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PERICARDIAL DISEASE (AL KLEIN AND CL JELLIS, SECTION EDITORS)

Radiation-Associated Pericardial Disease

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Abstract

Purpose of Review This review highlights the literature related to pericardial injury following radiation for oncologic diseases.

Recent Findings Radiation-associated pericardial disease can have devastating consequences. Unfortunately, there is considerably less evidence regarding pericardial syndromes following thoracic radiation as compared to other cardiovascular outcomes. Pericardial complications of radiation may arise acutely or have an insidious onset several decades after treatment. Transthoracic echocardiography is the screening imaging modality of choice, while cardiac magnetic resonance imaging further characterizes the pericardium and guides treatment decision-making. Cardiac CT can be useful for assessing pericardial calcification. Ongoing efforts to lessen inadvertent cardiac injury are directed towards the revision of radiation techniques and protocols.

Summary As survival of mediastinal and thoracic malignancies continues to improve, radiation-associated pericardial disease is increasingly relevant. Though advances in radiation oncology demonstrate promise in curtailing cardiotoxicity, the long-term effects pertaining to pericardial complications remain to be seen.

Keywords Pericardial disease · Radiation · Pericardial effusion · Constrictive pericarditis

Introduction

Treatment of oncologic disease has evolved considerably over the past few decades, and contemporary techniques are associated with both reduced toxicity and improved survival. Nonetheless, patients who received older regimens are vulnerable to treatment-induced complications later in life, and even patients who undergo modern, more refined methods remain susceptible to long-term sequelae. Radiation therapy is a cornerstone in the management of mediastinal and thoracic malignancies. While it enhances outcomes associated with these diseases, it is accompanied by vicious latent toxicity and mortality [1]. Of all cardiac structures, including the coronary arteries, myocardium, and conduction system, the pericardium has historically been the most commonly involved [2]. However, despite being one of the most pathognomonic forms of radiation-induced heart disease, it is among the least well-studied; existing literature is hindered by short-term follow-up and small sample sizes. With the growth of the cancer survivor population, it is imperative to maintain a shrewd awareness of pericardial complications, which may manifest clinically many years after radiation therapy. This review will focus specifically on the effect of radiation on the pericardium and its resultant pathologies and provide a practical approach to diagnosis and management.

Risk Factors

Malignancies for which radiation may unavoidably encompass the heart include mediastinal lymphoma, especially Hodgkin's disease, as well as breast, esophageal, and lung cancer. Radiation-induced pericardial complications occur at an estimated rate of 10%, but it can be as high as 50% in certain cancer populations [3, 4]. Pericardial injury may be acute or chronic in nature. Chronic pericardial disease presents in the order of decades following treatment, and, therefore, it is observed more often in malignancies with a younger age distribution and longer disease-specific survival. Neoplasms that fit this profile in particular include Hodgkin's disease and

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breast cancer, and the majority of robust evidence regarding the long-term cardiotoxicity of radiation therapy is derived from these disease sites [1, 5]. An important caveat is these long-term outcomes may not necessarily be applicable to current oncology patients given these data were obtained from regimens now considered antiquated. Even so, there are several known risk factors for radiation-induced pericardial disease, and their recognition has provided incentive to modify radiation protocols. These risk factors are broadly subdivided into radiation factors and patient factors (see Table 1).

Radiation Factors

Total Cardiac Dose > 30 Gray

One of the earliest risk factors identified for pericardial disease was high radiation dosage. In 1981, Brosius et al. examined autopsies from 16 patients aged 15–33 years who received cumulatively greater than 35 Gray (Gy) irradiation for mediastinal lymphoma and reported that 15 had evidence of thickened pericardia, 5 of whom also had cardiac tamponade [6]. The implication of radiation dose in pericardial complications has since been corroborated in numerous studies involving other disease sites [1, 7]. Pericardial effusions, primarily reported in esophageal cancer patients, occur at a rate between 4 and 9% when cardiac doses are > 30 Gy [1, 8, 9]. More specifically, symptomatic pericardial effusions usually occur with doses > 40 Gy [10]. Likewise, lung cancer patients who have received similar doses have a two-fold increase in risk of pericardial effusion [10]. Unfortunately, curative radiation doses usually exceed those associated with pericardial complications [11]. To date, there has not been a minimum radiation dose established as safe for the heart, but it appears that the risk of pericardial injury increases with higher doses [12].

