Review Article

Valvular Damage

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Abstract

Valvular heart diseases (VHD) may be observed in patients with cancer for several reasons, including preexisting valve lesions, radiotherapy, infective endocarditis, and secondary to the left ventricle dysfunction. The incidence of VHD is especially in younger survivors treated with thoracic radiation therapy for certain malignancies, such as Hodgkin's lymphoma and breast cancer. The mechanism of radiation-induced damage to heart valves is not clear and includes diffuse fibrocalcific thickening of the valve. VHD is commonly diagnosed after a long latent period, in the context of clinical symptoms, or suspected on the basis of a new murmur. The evaluation includes identification of anatomical valve abnormalities, valve dysfunction, and assessing the functional consequences of valve dysfunction on the ventricles. Echocardiography is the optimal imaging technique for diagnostic and therapeutic management. Cardiovascular magnetic resonance and computed tomography (CT) may be used to assess the severity of VHD, but cardiac CT is mainly useful for detecting extensive calcifications of the ascending aorta. Patients exposed to mediastinal radiotherapy and minimal valve dysfunction require follow-up of 2–3 years, with moderate valve disease yearly, with severe, should be assessed for valve surgery.

Keywords: Anthracycline, breast cancer, echocardiography, Hodgkin's lymphoma, mediastinal radiotherapy, valvular heart disease

Epidemiology

Although the prevalent cardiologic complication in oncologic patients is represented by systolic dysfunction and heart failure, valvular heart disease (VHD) occurs in many cases, especially as a late cardiotoxic effect of radiation therapy, which incidence is estimated near to 10% of treated patients.[1] Hemodynamically significant (> moderate) valve disease is more common >10 years' following radiation.[2]

It has been known since the 1960s that valve dysfunction can be caused by cancer therapy. VHD incidence is increased following cardiac irradiation,[3] but recent studies suggest that radiation-induced heart disease (RIHD) is decreasing, probably due to changes in radiation techniques.[4] Regarding chemotherapy, it has recently been reported that patients treated with anthracycline and aromatase inhibitors are at higher risk of developing cardiovascular diseases other than heart failure, such as VHD.[5]

Valvular disease induced by cancer therapy is still the subject of research to fully understand its pathogenesis and its ideal management. Its main characteristics are shown in Table 1.[6]

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Due to the latency of the presentation of valvular dysfunction, the diagnosis is delayed and more often incidental, and most of the studies that explore radio and VHD chemotherapy have been retrospective and observational.

Etiopathogenesis

VHD may be observed in patients with cancer for several reasons, including preexisting valve lesions, radiotherapy, infective endocarditis, and secondary to the left ventricle (LV) dysfunction.[1]

Radiation-induced valvular heart diseases

Radiotherapy has helped reduce the mortality rate of some cancers over the past 60 years. In patients with Hodgkin's lymphoma (HL), when combined with chemotherapy, radiotherapy improved survival by almost 60%.[7] In patients with breast cancer, relapse rates decreased by about half, resulting in a 15-year survival of 60%.[8] Radiotherapy is

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Table 1: Key features of therapy-induced valvular heart diseases

No immediate apparent effects
Valve disease incidence increases significantly after >20 years following irradiation: mild AR up to 45%,> moderate AR up to 15%, aortic stenosis up to 16%, mild mitral regurgitation up to 48%, mild pulmonary regurgitation up to 12%
Valve apparatus and leaflet thickening, fibrosis, shortening, and calcification predominant on left-sided valves (related to pressure difference between the left and right side of the heart)
Valve regurgitation more commonly encountered than stenosis. Stenotic lesions more commonly involving the aortic valve
Some studies suggested a higher incidence and prevalence in women

AR=Aortic regurgitation

also useful for other cancers such as metastatic testicular, pulmonary, or esophageal. Unfortunately, the radiation field involved often covers portions of the heart and probably induces cardiac damage.

