Radiation-Induced Heart Disease

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Cancer incidence and survivorship have had a rising tendency over the last two decades due to better treatment modalities. One of these is radiation therapy (RT). Radiation to the heart is a common complication of RT, especially in patients with lymphoma, breast, lung, and esophageal cancer.

radiation therapy echocardiography cardiotoxicity heart disease

1. Introduction

The main goal of RT is to damage the genetic material of cancer cells, therefore inhibiting their growth and replication. This is accomplished by exposing the desired tissue to ionizing radiation which generates high-energy ions that deposit inside the cells, blocking their proliferation and/or inducing apoptosis [1]. One downside of this is the exposure of non-cancer “healthy” cells which suffer the same deteriorating effects. RT has improved over the years and now the number of healthy cells affected is significantly reduced; nevertheless, the risk of collateral damage to healthy tissues and organs is still an issue [2].

Radiation-induced heart disease (RIHD) is one of the major concerns when exposing patients to thoracic RT; this can occur years after treating diseases such as lymphoma, breast, lung, and esophageal cancer, to name the most frequent. Some of the increased risks of patients who receive RT when compared to the general population are the development of accelerated ischemic heart disease and valvular and pericardial disease [3][4].

2. Pathophysiology of RIHD

Traditional RT (photon beam) affects the heart via micro and macrovascular mechanisms [5] which can lead to valvular disease [6], pericardial disease [7], conduction abnormalities [8], cardiomyopathy [9], and accelerated coronary artery disease [10]. One of the most understood pathophysiologic mechanisms is the macrovascular damage associated with the earlier development of age-related atherosclerosis [11]. This phenomenon is explained by endothelial damage that RT generates in the coronary arteries [12] which, consequently, causes an inflammatory response that releases a large number of cytokines responsible for macrophage activation and deposition of lipoproteins [13]. A similar mechanism to the formation of atherosclerotic plaques is seen in traditional coronary artery disease but in an accelerated fashion [14]. One retrospective study, which included 2168 women who underwent RT for breast cancer, found that their risk for major coronary events was increased by 7.4%; this increment begins 5 years after receiving RT and continues for 30 years. The risk was also higher for patients who received left- vs. right-sided RT. This study also proved that the risk increases with preexisting cardiac risk factors

and higher radiation doses [10]. One systematic review, including six studies from 1996 to 2016, involved patients with low risk of CAD who received left breast/chest wall RT. Follow-up of the studies was limited to 6–12 months after RT. Four of these studies showed that cardiac exposure to radiation was associated with early myocardial perfusion defects [15]; these were mainly seen in the apical and anterolateral segments of the left ventricle (LV) and not associated with changes in the ejection fraction [16]. The same systematic review also proved that perfusion defects were strongly dose dependent and that patients who underwent cardiac radiation-sparing techniques, such as DIBH, had better outcomes [15]. In another study that included 7033 patients with Hodgkin disease who received chest RT, the risk for death from myocardial infarction was double when compared to the general population and it persisted for 25 years after treatment [17]. This risk was higher and independently associated in patients who were exposed to: (a) supradiaphragmatic total nodal RT (RR 9.0, CI 5.4–14.1), (b) mantle RT (RR 3.2, CI 2.3–4.2), (c) anthracyclines (RR 3.2, CI 1.9–5.2), and (d) vincristine (RR 2.0, CI 1.3–2.9) [17].

3. Risk Factors for Reaching the Threshold of RIHD

RIHD is associated with risk factors such as high radiation exposure, the use of other cardiotoxic medications (anthracyclines), prior history of heart disease, young age, and traditional cardiovascular risk factors. Patients who receive anterior left chest radiation were significantly associated with a higher risk of developing coronary heart disease (RR 1.29, CI 1.1–1.5) and cardiac death (RR 1.22, CI 1.08–1.37) when compared against those receiving right-sided RT [18]. High cumulative doses of radiation are associated with a higher risk of RIHD; one prospective study involving 2232 Hodgkin disease patients found that exposure to RT doses above 30 Gy increased their risk of cardiac mortality by 3.5-fold [19].

One study evaluated the risk of developing symptomatic congestive heart failure and myocardial infarction in 299 breast cancer patients who received chemotherapy +/− RT and then compared them against healthy controls from the Framingham epidemiologic study. The results showed that patients who received high doses (450 mg/m^2) of anthracyclines concomitantly with left-sided RT had a tenfold increased risk of developing these cardiac events [20]. Young age was also proven to increase the risk of developing RIHD [21]; a study that evaluated patients younger than 25 years old who received RT showed a 7.5 times increased risk of developing coronary artery disease [22]. The presence of comorbidities, such as preexisting cardiac disease, diabetes, hypertension, obesity, and hypercholesterolemia, have also been associated with a higher risk of developing RIHD [23][24]. Genetic mutations in genes responsible for DNA repair pathways have been associated with increased radiation sensitivity and a higher risk of adverse effects [25].

4. Screening

Based on the above, it is essential to screen patients at risk for radiation-induced heart disease (RIHD). The best methods and frequency remain uncertain. Although guidelines/expert consensus for its evaluation have been published, the assessment and monitoring of heart function is similar to the standard procedures and tests cardiologists use in other patient settings [5][26].

