Adverse Cardiovascular Effects of Radiation Therapy

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Radiation therapy is a key part of treatment for many cancers. Vast advancements in the field of radiation oncology have led to a decrease in malignancy-related mortality, which has uncovered some of the long-term side effects of radiation therapy. Specifically, there has been an increase in research looking into the cardiovascular side effects of chest radiation therapy for cancers of the esophagus, breast, and lung tissue as well as lymphomas.

radiation cardiotoxicity screening prevention surveillance

1. Introduction

Vast advancements in cancer-related therapies have been associated with a decline in malignancy-related mortality, leading to a significant increase in the number of survivors. This has brought greater recognition to the adverse effects of cancer therapies, specifically the cardiovascular toxicity profile. Cardiovascular disease is the leading cause of non-malignancy-related deaths in cancer survivors and is known to be related to the amount of chest irradiation patients undergo [1]. For instance, patients who have undergone irradiation for breast cancer have a 3.1% increased risk of cardiac death per each Gray unit of thoracic radiation [2]. Nonetheless, radiation therapy plays a significant role in the treatment of cancer and is used on more than 50% of patients diagnosed with cancer [2]. The benefits of radiation therapy can be curative, adjunctive, and/or palliative. Cardiovascular toxicities, including coronary artery disease (CAD), valvular heart disease, heart failure (HF), myocarditis, cardiomyopathies, arrhythmias, and pericardial syndromes are some of the known sequelae of chest irradiation. As it is often used for the treatment of lymphomas and cancers of the esophagus, breast, and lung tissues, these are the most common cancers that expose the heart to irradiation [1][2]. Similarly, pre-existing cardiovascular disease can complicate radiation treatment.

2. Pericardial Disease

2.1. Incidence and Pathophysiology

Pericardial disease is a very common manifestation of radiation-induced heart disease. It can range in severity from asymptomatic pericardial calcifications to diffuse constrictive pericarditis and cardiac tamponade. One study found that out of 167 patients who underwent radiation for primary esophageal cancer, pericardial effusions developed in 35.9% of patients. Of these, 8.4% had symptomatic effusions requiring treatment. The average pericardial doses of radiation were significantly higher in patients who developed symptomatic pericardial disease

[3]. A smaller study of autopsy reports in patients with a history of chest radiation found that 70% of patients had evidence of pericardial disease ranging from effusion to constrictive pericarditis [4]. High doses of radiation to the mediastinum can cause inflammation in the pericardium [4][5]. Over time, as the immune system responds to the localized inflammation, the adipose tissue of the pericardium is replaced with collagen and fibrin, resulting in fibrosis and calcification. The distribution of pericardial disease is highly dependent on the proportion of the heart that was within the irradiation field [4][5]. Fibrosis also impairs venous drainage of the pericardial space, which can present as either acute or chronic pericardial effusion, and in some cases, cardiac tamponade [6].

Given that a large portion of patients with pericardial disease are asymptomatic, it is thought that the total number of patients with radiation-induced pericardial disease is under-reported [6]. Acute pericarditis and pericardial effusions are generally seen in conjunction with very high doses of radiation, like those administered in cases of Hodgkin's lymphoma or esophageal cancer. Most cases of pericardial disease tend to present 5–10 years after radiation exposure [6].

2.2. Management

The management of pericardial disease depends on the acuity and presence of symptoms. For pericardial effusions that were incidentally found and if the patient is hemodynamically stable and asymptomatic, close monitoring is recommended. For patients who are symptomatic, pericardiocentesis should be pursued. In cases of cardiac tamponade, pericardiocentesis is emergent.

The management of radiation-induced acute pericarditis is similar to that of other causes of pericarditis. The standard recommended treatment is nonsteroidal anti-inflammatory agents (NSAIDs). There are not many studies that look at the use of colchicine in these patients, however, it has been shown to be effective in some cases [7]. The use of steroids has also not been well-established and should be reserved for the management of hemodynamically significant pericarditis in the acute time frame post-radiation [8]. For resistant or recurrent pericarditis, beta receptor antagonists can be used [8]. A proposed mechanism by which beta-blockers can reduce recurrence and assist with symptom management is related to the reduction of pericardial layer friction by decreasing heart rate [9].

The literature shows that 20% of patients with acute pericarditis will develop chronic constrictive pericarditis [10]. Radiation-induced constrictive pericarditis has very unfavorable outcomes. The treatment options for these patients are often limited to either a partial or total pericardiectomy. In a study looking at surgical outcomes in patients undergoing surgical interventions for radiation-induced constrictive pericarditis, the 5-year survival rate was only 51%, compared to 83% for non-radiation-related diseases [11]. Another study of 163 patients who underwent pericardial stripping found a 7-year survival rate of only 27% [12].

