stenotic lesions (OR=7.22) in patients who received left-sided irradiation *versus* those who required right-sided irradiation. "Hot spot" radiation targets, such as radiation to the internal mammary chain, which exposes anterior structures of the heart (*e.g.* LAD), have been associated with an increased risk of ischemic heart disease (19). However, other conflicting data report that breast cancer patients receiving post-mastectomy radiotherapy to the internal mammary chain did not have an increased risk of ischemic heart disease after 12 years of follow-up (20).

Multiple studies have demonstrated an increased risk of fatal myocardial infarctions in Hodgkin's lymphoma patients compared to the general population. In a British cohort study evaluating more than 7,000 Hodgkin patients, there was an absolute increased excess risk of myocardial infarctions (125.8 per 100,000 person-years) and an increased risk of death from myocardial infarctions (standard mortality ratio (SMR)=2.5) relative to the general population. In patients who received concomitant anthracycline or supradiaphragmatic radiotherapy, there was increased mortality from myocardial infarctions (SMR=9.5 and 14.8, respectively). The risk of death from myocardial infarction remained statistically significant for at least 25 years (21). Another evaluation of more than 2,000 Hodgkin's lymphoma patients, who were followed-up for an average of 9.5 years, found an increased risk of cardiac death (RR=3.1), as well as an increased risk of death from acute myocardial infarction (RR=3.2) in those undergoing radiotherapy (5).

The risk of myocardial ischemia is also well documented in breast cancer patients who have undergone adjuvant radiation treatment. Breast cancer patients who received radiotherapy to the chest wall had a rate of coronary events that increased linearly by 7.4% per Gy. The risk of developing ischemic heart disease started to increased during the first 5 years of treatment and continued for at least 20 years after radiotherapy, independent of underlying cardiac risk factors.

The increased proportional rates of coronary events per Gy were similar amongst women with and without prior cardiac risk factors at the time of the radiation treatment, but the absolute increase in risk was greater in women with preexisting cardiac risk factors (1).

Currently there are no specific recommendations by the American Heart Association or the American College of Cardiology for routine screening in asymptomatic patients who have been exposed to chest radiotherapy (22). Patients should be closely monitored for symptoms of coronary artery disease. Additionally, such patients should undergo risk factor modification, such as blood pressure control, dyslipidemia management, weight loss reduction, diabetic glycemic control, and smoking cessation. Patients who have traditional risk factors for coronary artery disease should then undergo guideline-directed medical therapy, as recommended by the cardiovascular and diabetic societies (22, 23).

Damage to the cardiac conducting system can additionally occur as a result of chest radiotherapy, rarely occurring without radiotherapy-induced injury to other cardiac structures (24, 25). Upon initial exposure, repolarization abnormalities are common but transient (26). Conduction abnormalities that can occur include QT-prolongation, sick sinus syndrome, all levels of atrioventricular (AV) block, right and left bundle branch blocks, supraventricular tachycardia, ventricular tachycardia, premature atrial contractions, and premature ventricular contractions (24, 25, 27-29). Etiologies of conduction system damage that have been described include direct mechanisms, such as radiation-induced myocardial fibrosis, as well as indirect mechanisms, such as tissue damage caused by radiation-induced coronary artery disease (30, 31). Conduction blocks are more common infranodally and manifest more frequently as right bundle branch block relative to the left (24, 32). In addition to the above described conduction abnormalities, loss of circadian and respiratory phasic heart rhythms suggests that this resembles a denervated heart. The time scale of the development of conduction abnormalities due to radiotherapy is difficult to characterize, but -with regards to AV block- the risk of occurrence is higher after at least 10 years have passed since radiotherapy. The most common presenting symptom of such conduction abnormalities is syncope, with an average time to clinical presentation of 12 years after chest irradiation (30, 34, 35). Admittedly, little is known about the frequency of sub-clinical electrocardiogram abnormalities with regards to prevalence and the prediction of progression to clinical significance. Such silent conduction abnormalities have been reported to cause death, with no prior clinical presentation. Recommendations regarding the value of screening remain unclear, but it may be of greater yield to screen those who already show clinical signs of other cardiac damage due to chest radiotherapy, more specifically, including coronary artery disease and congestive heart failure.