Table 1 Factors associated with radiation-induced pericardial syndromes

Radiation factors
Total cardiac dose > 30 Gy
Daily dose fraction > 2 Gy/day
Volume of irradiated pericardium or myocardium
Lack of shielding or blocking
Relative weighting of radiation portals
Patient factors
Tumor location close to heart border
No known association or evidence lacking Younger age
Increased time since radiation exposureConcurrent chemotherapy
Pre-existing cardiac risk factors
Baseline cardiac disease

Daily Dose Fraction > 2 Gy/Day

In the field of radiation oncology, the total dose of radiation received by a patient is usually divided into multiple, smaller doses termed "fractions." As expected, greater fraction size is a risk factor for pericardial toxicity. Martel et al. found that in patients with esophageal cancer, pericarditis occurred exclusively in patients who had received a dose of 3.5 Gy per fraction, suggesting that large fraction size is a significant risk factor for pericarditis [13]. As a result, the recommendations are that dose-per-fraction to the heart not to exceed 2.0 Gy [13]. There is few data regarding chronic pericardial injury related to fraction size. Among Hodgkin's disease patients who underwent radiation between 1971 and 1984, there was a trend towards higher 5-year cumulative incidence rates of pericarditis with increased fraction size; however, this was not statistically significant [12],

Volume of Irradiated Pericardium or Myocardium

The effect of parameters beyond simple measures of radiation dose or fraction size has also been evaluated. Among left-sided breast cancer patients, the maximum heart distance in the field of treatment, measured anterior to posterior, is a simple and reliable predictor of mean heart dose [14]. Wei et al. also examined dose–volume histogram parameters of both the heart and pericardium in a retrospective study of 101 patients with esophageal cancer. Heart volume in excess of 46% exposed to > 30 Gy was associated with a 73% rate of pericardial effusion, compared to 13% when less than 46% of heart volume was exposed to > 30 Gy. Pericardial volume exposed to greater than 3 to 50 Gy was also associated with pericardial effusion [3].

Lack of Shielding and Relative Weighting of Radiation Portals

Cardiac structures may be exposed to radiation either directly or indirectly via scatter radiation. Shielding, also known as blocking, is a strategy employed to protect cardiac structures, and its absence is a risk factor for pericardial disease. In a cohort of 377 Hodgkin's disease patients, the rate of pericarditis observed with irradiation of the entire pericardium was 20%. With left ventricle shielding, this rate was decreased to 7%, and with subcarinal block, it was further reduced to 2.5% [15]. Relative weighting of anterior and posterior irradiation portals, which manipulates the dose of radiation administered to various depths of the heart, also affects the rate of pericarditis. The reduced rate of pericarditis to 2.5% in the aforementioned study was also achieved by equally weighing anterior and posterior fields [15].

Patient Factors

Tumor Location Close to Heart Border

As anticipated, tumor location is an important factor in the amount of inadvertent radiation exposed to the heart. Neoplasms adjacent to the heart may limit the ability to shield the heart and exclude it from the radiation field, while still delivering adequate doses to the appropriate target.

A retrospective analysis of 44 patients with non-small cell lung cancer and tumor within 6 cm of the heart treated with stereotactic radiation demonstrated that lower lobe tumors and central tumor location were associated with higher cardiac doses, as compared to upper lobe tumors and peripheral tumor location. Overall, the distance between the tumor and the heart was associated with the mean heart dose [16]. Of note, this particular study examined cardiac events which included heart failure and arrhythmias but not pericardial outcomes.

In the breast cancer patient population, tumor laterality also influences the cardiac dose and the risk of pericardial complications. In a large, well-known cohort of 35,000 Danish and Swedish breast cancer patients treated with radiotherapy, the mean dose in patients with left-sided breast cancer was greater than 5 Gy, while those with right-sided breast cancer received a cardiac dose ranging between 2 and 4 Gy. Notably, there was a 1.6 (confidence interval [CI] at 1.06–2.43)-fold greater likelihood of pericarditis associated with left-sided versus right-sided tumors [5]. Pericarditis in both left and right breast cancer patients was primarily acute, whereas chronic pericarditis was observed in smaller numbers. A different study demonstrated, from among 175 patients who received adjuvant concomitant treatment with radiotherapy and trastuzumab, that more left breast cancer patients experienced pericardial effusions (9 [11%]) than right breast cancer patients (1 [1%]) [17]. Overall, the risk of radiation injury is highest in Hodgkin's lymphoma, followed by left-sided breast cancer, and then right-sided breast cancer [18].