Recent screening studies in HL survivors have reported that 32% of those given mediastinal irradiation developed asymptomatic valvular defects after 6 years,[9] while at 20 years, 42% had imaging evidence of valvular dysfunction.[10]

Radiation-induced VHD is an increasingly recognizable entity that occurs late after mediastinal radiotherapy, affects 10% of treated patients, with a mean diagnosis time of 22 years, while a minority of patients has a complete normal function of aortic valve (AV) at the follow-up at 20 years.[11,12]

The mechanism of valve damage is unclear. It is caused by exposure to radiation of the cusps and leaflets of heart valves, which undergo fibrotic alterations through the proliferation of fibroblasts and the increase of collagen synthesis. The increase in the formation of osteogenic factors, therefore, induces osteogenesis that causes calcification of the valve [Figure 1].

This cannot be explained by microvascular changes, as we can do with other RIHD because the valves are largely avascular. Left-sided valves are more commonly affected by radiation exposure than right-sided valves; this fact suggests that higher systemic pressure plays a role in the pathogenesis.[4]

The earliest change appears to be the formation of valvular retractions and accompanying regurgitation preferentially involving the MV and AV, occurring within the first 10 years.[13-17]

In a postmortem analysis, up to 81% of patients who received at least 35 Gy to heart showed evidence of valvular dysfunction and fibrosis. Specimens revealed focal thickening of the valvular endocardium by elastic fibers.[18] Veinot and Edwards conducted a study with multiple cardiac tissue specimens, in which the majority of patients had radiotherapy-related VHD with a mean dose of 46 Gy after a significant latency period, developing cusps or leaflets fibrosis, without changes indicative of chronic inflammation or neovascularization, thus confirming other radiotherapy-related mechanisms that induce valvular pathology.[14]

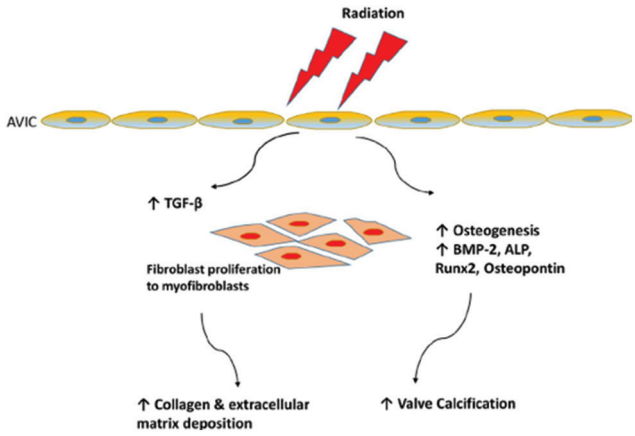

Figure 1: Radiation exposure of aortic valve interstitial cells (AVICs), causes upregulation of tissue growth factor-β and osteogenic factors (bone morphogenetic protein-2, osteopontin, alkaline phosphatase, and the transcription factor RUNX2, leading to fibrosis and valve calcification Gujral *et al.*[33]

The natural history of VHD varies with radiation dose and the decade in which the patient was treated. This has recently been shown in a cohort of 1852 survivors of LH in the Netherlands. Thirty-year cumulative risk of VHD stratified by the radiation received was 3%, 6%, 9%, and 12% for total radiation <30 Gy, 31–35 Gy, 36–40 Gy, and >40 Gy, respectively. For patients with mediastinal involvement currently treated with 20 or 30 Gy, the absolute difference in 30-year VHD risk in irradiated versus nonirradiated patients was 1.4%.[3] Another study of survivors irradiated with obsolete protocols between 1965 and 1995 revealed 13- and 30-year cumulative incidences of 10% and 20%, respectively. Prior history of radiation increased the risk of VHD 7-fold.[19]