3. Coronary Artery Disease

3.1. Incidence and Pathophysiology

Coronary artery disease (CAD), including acute coronary syndrome and myocardial infarction, is the most common manifestation of radiation-induced cardiovascular disease. It has been widely studied in patients with a history of thoracic radiation treatment for Hodgkin's Lymphoma, and it is estimated that up to 85% of patients who underwent treatment went on to develop coronary artery disease [13]. Another retrospective study of 415 patients who underwent radiation therapy for the treatment of Hodgkin's Lymphoma noted that the mean time leading to the development of coronary artery disease was 9 years [14]. Additionally, a randomized trial of breast cancer patients comparing those who underwent radiation in addition to surgery and those who underwent surgery alone noted a significantly higher mortality rate due to coronary artery disease in the post-radiation therapy group, and that the relative risk of the development of CAD appeared to be linearly proportional to the amount of radiation the heart received [15]. Patients with a prior history of radiation therapy also have a 2.5 times increased risk of fatal MI as compared to that of the general population [16].

3.2. Management

The management of coronary artery disease in this population necessitates increased vigilance and screening. Percutaneous interventions are preferred over coronary artery bypass graft (CABG) surgeries given the post-radiation changes that affect other elements of the thoracic space, leading to increased postoperative wound complications. In patients with a history of thoracic radiation treatment, the usual arterial and venous conduits are often fibrotic and stenosed as well, making them poor choices for grafts. Additionally, thoracic radiation results in scarring and fibrosis of the skin and subcutaneous tissues, which puts this population at higher risk for bleeding complications and poor wound healing. A study in 2013 reported an overall survival rate of 45%, at a mean of 7.8 years after CABG, for patients who underwent mediastinal radiation [17]. This population also tends to have significant atherosclerosis and calcification of the thoracic aorta, which significantly increases the risk of stroke when placed on cardiopulmonary bypass [17]. Several studies have demonstrated poor outcomes and worse mortality post-CABG in this population, which have been attributed to the extent of radiation-induced fibrosis and scarring in the mediastinum, and as a result, percutaneous interventions are preferred [18].

4. Cardiomyopathy

4.1. Incidence and Pathophysiology

Radiation therapy that involves the thorax significantly increases the risk of nonischemic cardiomyopathy. Cardiomyopathies are estimated to affect about 10% of patients who undergo radiation therapy [5]. Several mechanisms for this have been described, including restrictive physiology related to pericarditis and fibrotic changes caused by radiation. High doses and large fields of radiation are associated with inflammation, injury, and death of the myocardial cells. As a result, the myocardium is infiltrated by myofibroblasts which leads to an increase in collagen deposition [5][19]. The myocardium becomes stiff and fibrosed, resulting in a restrictive cardiomyopathy with diastolic dysfunction [5][19]. Radiation can also result in endothelial injury to the coronary vasculature, leading to poor oxygenation in the myocardial tissue. Over time, this leads to myocyte death and myofibroblast proliferation which also results in collagen deposition and fibrosis.

4.2. Management

Nonischemic cardiomyopathy secondary to thoracic radiation presents with the same symptomatology as ischemic cardiomyopathy, including dyspnea on exertion, lower extremity edema, orthopnea, and exercise intolerance. Heart failure symptoms are managed with standard goal-directed medical therapy including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, neprilysin inhibitors, and sodium-glucose cotransporter-2 inhibitors [20]. The data are lacking in evaluating the mortality benefit of GDMT in this population compared to other etiologies of cardiomyopathy, such as ischemic or hypertensive [20]. In advanced stages of radiation-induced cardiomyopathy, heart transplant remains the main-stay of life-prolonging therapy. However, the 5-year survival rate in these patients is lower compared to the cardiomyopathy of other etiologies (58% vs. 73%), which has been attributed to sternal wound complications and postoperative respiratory and renal failure [6][21].

In addition to these therapies, many nutraceuticals have been shown to reduce cardiotoxicity in clinical models, although current guidelines do not mention the use of nutraceuticals in the management of cardiotoxicities. Quercetin has been shown to protect radiation-induced DNA from damage and apoptosis in the kidney and bladder tissues of rats [21]. In a more recent study, polydatin was shown to reduce cardiotoxicity by decreasing pro-oxidative stress and pro-inflammatory cytokines [22].