No Known Association or Evidence Lacking

Younger Age and Increased Time Since Radiation Exposure

It is unclear whether younger age at time of radiation exposure or increased time interval since radiation exposure increases predisposition to pericardial complications, as the effect of age has been studied more extensively in the context of other radiation-related cardiac complications. Hancock et al. reviewed the records of 635 patients under 21 who received thoracic radiation for Hodgkin's disease between 1961 and 1991 and reported that 40 patients experienced acute pericarditis and 12 patients required pericardiectomy for severe constrictive pericarditis. It is important to recognize that many of these patients were treated with minimal to no cardiac blocking, and radiation techniques have changed substantially since this study was published [19]. The same group found that death from non-ischemic cardiac diseases, an endpoint which consisted of the aggregate mortality from valvular heart disease, congestive heart failure, pericarditis or pancarditis, and cardiomyopathy, was considerably higher among patients who underwent thoracic radiation for Hodgkin's disease during the first three decades of life [20].

Concurrent Chemotherapy

There is relatively minimal data regarding the effect of concurrent chemotherapy on pericardial complications in patients who have received thoracic irradiation. To date, investigations pertaining to the impact of chemotherapy have focused on other cardiac outcomes, such as ischemia and heart failure, rather than pericardial syndromes, and existing studies are limited by small cohorts. From a practical standpoint, isolating the effect of chemotherapy is challenging in treatment regimens where both chemotherapy and radiation are used synergistically. One large retrospective analysis of 14,358 adult survivors of various childhood and adolescent cancers examined the independent effects of cardiac radiation exposure, anthracycline dose, and exposure to other chemotherapy agents on cardiac outcomes using an adjusted multivariable model. This group reported that pericardial disease was independently associated with exposure to an anthracycline dose of 250 mg/m^2 or more and exposure to any dose of cyclophosphamide [1].

The effect of chemotherapy in specific populations, such as lung and esophageal cancer patients, has been studied with conflicting results. In a recent clinical trial examining radiation therapy versus proton therapy in 201 non-small cell lung cancer patients, receipt of adjuvant chemotherapy was associated with the development of radiation-induced pericardial effusion (hazard ratio [HR] at 2.82 (CI 1.71–4.65)) [21]. However, Xue et al. found that the incremental risk of pericardial effusion following chemotherapy in the setting of radiation was of only borderline significance in 94 non-small cell lung cancer patients [7]. Among patients with esophageal cancer, concurrent radiation and chemotherapy with cisplatin-based or 5-fluorouracil-based regimens did not increase the risk of pericardial disease as compared to radiation alone [3, 22]. Additional studies are needed to more precisely determine whether chemotherapy plays a role in priming the pericardium to injury from radiation or vice versa.

Pre-Existing Cardiac Risk Factors and Baseline Cardiac Disease

Though pre-existing cardiac disease and cardiac risk factors, including hyperlipidemia and diabetes mellitus, are known to increase the risk of other types of radiation-induced heart disease, such as coronary artery disease and heart failure after thoracic irradiation [1], these patient characteristics do not influence the risk of pericardial disease. Ning et al. studied a non-small cell lung cancer population and did not find that a history of smoking, diabetes, or pre-existing heart disease affected the risk of development of pericardial effusion after radiation [21]. Xue et al. also concluded that smoking status and cardiovascular disease did not influence incidence of pericardial effusion following radiation in lung cancer patients [7].

Clinical Features

Radiation causes a spectrum of pericardial irritation which can be acute or chronic in nature.

Early Acute Pericarditis

Early acute pericarditis is rare. Rather than a direct toxic effect on the heart, this form of pericardial injury has been postulated to occur when radiation incites inflammation and necrosis of tumor located adjacent to the heart [23]. However, in animal studies, acute inflammation of the pericardium has been observed within 6 to 12 h in rabbits who received high-dose radiation in the absence of tumor adjacent to the heart [24]. Therefore, it is possible that early acute pericarditis may be precipitated by both tumor necrosis in close proximity to the pericardium and radiation injury to the pericardium itself. Clinically, the timing of early acute pericarditis usually coincides with ongoing radiation or occurs shortly thereafter. Its clinical presentation is similar to other forms of acute pericarditis and can include pleuritic chest pain, electrocardiographic findings of diffuse ST changes and PR depression, pericardial friction rub, tachycardia, and fever. It may also be complicated by the development of a pericardial effusion [25]. Given its relatively benign implications, as well as the importance of continuation of therapy in order to better treat or eradicate malignancy, acute pericarditis does not preclude resumption of radiation.