Wethal *et al*. showed how the progression to fibrotic thickening and calcification of the valves occurs much later, in particular, the stenosis, which often appearing 20 years after radiation.[20] These results confirmed that valve retraction is the predominant early change that causes regurgitation, and after a longer latent interval, the valves become significantly thickened, calcified, and stenotic. Multiple studies have supported the higher incidence of AV and MV disease, probably due to high pressure on the left side.[20-22]

Consistent with these observations, another study found that 6% of asymptomatic patients previously treated with >35 Gy of radiation, 6% had clinically significant dysfunction, and 26% had > Grade II aortic regurgitation. This is equivalent to a 34-fold increased risk compared to the Framingham population. Furthermore, 26% demonstrated a marked calcification of the aortic-mitral curtain.[20]

Radio- and chemo-therapy combination and valvular damage

The use of sequential chemotherapy is one of the factors linked to the development of radiation-induced VHD [Table 2]. The combined risk of radiation and chemotherapy for the

development of VHD is greater and increases for the older patients, regardless of follow-up duration.

Several studies in patients with HL showed that if >63% of the left atrium received 25 Gy or if >25% of the LV received 30 Gy, this predicted development of AV or MV disease and the risk of valve defects increase as the percentage volume of heart chambers receiving 30 Gy.[23]

van Nimwegen *et al*., in a retrospective study recording cardiovascular events in 2524 patients exposed to HL treatment with mediastinal radiotherapy and anthracycline, showed that the cumulative incidence of any type of cardiovascular disease was 50% at 40 years after diagnosis, for cardiac heart disease (CHD) and VHD as first events were 22.9% and 25.9%, respectively, and that the risk of any VHD event Hazard Ratio (HR 5.2), increased with a higher prescribed mediastinal radiation dose. Similarly, anthracycline-containing chemotherapy was associated with increased risks of VHD (HR, 1.5) in a dose-dependent manner.[24]

Three other studies have examined the relationship between VHD and RT for HL, confirming this association and its growth with higher doses.[10,25,26]

An association between anthracyclines and VHD has been observed,[19,27] but its pathophysiologic mechanism is not yet clear. It has been supposed that the combination of anthracycline-containing chemotherapy with dilation of the ventricles may cause valvular dysfunction, or that anthracyclines damage the papillary muscles of the valves, leading to valvular regurgitation.[28] Anthracyclines may also have a direct toxic effect on the valves, and not simply functional regurgitation related to cardiomyopathy and ventricular dilatation, causing more often AV degeneration than MV.[29]

Diagnosis

Radiation-induced VHD is commonly diagnosed after a long latent period, in the context of clinical symptoms of heart failure that valve insufficiency is either contributing or suspected VHD on the basis of a new murmur.

Table 2: Risk factors for radiotherapy-induced valvular heart diseases

Risk factors	Critical
Increase the dosage of radiation	The risk of developing VHD increase at radiation dose increased with a linear pattern between 30 and 40Gy
Interval from irradiation	Progressive increase in the development of VHD over time
Left-sided breast cancer	Radiation of heart area
Combination with anthracycline-based chemotherapy	Anthracycline-containing chemotherapy increase the risk of VHD in patients receiving mediastinal radiotherapy
Decade in which the patient was treated	Effects of obsolete protocols used between 1965 and 1995

VHD=Valvular heart diseases

The evaluation includes identification of anatomical valve abnormalities, valve dysfunction, and assessing the functional consequences on the ventricles. Echocardiography is the optimal imaging technique for noninvasive diagnostic evaluation and therapeutic management of cancer-therapy induced cardiac diseases, providing detailed information about LV systolic and diastolic dysfunction, myocardial damage, pericardial, and valvular disease.[30,31]

Systematic assessment of radiation-induced valvular heart diseases by cardiac imaging

Transthoracic echocardiography is considered the gold standard for diagnosis and follow-up of VHD after radiation therapy involving the heart. Nevertheless, transesophageal echocardiography, cardiovascular magnetic resonance, and computed tomography [Figure 2] could provide an added value in some cases.[32] The advantages of each technique are summarized in Table 3.