4.1. Pericardial Disease

Pericardial disease (effusion and/or constriction) is a common complication of RT; its clinical presentation can be classified into acute or chronic disease [27]. The acute phase occurs days to months after RT, while the chronic phase may develop months to years later. Before the implementation of new methods to deliver RT, the incidence of pericarditis post RT used to be around 70% in patients with carcinomas (breast, lung, and esophagus), Hodgkin disease, and non-Hodgkin lymphoma (Hodking and All B-cell type NHL) [7][28]. In the last decades, the incidence has decreased to 6–30% but remains as the most common complication of RIHD [29][30]. A detailed history with physical examination is important for its diagnosis, but it is nonspecific and often requires an ECG and/or imaging studies to be able to differentiate constrictive from restrictive disease. Imaging can also offer information on mimics of constrictive pericarditis, such as pericardial tamponade, restrictive cardiomyopathy, right ventricular infarct/failure, pulmonary embolism, acute mitral regurgitation, or severe tricuspid regurgitation, providing a more accurate diagnosis [27].

Evaluation

Echocardiography is the first-line imaging method to evaluate patients with suspected or confirmed pericarditis [31]. This is due to its high sensitivity to detect anatomical and hemodynamic changes, especially in constrictive disease [32]. Contrast-enhanced CT and late gadolinium enhancement CMR can be used as complementary methods when needed; they can provide information on pericardial thickening, edema, or fibrosis[33][34][35].

4.2. Myocardial Dysfunction

There are early complications of RT, such as inflammation, repolarization abnormalities, and mild myocardial dysfunction, but cardiotoxicity is more evident after 10 years, especially in patients who are exposed to doses above 30 Gy [36]. These chronic alterations include diffuse myocardial fibrosis with relevant systolic and diastolic dysfunction, conduction disturbances, and autonomic dysfunction [37]. All of them can contribute to LVEF abnormalities [26].

LVEF is an excellent predictor of myocardial systolic function; decreased values can be a surrogate of late cardiotoxicity. However, LVEF can be insensitive to detect subclinical or early myocardial dysfunction. These subclinical findings can be assessed with other methods such as 2D speckle tracking echocardiography (2D-STE) [38].

Evaluation

Echocardiography is essential to identify and monitor myocardial dysfunction. This method provides an accurate, fast, and noninvasive approach to measure LVEF and evaluate LV systolic and diastolic function [5][26][39].

LV systolic function: There are many techniques to evaluate the LVEF, but guidelines recommend using 2D volumes Simpson’s biplane methodology by echocardiography (a modality requiring area tracings of the LV cavity)

as the first choice [40]. Two-dimensional echocardiography can evaluate global systolic function, and a drop below its normal range (<50%) can reflect RIHD. Nevertheless, subtle changes associated with early cardiac involvement are difficult to assess; some studies have demonstrated that 2D-STE is a good screening method to detect early changes in myocardial mechanical function [41][42]. Two-dimensional speckle tracking echocardiography evaluates myocardial function by measuring cardiac deformation throughout the cardiac cycle. Strain is analyzed in three different spatial domains of contractility (longitudinal, circumferential, and radial) and its main benefit in RT is its capacity for detecting myocardial dysfunction even when the LVEF is normal [39][43]. Global longitudinal strain is widely recognized and used for this matter, while circumferential and radial strain are reserved for research purposes. Strain rate is a more comprehensive 2D-STE technique that is mainly used for research and evaluates the same three spatial domains during systole (SRs) and early (SRe) and late diastole (SRa).

LV diastolic function: The evaluation of LV diastolic function is an integral component of the standard echocardiographic examination. The identification of these changes in the early phase of RT may be relevant, especially in breast cancer patients who have other risk factors for developing heart failure or are being treated with cardiotoxic medications [44]. LV diastolic function can be assessed using traditional echocardiographic parameters such as mitral inflow, tricuspid regurgitant velocity, or tissue Doppler of the mitral annulus and left atrial volume [45]. However, some studies have shown that these parameters are not able to detect early diastolic disfunction post RT [46][47].

Some studies have shown that 2D-STE may play an important role in detecting early diastolic dysfunction by measuring abnormalities in the early diastolic (SRe) and late diastolic strain rate (SRa) [46][48][47].

Sritharan et al. included 40 women with left-sided breast cancer undergoing photon RT with doses between 42.4 to 50 Gy. The investigators evaluated the diastolic function of these patients by measuring their diastolic strain rates at baseline, during RT, and 6 weeks post RT. Authors found that SRe and SRa were significantly reduced (longitudinal SRe (s−1)1.47+/−0.32 vs. 1.29+/−0.27; longitudinal SRa (s−1)1.19+/−0.31 vs. 1.03+/−0.24; $p < 0.05$) when comparing baseline vs. 6 weeks post RT [47]. Another study, which included 50 patients with breast or other thoracic cancers, evaluated conventional echocardiographic parameters and 2D-STE to predict myocardial dysfunction in subjects who received either photon or proton RT. While normal echocardiographic parameters were not able to detect differences between the two therapies, 2D-STE global circumferential, longitudinal, and radial SRe was abnormal in patients who received photon vs. proton beam therapy which was present even after 1 year's follow-up [48]. These studies prove that early diastolic dysfunction is present after RT and that 2D-STE is a good tool to evaluate it.