Chronic Pericardial Diseases

The pathophysiology underlying the late forms of pericardial injury caused by radiation is related to the formation of pericardial fibrosis and neovascularization in response to episodic microvascular and macrovascular ischemia [26]. The parietal pericardium is affected to a greater extent than the visceral pericardium and undergoes subsequent thickening with loss of compliance. In tandem with fibrous deposition, there is also collagen production by fibroblasts, which replaces adipose tissue that normally comprises the external layer of the parietal pericardium. Eventually, there is development of adhesions between the visceral and parietal pericardium [23].

Delayed Pericardial Effusion

One of the delayed complications of radiation therapy includes chronic pericardial effusion. Microvascular damage from radiation can impair the ability of the venous and lymphatic system of the heart to drain fluid, resulting in a pericardial effusion of either hemorrhagic or serous composition with a fibrin-rich exudate [25]. Due to its gradual development which allows for the pericardium to adapt by stretching, delayed pericardial effusion almost universally presents as a hemodynamically inconsequential finding. Among esophageal cancer patients, the incidence is as high as 50% and the majority of cases are asymptomatic [21]. Rarely, it presents with instability due to cardiac tamponade from diminished diastolic filling and cardiac output. Chest X-ray may demonstrate an enlarged cardiac silhouette, and electrocardiogram may show low QRS amplitude. The timing of onset varies, and there may be a long period of latency. In 81 patients with Hodgkin's lymphoma in 1975, 24 (29.6%) were found to have satisfied X-ray criteria for pericardial effusion, primarily in the first 12 months following radiation [27]. Among patients with locally invasive inoperable esophageal cancer undergoing radiation therapy, pericardial effusion was observed 1 to 17 months post-radiotherapy with a median time to onset of 6 months [3]. Regardless, it is likely that silent pericardial effusions are common during and immediately following radiation therapy.

Chronic Pericarditis

Chronic pericarditis is the most clinically problematic form of radiation-induced pericardial disease and includes constrictive pericarditis and effusive-constrictive pericarditis. Among patients who received mediastinal radiation during childhood for Hodgkin's disease, constrictive pericarditis was reported to occur at an incidence of 7% [28]. In a different retrospective review of patients with constrictive pericarditis related to radiation, the majority of cases were related to Hodgkin's disease (9/15) [29]. Risk of constrictive pericarditis in patients with Hodgkin's lymphoma nowadays has likely declined with less cardiac exposure in modern radiation protocols.

Constrictive pericarditis results from progressive fibrosis and collagen deposition that causes loss of compliance and stiffening of the pericardial sac. Also called delayed pericarditis, it may develop insidiously months or years after radiotherapy. Constrictive pericarditis is seen in approximately

20% of patients who experience acute pericarditis [23]. Patients with radiation-related constrictive pericarditis present with symptoms similar to other etiologies of constrictive pericarditis, namely right-sided congestion. These include jugular venous distention, weight gain, chest pain, and exertional dyspnea [30]. On physical examination, common findings include ascites, pleural effusions, hepatomegaly, lower extremity edema, Kussmaul sign, and pericardial knock [31]. Electrocardiogram may show tachycardia with or without low-voltage QRS complexes. Calcifications can be visible on chest X-ray in some but not all patients. If an associated pericardial effusion is present, it is most often asymptomatic. On the other hand, if there is a sizeable pericardial effusion causing cardiac tamponade, then a diagnosis of effusive-constrictive pericarditis should be entertained. Effusive-constrictive pericarditis is a condition with hemodynamic characteristics of both constriction and a coexisting pericardial effusion. This condition is considered in circumstances where there is failure of the right atrial pressure to decrease by 50% or to less than 10 mmHg after pericardiocentesis [32].

Investigations: Imaging Modalities

Transthoracic Echocardiogram

Transthoracic echocardiography is a cost-effective and safe tool for the initial evaluation of pericardial disease; it also allows for the concurrent assessment of other cardiac structures injured by radiation. For pericardial effusions, it facilitates the evaluation of size and hemodynamic significance and, if needed, guides drainage (see Fig. 1). For constrictive pericarditis, it is a valuable diagnostic tool (see Fig. 2). Several echocardiographic features support a diagnosis of constrictive pericarditis, and these include interventricular septal bounce, tubular-shaped ventricles, dilated hepatic veins, dilated inferior vena cava, myocardial tethering, respiratory variation of the mitral peak *E* velocity of > 25%, and variation in the pulmonary venous peak D flow velocity of > 20% [30, 33, 34]. Peak *E*′ velocities that are greater for septal versus the lateral mitral valve annulus also support a diagnosis of constrictive pericarditis [35]. Echocardiography is less useful than CT or MRI for the detection of pericardial thickening (> 3 mm) and calcification.