The criteria for diagnosis do not differ from that used for traditional degenerative valvular pathology, and early echocardiographic findings are characteristic but nonspecific [Figure 3]. Diffuse thickening of valve leaflets and subvalvular apparatus may occur without functional abnormality, but there are several unique characteristics of radiation-induced damage [Table 4].[6]

The characterization of the damage

Left-sided valves are affected preferentially over right-sided valves, particularly AV. Moderate or severe aortic, mitral, tricuspid and pulmonary regurgitation are showed in 15%, 4.1%, 4.1%, and 0% of patients, respectively, and aortic stenosis in 16% of patients who were irradiated >20 years previously compared with <0.5% of age-matched and sex-matched controls.[33]

Typically, the valves become thickened and restricted as collagen is deposited and ultimately calcified. The restriction leads first to regurgitation and then can progress to stenosis if severe. Focal calcification of the valve leaflet/cusps involving the aortic-mitral curtain, classically affected with gradual thickening extending all the way from the MV to the aortic root, can be seen easily on parasternal windows [Table 5].[34]

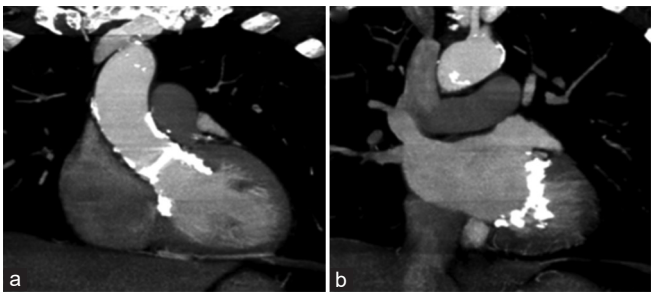

Figure 2: Cardiac computed tomography images from a 56-year-old man, 27 years' postmantle irradiation for Hodgkin's disease. Images demonstrate calcified aorto-mitral curtain and aorta (a), and mitral valve annulus (b)

Table 3: Utility of different imaging techniques for radiation-induced - Valvular heart diseases evaluation

Technique	Utility
TTE	Widespread availability, feasibility, lack of radiation exposure, and acquisition of additional cardiac imaging information (systolic and diastolic function, valvular, pericardial, and hemodynamic data) make TTE the methodical of choice for baseline and repeated evaluation after radiation therapy
Transesophageal echocardiography	Adds important information, especially when significant calcification or fibrosis is present and limits transthoracic image quality
3-Dimensional echocardiography	Accurate evaluation of mitral valve morphology
CMR	Useful in those with suboptimal echocardiography or results are incomplete or discrepant and for the assessment of myocardial fibrosis
CT	Preferred for detection of extensive calcifications of the ascending aorta, which may lead to a higher operative risk and sometimes prohibit conventional cardiovascular surgery

TTE=Transthoracic echocardiography, CMR=Cardiovascular magnetic resonance, CT=Computed tomography

Table 4: Factors conditioning the onset of radiation-induced heart diseases

Total radiation dose >30-35 Gy
Dose of radiation fraction/day >2 Gy
Amount and areas of the heart treated
Presence of tumor within or adjacent to the heart
Left-sided tumors
Younger age at exposure
Use of concomitant cardiotoxic chemotherapeutic drugs (e.g., anthracyclines, trastuzumab)
Type of radiation source (cobalt) and technique (reduced with CT plane)

CT=Computed tomography

Radiation-induced diffuse valvular thickening is similar to rheumatic mitral disease, but unlike rheumatic valve disease, there is a lack of commissural fusion. The two can be distinguished on three-dimensional echocardiography [Figure 4] by the loss of the commissural fissure that is characteristic of rheumatic disease but not seen with radiation VHD.[35]