## Cardiomyopathy and Pericardial Disease

Myocardial fibrosis in irradiated patients correlates with the release of inflammatory cytokines. Inflammatory mediators and growth factors seem to affect the myocardium on a cellular level (36). Endothelial damage from irradiation leads to microvascular injury and a resultant increased vascular permeability. Additionally, endothelial cell swelling with cytoplasmic vacuolization leads to detachment of the endothelium from the underlying matrix (36, 37). Progressive loss of the endothelium and exposure of the underlying matrix allows for platelet activation and adhesion, thus creating a prothrombotic environment (36, 38). Von Willebrand factor deposition, elevated production of reactive oxygen species, and stimulation of the renin-angiotensin-aldosterone system from endothelial injury all increasingly contribute to myocardial fibrosis (36, 39, 40). Increased release of pro-fibrotic inflammatory cytokines (*e.g.* transforming growth factor-B) promotes cell proliferation and, ultimately, fibrosis (41).

Ventricular dysfunction from irradiation can lead to either systolic or diastolic dysfunction, with the latter being more prevalent. Subclinical disease is more common but progressive disease may occur insidiously. In Hodgkin's patients who received mediastinal radiation of at least 35 Gy, there was a high prevalence of diastolic dysfunction amongst asymptomatic survivors. Patients with diastolic dysfunction had exercise-induced ischemia more commonly than those without diastolic dysfunction (23% *vs*. 11%). Additionally, these patients had worse event-free survival compared to patients with normal diastolic function (HR=1.66) (42). In another study evaluating asymptomatic Hodgkin's patients, 57% had an abnormal left ventricular ejection fraction, while 27% had an abnormal right ventricular ejection fraction (43).

Regional wall motion abnormalities, more common in irradiated patients, have been shown to increase in frequency with time (13% with a latency period of 2-10 years after radiotherapy, 18% with a latency period of 11-20 years, and 29% with a latency period >20 years) (44). Regarding irradiated breast cancer patients, 52% exhibited perfusion defects at 3 years post-radiotherapy (45).

Pericardial damage after chest radiotherapy treatment is also common and well-documented (3, 27). Pericarditis caused by radiation can be acute, delayed, or chronic. Risk factors for the development of pericarditis include higher total doses of radiation, increased volume of heart exposed to radiation, and the presence of tumor adjacent to the heart (46-48). Acute pericarditis due to chest irradiation presents within a few weeks of treatment (47). Clinical presentation can be silent or occur quite abruptly, presenting with typical symptoms, such as fever, pleuritic chest pain, tachycardia, and dyspnea (5, 47, 49). On electrocardiogram, typical ST-segment and T-wave changes can occur as can a decrease in QRS voltage (47, 49, 50). The etiology of this type of acute pericarditis is most likely necrosis

and inflammation of the tumor itself and not a direct effect of the radiation therapy upon the pericardium as it is more prevalent in patients with a large tumor burden. The majority of cases of acute radiation pericarditis do not require extensive treatment and recover without long-term consequences, with continuation of irradiation as indicated (5, 49, 51, 52). Delayed pericarditis may present within a few months up to 2 years after radiotherapy, presenting similarly as described above, but more frequently with large pericardial effusions, a minority of which cause life threatening pericardial tamponade (46).