4.3. Valvular Disease

Acute radiation effects in heart valves are commonly subtle, clinically less relevant, and challenging to assess. The incidence of radiation-induced valvular heart disease (RIVHD) is directly related to the dose of RT [49]. Additionally, RIVHD is time dependent; in a cohort of Hodgkin lymphoma patients, it was present in 1% at 10 years, 5% at 15 years, and 6% at 20 years [6]. Evidence suggest it is more common on the left side valves and changes consist of

leaflet thickening, fibrosis, and calcification. RIVHD described 20 years post RT included mild mitral valve regurgitation in up to 48% of patients, mild aortic regurgitation in 45%, moderate to severe aortic regurgitation in 15%, mild to moderate aortic stenosis in 16%, and mild pulmonary regurgitation in 12% [5].

Evaluation

Appropriate workup for patients with RIVHD includes a thorough clinical with physical examination and diagnostic testing.

Echocardiography is, again, the method of choice for the initial evaluation of these patients because it is highly sensitive in detecting any degree of valvular heart disease. It is also appropriate to evaluate for valvular thickening and calcification [50][51].

4.4. Coronary Artery Disease

RT has been shown to be related with an increased risk of ischemic heart disease in patients with breast cancer and Hodgkin disease [6][22][52]. This risk is related to the accelerated atherosclerosis seen in RT which was described previously. One study performed in breast cancer patients suggested that CAD may develop as early as 5 years post RT [10]. Because of this, is recommended to evaluate and screen these patients before they develop significant disease. Screening will depend on the time they underwent RT and the patient's risk factors.

Evaluation

The most useful methods to evaluate CAD include echocardiography, stress echocardiography, cardiac CT, CMR, and perfusion SPECT [53][54][55][56].

Echocardiography: Echocardiography is a valuable tool for assessing the cardiac structure and function in patients with coronary artery disease; it can determine the presence and extent of regional wall-motion abnormalities at rest which correlates well with CAD [54]. When this information is not sufficient to determine CAD, performing a test of inducible ischemia is recommended [57].

Stress echocardiography (exercise or dobutamine) has a low cost, minimal risk, and no exposure to ionizing radiation [58]. It is frequently used to evaluate patients for myocardial ischemia. It can recognize structural and functional alterations not evident at rest [59]; this method is highly sensitive and specific to detect abnormalities in the epicardial coronary arteries. Exercise testing is the recommended option because it can assess the physiologic functional performance. Heidenreich et al. included 294 asymptomatic patients with Hodgkin's disease treated with mediastinal irradiation (≥35 Gy). Stress echocardiography (exercise and dobutamine) was used to evaluate CAD in these patients at baseline, 2–10 years, 11–20 years, and >20 years post RT. They found a prevalence of CAD of 7.5% 15 years after RT. Stress echocardiography had a positive predictive value of 80% to detect severe three-vessel disease and 87% for left main CAD after Hodgkin disease. The study also found that the presence of resting

wall-motion abnormalities or ischemia on stress testing was associated with an increased risk of future cardiac events [53].

Coronary CT angiography has been used for follow-up in small groups of patients after RT for Hodgkin's disease. These studies demonstrated advanced coronary calcification and advanced obstructive CAD in relatively young patients [55][60]. It is unclear whether CT can distinguish general atherosclerotic CAD from lesions caused by RT. In the absence of symptoms of CAD, there are currently insufficient data to recommend routine use of coronary CT angiography in patients who underwent high-dose RT.

Cardiac magnetic resonance (CMR) offers precise visualization of anatomical structures, assessment of cardiac function, and characterization of myocardial tissue, all within a noninvasive imaging modality [56]. T1 mapping can detect diffuse myocardial fibrosis and follow its changes over time. A study evaluated CMR images acquired during rest, adenosine stress, and late enhancement in 31 Hodgkin survivors 20 years after receiving RT. They found that CMR could detect reduced LVEF, hemodynamically relevant valvular dysfunction, late myocardial enhancement, and perfusion defects in approximately 70% of patients [61].

Radionuclide imaging (SPECT and PET) provides information on myocardial perfusion and wall-motion abnormalities that can be useful to follow-up patients who received RT and have a high risk of CAD [62]. Marks et al. [16] evaluated 114 patients treated with RT for left-sided breast cancer. A SPECT scan was used to assess myocardial perfusion, regional wall motion, and EF. It was performed at baseline, 6, 12, 18, and 24 months after RT. SPECT was able to identify an increased incidence of perfusion defects over time (27% at 6 months, 29% at 12 months, 38% at 18 months, and 42% at 24 months). It also detected wall-motion abnormalities in patients with perfusion defects vs. patients with no perfusion defects ((12 to 40%) vs. (0 to 9 %) $p < 0.007$).

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