Computed Tomography

Computed tomography (CT) is used to evaluate the extent of pericardial disease and surgical feasibility of pericardiectomy in constrictive pericarditis. It is better equipped than echocardiography to characterize the degree of calcification and pericardial involvement which can be regional or diffuse [30] (see Fig. 2). In constrictive pericarditis, the pericardium is usually, but not always, thickened [36, 37]. Manifestations of venous congestion may be visible, including pleural effusions and ascites [18]. CT is also helpful in demonstrating the extent of mediastinal fibrosis and aortic calcification as part of presurgical planning. Radiation-induced calcification of the ascending aorta can be problematic for cannulation in cardiopulmonary bypass and may necessitate a peripheral access option for cannulation. Pulmonary fibrosis, if present, is associated with adverse surgical outcomes, including mortality [38].

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) characterizes the pericardium in further detail than CT. It provides comprehensive evaluation regarding the degree of pericardial thickening, inflammation, and fibrosis, which are characteristics that influence surgical planning and timing. Pericardial late-gadolinium enhancement suggests ongoing inflammation which may require anti-inflammatories prior to, or in lieu of, immediate surgery [39, 40]. Conversely, CMR tagging demonstrates chronic fibrotic adhesions of pericardial layers [30]. Similar to echocardiography, CMR provides insight into constrictive physiology. Real-time cine CMR or real-time free-breathing phase-contrast imaging identifies respiro-phasic septal shift [30, 41]. There may also be extrinsic compression of cardiac chambers by a rigid and calcified pericardium, as well as dilatation of the inferior vena cava [42].

Management

Early Acute Pericarditis

Acute pericarditis is managed medically with the use of traditional medications, such as non-steroidal anti-inflammatory agents and colchicine. Some cases may self-resolve without any treatment at all [43]. As mentioned, patients with acute pericarditis are at an increased risk of constrictive pericarditis in the future [23].

Delayed Pericardial Effusion

If a pericardial effusion is found incidentally, and is otherwise clinically silent, there is no indication to pursue drainage. This is the case in the majority of pericardial effusions, as they are often asymptomatic and abate spontaneously [22]. Conversely, if the patient reports shortness of breath or presents with hemodynamic compromise, then removal of pericardial fluid is warranted. In general, florid cardiac tamponade is rare, given that fluid accumulation tends to occur slowly and over a long period of time. In circumstances where there is persistent re-accumulation of pericardial fluid despite manual removal, then pericardial window may be required.