5. Valvular Disease

5.1. Incidence and Pathophysiology

Thoracic radiation poses a significant risk for developing valvular heart disease in the long term. Studies have demonstrated that the risk increases significantly in patients who receive total radiation doses of >30 Gy units. A study evaluating the 30-year cumulative risk of valvular heart disease in patients undergoing thoracic radiation found that patients receiving a total radiation dose of <30 Gy had a cumulative risk of 3% compared to 12.4% for those receiving >40 Gy [23]. Similarly, another study demonstrated a 45% prevalence of valvular disease in 15-year lymphoma survivors who received a total radiation dose >30 Gy, marking it as an independent risk factor for valvular heart disease [24]. The pathophysiology of valvular disease after radiation is associated with fibrosis and the thickening of valve leaflets. Left-sided valves are more commonly affected, specifically the aortic valve. Additionally, regurgitation is seen more commonly than stenosis, which is thought to be secondary to the effects of higher-pressure circulation on damaged valves [25]. Pathology studies of excised valves demonstrated increased collagen and decreased calcified tissue when compared to patients who did not have prior radiation exposure. On echocardiography, radiation-induced valvular damage characteristically leads to diffuse valvular thickening, calcification, and fibrosis of the aortic apparatus including the root, leaflets, and annulus. It may also affect the mitral valve annulus and leaflets [19].

5.2. Management

The management of valvular disease includes both surgical and transcatheter approaches. Notably, surgical valve replacement procedures in post-chemoradiation patients can be particularly difficult due to the presence of chest wall scarring and the possibility of delayed wound healing in the setting of radiation. The 2020 ACC/AHA guidelines for valvular heart disease include prior radiation therapy as a factor associated with prohibitive surgical risk for patients with severe symptomatic aortic stenosis [26]. Several studies demonstrate the increased mortality risk for patients who undergo surgical procedures after radiation therapy [17].

For aortic valve replacement, the transcatheter approach has been demonstrated in numerous studies to have superior outcomes in comparison to surgical repair. An observational study in 2019 of patients with severe aortic stenosis and a history of chest irradiation found that patients who underwent transcatheter aortic valve repair (TAVR) had lower 30-day and 1-year mortality rates than with surgical aortic valve repair (SAVR), fewer episodes of postoperative atrial fibrillation, and shorter lengths of hospital stays [26]. A year later, a larger study of patients who had undergone mediastinal radiation found TAVR was associated with lower in-hospital mortality in comparison to SAVR (1.2% vs. 2.0%, adjusted odds ratio: 0.27; $p < 0.02$).

The consensus of available data demonstrates TAVR to be the superior alternative to SAVR in patients with radiation-induced aortic valvular disease. Given the increased surgical risk for patients who have undergone radiation therapy, TAVR should be considered the preferred treatment method for aortic valve repair as it is associated with lower mortality rates, shorter length of hospital stays, and fewer postoperative complications [6][24][25].

There are limited studies on the effects of mitral valve intervention and its outcomes. A small study exists, including 15 patients, that found transcatheter edge-to-edge repair with MitraClip therapy was associated with improvement in both six- and twelve-month follow-up along with a reduction in mitral valve regurgitation, suggesting that the transcatheter approach may be beneficial. However, it should be noted that hemodynamic mitral valve stenosis developed in three of the fifteen patients, which further highlights the progressive nature of radiation valvulopathy [27].

6. Conduction System Disease

6.1. Incidence and Pathophysiology

Conduction system disease can result from a variety of mechanisms related to radiation. Radiation can result in direct inflammation and injury of the conduction system, or via fibrosis and ischemia of the surrounding myocardial tissue. ECG abnormalities were seen in up to 75% of patients who received chest radiation with a total dose of >40 Gy units [28]. Transient and asymptomatic arrhythmias may be seen briefly within the first year of therapy and usually are harmless, however permanent damage to the conduction system usually presents 10 years after RT completion [29]. It can present in a variety of ways, depending on which part of the conduction system is affected. Patients can have prolonged QT intervals, sinus node or atrioventricular node dysfunction, fascicular blocks, or even ventricular tachycardias. Right bundle branch blocks are more common than left bundle branch blocks

because the right-sided conduction system is anterior and more likely to be exposed to radiation [29]. Conduction system disease is estimated to affect 4–5% of patients with a history of radiation therapy, and often presents in conjunction with other types of radiation-induced heart diseases like cardiomyopathy and coronary artery disease [13].

6.2. Management

Patients who develop symptoms or evidence of conduction disease warrant the same workup as individuals without a history of radiation therapy. Patients should be referred to an electrophysiologist and ambulatory cardiac monitoring should be performed when arrhythmias are suspected. The management of conduction system disease, similarly to that of the general population, is dependent on the manifestation, and ranges from monitoring and receiving antiarrhythmic agents to device implantations or ablations.

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