Indications for Management

The pivotal role of follow-up

The European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend a focused yearly history and physical examination with echocardiography in symptomatic patients; screening transthoracic echocardiogram at 10 years postradiation for asymptomatic patients, and serial exams every 5 years thereafter in patients with normal valves.[30,32]

Echocardiography is considered the best option for serial imaging,[31,35] and it has been chosen as a reference method for most of the scientific researches on cancer therapy-induced VHD. Heidenreich *et al*. observed that >60% of patients irradiated for HL >20 years earlier had echocardiographic signs of valvular regurgitation, rarely identified by physical examination.[21]

An increased risk of left-sided, particularly AV, valvular regurgitation, was found even by Lund *et al*., in 129 patients

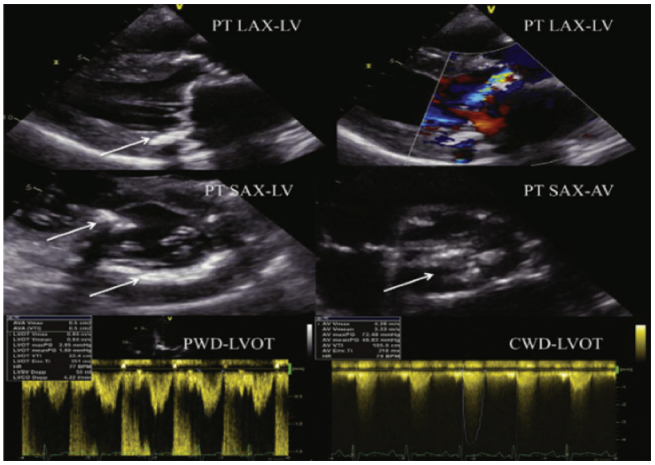

Figure 3: Echocardiographic analysis of a patient with radiation-induced valvular heart disease. Extensive calcifications of the aortic and mitral valve (arrows) and the left ventricle. Significant aortic stenosis and regurgitation

with HL treated with high-dose mediastinal radiation therapy.[22] After a mean follow-up of 9.5 years, the morbidity of VHD was about 2.8%–2.9% in women who had undergone adjuvant radiotherapy for breast cancer.[36]

In a population of 305 patients treated with a high cumulative dose of anthracycline that varied for childhood malignancy, color flow Doppler detection of mitral regurgitation was evident in 11.6% of patients, compared to only 1.8% of a normal population of similar age.[28]

Surveillance monitoring is paramount because the timing of medical or surgical intervention can be crucial for optimal patient outcomes. Most late cardiovascular sequelae of thoracic irradiation, including valvular pathology and its consequences, can be accurately assessed by combined rest and stress echocardiography. When possible, this approach should be chosen over a stress thallium/methoxyisobutylisonitrile for the radiation-free and functional advantages.[37,38]

Gujral *et al*. proposed an algorithm for a practical follow-up of patients exposed to mediastinal radiotherapy,[33] as shown in Figure 5.

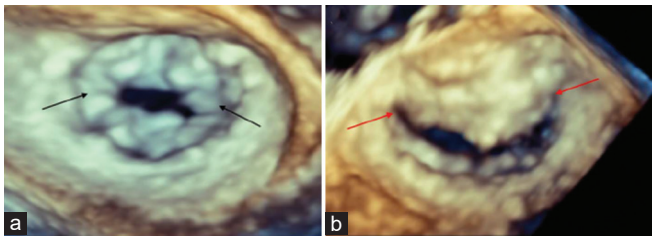

Figure 4: Three-dimensional transesophageal echocardiogram demonstrating the difference between rheumatic valve disease and radiation-induced valve disease. (a) Rheumatic mitral valve with bilateral commissural fusion (black arrows). (b) In contrast in radiation-induced valve disease, there is no commissural fusion (red arrows)

Evidence about treatment

There are no specific guidelines for the timing of surgery in patients with radiation-induced VHD; therefore, this should be performed according to the current international guidelines for VHD.

