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
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%.

阀叶器质和叶瓣增厚、纤维化、缩短，钙化倾向左侧心脏。

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, while at 20 years, 42% had imaging evidence of valvular dysfunction.

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.

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.

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.

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. 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.

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 HL 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%.

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.

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 irradiation. 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.

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.

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.[22]

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.

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]

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**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

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**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)
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.\textsuperscript{[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.\textsuperscript{[30,32]}

Echocardiography is considered the best option for serial imaging,\textsuperscript{[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.\textsuperscript{[21]}

An increased risk of left-sided, particularly AV, valvular regurgitation, was found even by Lund et al., in 129 patients with HL treated with high-dose mediastinal radiation therapy.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[37,38]}

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

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

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