Approximately 20% of patients with delayed pericarditis can develop chronic pericarditis, which may manifest as pericardial effusion or as constrictive pericarditis. Chronic pericarditis can be silent or can present with fever, chest pain, shortness of breath, pleural effusion, raised JVP, and even pulsus paradoxus (47, 49, 51). Chronic pericarditis can occur independent of any acute or delayed pericarditis. The mechanism of chronic disease is thought to be the result of collagen and fibrin replacement of normal pericardial adipose tissue, thus thickening the pericardium and causing the layers to adhere to each other or to the heart and pleura. An additional mechanism appears to involve increased vascular permeability and fluid extravasation secondary to irradiation (53-55). On echocardiography, pericardial thickening may be observed, and there can be evidence of impaired ventricular filling with elevated end-diastolic pressure (56). Unstable chronic pericardial effusions are treated by pericardiectomy once diastolic filling is significantly impaired by pericardial fibrosis. In a small series, pericardiectomy appeared to be superior to pericardiocentesis in this setting (57, 58).

## Valvular dysfunction

Though previously controversial, it is now well-established that patients who receive radiation exposure to the heart have an increased risk of valvular disease requiring for valve replacement. The avascular cusp and leaflets of the valves may undergo diffuse fibrosis, with or without calcific changes (3, 16, 27). These fibrotic changes may affect all four valves as has been confirmed on multiple studies; however, the left heart valves are much more commonly affected than those of the right heart (59).

The etiology of radiation-induced valvular endocardial fibrosis is unclear, but it is independent of microvascular disease, and the left-sided predominance suggests that higher systemic pressures may play a role in development of valvular pathology. The risk of developing valvular disease after chest radiotherapy increases with higher total dose administered, and is suggested to increase with higher volumes of heart exposure, younger age at time of exposure and longer passage of time since exposure (3, 5, 59).

Most patients who undergo enough radiation exposure to the heart (>30-35 Gy) develop calcification of the left heart valves (90%). Similarly, fibrotic thickening of the valves is observed quite often but less so than calicification (70-75%) (3, 59-61). These include many people who have normal valves documented upon the completion of therapy, but, then, have progression of valvular changes over the subsequent 10-20 years (5). Observable fibrotic changes do not necessarily correlate with clinically significant valvulopathy as many patients have either a delay in symptoms or remain asymptomatic. Though there is much variability in the time course of presentation, a small review of cases calculated an average time from the development of subclinical valvulopathy to the clinical presentation of attributable symptoms to be 5 years. On average, symptoms presented 16.5 years post-exposure compared to asymptomatic valvular disease detection occurring after 11.5 years. Providing for variation amongst patients in whom different valves are involved, the overall combined mean interval to heart failure is approximately 22 years post-exposure (59, 62).

Out of all valvular dysfunction attributable to radiotherapy, valvular insufficiency appears more commonly than stenosis. Valvular stenosis, however, more often requires valvular correction (59). It has been suggested that screening for valvular disease with echocardiography should begin at 10 years post-exposure and continue annually thereafter (44). This patient population should also undergo echocardiographic preoperative evaluations when being evaluated for coronary bypass, as many patients will have co-existent coronary and valvular disease (approximately 28% of such CABG patients required concomitant valve surgery) (63). Severe valvulopathy should be treated with valvular replacement (64, 65). Mediastinal fibrosis resulting from chest radiotherapy must be considered in conjunction with a patient's surgical risk, as this is the highest independent predictor of perioperative mortality (most likely due to increased technical difficulty) and is associated with a more dismal 30-day mortality rate compared to patients who have minimal pericardial fibrotic constriction (59, 63, 64). For particularly difficult patients such as these, transaortic valve replacement (TAVR) remains an option (66).

## Conclusion

Radiation-associated cardiac injury has become a significant source of morbidity and mortality in a growing population of cancer survivors who have undergone chest irradiation. Although there have been significant improvements in radiotherapy techniques, dosing, and treatment modalities, there remains significant risk of post-radiotherapy subclinical disease in asymptomatic patients, which over years can progress to significant disease of the coronary arteries, myocardium, valves, conduction system, and pericardium. The degree of radiation-induced cardiac injury varies between individuals in terms of clinical significance and rate of progression. It is, thus, important to continue considering irradiation as a significant cardiac risk factor as, although screening seems clearly indicated, optimal strategies for screening and for long-term follow-up remain unclear.

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