AV replacement is the most common procedure in these patients, though mitral and tricuspid valve disease may also require intervention. Cardiac surgery is also frequently challenging in such patients because of mediastinal fibrosis, impaired wound healing, and associated CHD. Therefore, patients should be referred to a center with more experience in operating on these patients.

Crestanello *et al.* examined whether conventional reparative techniques could be applied to irradiation-related VHD. They reported that 32% of previously irradiated patients who underwent mitral and/or tricuspid valve repair experienced severe valve deterioration, probably due to the progression of radiation-induced tissue injury. In light of these findings and the known dangers of reoperation in this cohort, the authors concluded that the replacement of the mitral and tricuspid valve may be superior to repair in these patients.[39]

Accordingly, over the past years, transcatheter AV implantation (TAVI) has proven equal or superior to surgical valve replacement in high-risk patients. In the PARTNER Registry, approximately 5% of patients enrolled had a history of prior chest wall radiation, with initial favorable results.[40] In some cases of severe aortic stenosis with significant extracardiac late sequelae of radiotherapy, TAVI might be the best treatment option considering long-term cardiovascular outcome.

Recent guidelines on VHD management suggest that in patients who are at increased surgical risk (STS or EuroSCORE II >4% or logistic EuroSCORE I >10% or other risk factors such as frailty, porcelain aorta, or sequelae of chest radiation), the decision between surgical AV replacement and TAVI should be made by the heart team according to the individual patient characteristics.[41]

New tools for prevention of radiation-induced cardiac damage

Long-term cardiac injury after radiation treatment depends on several factors, as shown in Table 4.

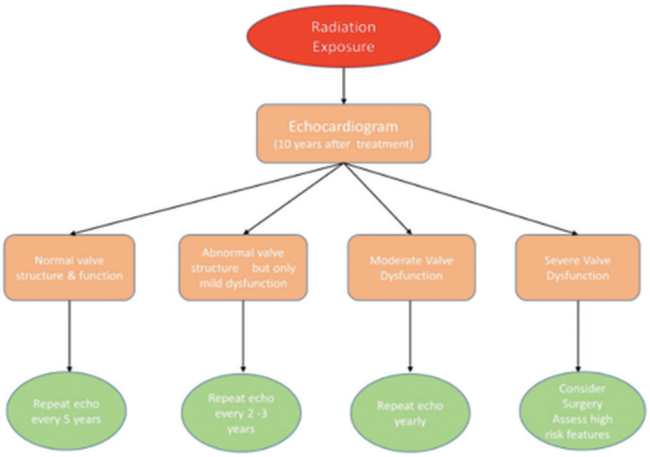

Figure 5: Following this algorithm, patients exposed to mediastinal radiotherapy with structurally abnormal valves (calcification/thickening), but minimal valve dysfunction, require follow-up 2–3 years, patients with moderate valve disease yearly, patients with severe valve dysfunction should be assessed for valve surgery

Table 5: Echocardiographic characteristics of radiation-induced valvular heart diseases

Fibrosis and calcification of the aortic root, aortic valve annulus, aortic valve leaflets, aortic-mitral curtain, mitral valve annulus, and the base and mid-portions of the mitral valve leaflets, contiguous, or randomly dispersed
Uniform valvular thickening from fibrosis
Aorto-mitral curtain thickening
Left-sided valves >right-sided valves; particularly aortic valve
Regurgitation prior to stenosis
Preservation of mitral commissural fissures

Radiotherapy techniques have evolved over the past few decades. Techniques to reduce radiation dose to normal tissues and/or the radiotherapy field size have emerged. New techniques, including intensity-modulated radiotherapy and proton therapy, are better able to spare normal tissue by improving conformity to target structures. The optimal field size and technique and respiratory gating depend on the individual patient characteristics, including tumor size, location, and nodal involvement and the use of individualized therapy could minimize normal tissue toxicity and long-term complications.[42]

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Conflicts of interest

There are no conflicts of interest.

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