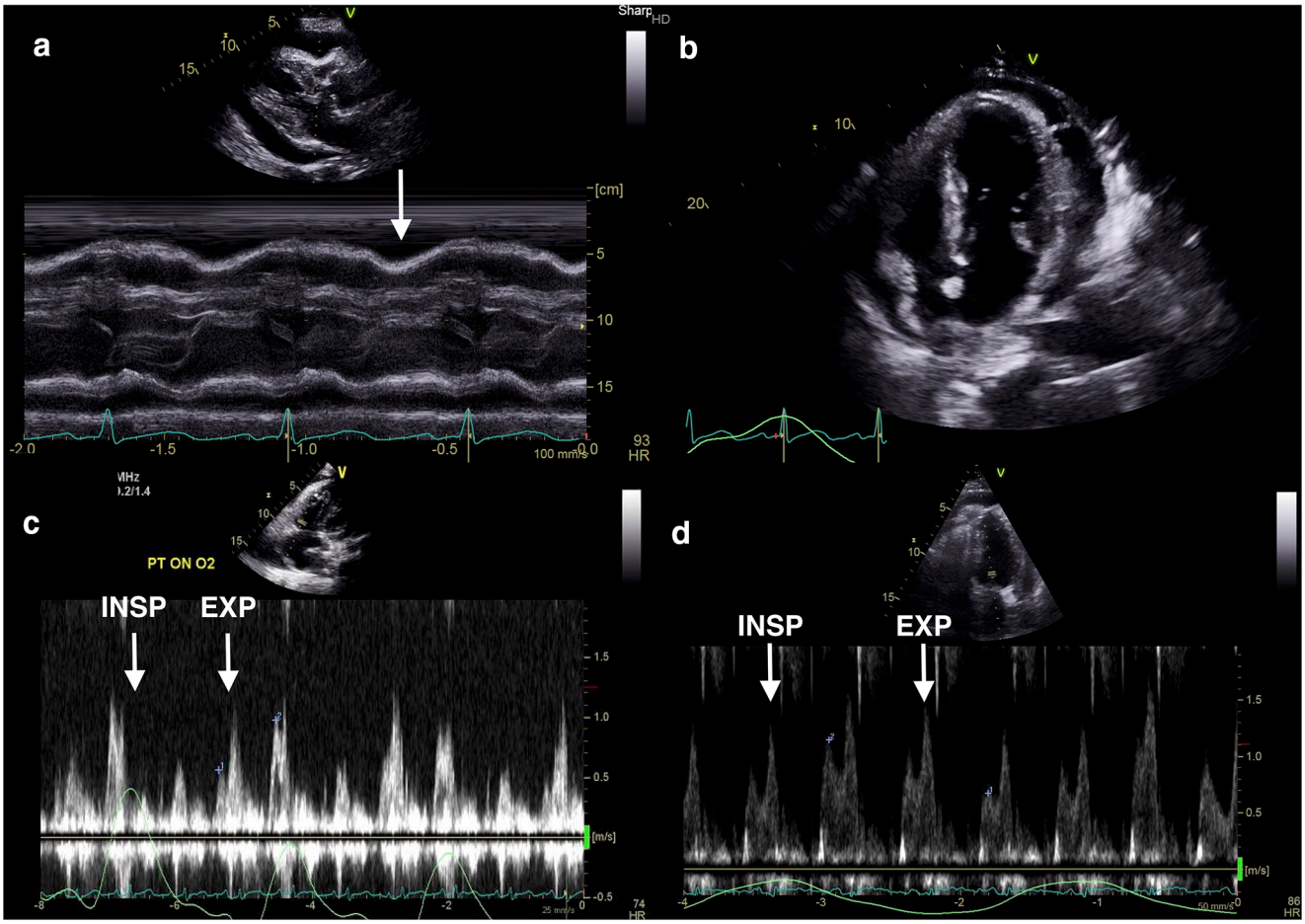

Fig. 1 A 66-year-old woman with history of chemotherapy and radiation therapy for breast cancer 1 year prior presents with shortness of breath, and she is found to have a pericardial effusion with tamponade physiology. **a** Parasternal long-axis view with M-mode demonstrates right ventricular collapse during diastole (*arrow*). **b** Four-chamber apical view shows right atrial collapse during diastole. **c** Continuous pulsed-wave Doppler demonstrates > 40% variation of tricuspid valve inflow velocity with respiration. **d** Continuous pulse-wave Doppler shows > 25% variability of mitral valve inflow pattern with respiration

Asymptomatic pericardial effusions are followed with serial echocardiograms and resolve within 2 years or more [44].

Chronic Pericarditis

In patients with early-stage constrictive pericarditis, medical management with anti-inflammatories can be attempted in case of transient constriction to leverage any element of reversibility. It is also important to resolve any underlying pericardial inflammation before considering surgery, as residual inflammation can increase the technical difficulty of achieving complete pericardiectomy. Mild symptoms are temporarily mitigated with diuretics to reduce ascites and edema. However, the natural history of constrictive pericarditis is progression of right-sided congestion, with a cascade of complications, including hepatic dysfunction, renal injury, and atrial fibrillation. In such patients, a cardiothoracic surgery consultation for complete pericardiectomy is warranted.

In chronic constrictive pericarditis, the only definitive treatment is pericardiectomy. Unfortunately, pericardiectomy outcomes for constrictive pericarditis related to radiation are dismal [29, 45–47, 48••]. The post-pericardiectomy 5-year survival rate of radiation-induced pericardial disease was previously reported as 11%, as compared to 80% in idiopathic cases [48••]. These poor survival rates are attributable to a number of factors. Pericardiectomy alone is a technically complex task. Moreover, radiation-induced pericardial disease is rarely present in isolation, as there are often other stigmata of diffuse radiation injury, such as valvulopathy and coronary artery disease [49••]. These entities often also require surgical intervention and, as such, increase perioperative morbidity and mortality. Furthermore, mediastinal fibrosis creates a challenging surgical endeavor even during a primary operation. Lastly, pericardial stripping may not necessarily result in relief of symptoms; often, patients have underlying restrictive cardiomyopathy and severe diastolic dysfunction from myocardial fibrosis. For these reasons, proceeding with pericardiectomy

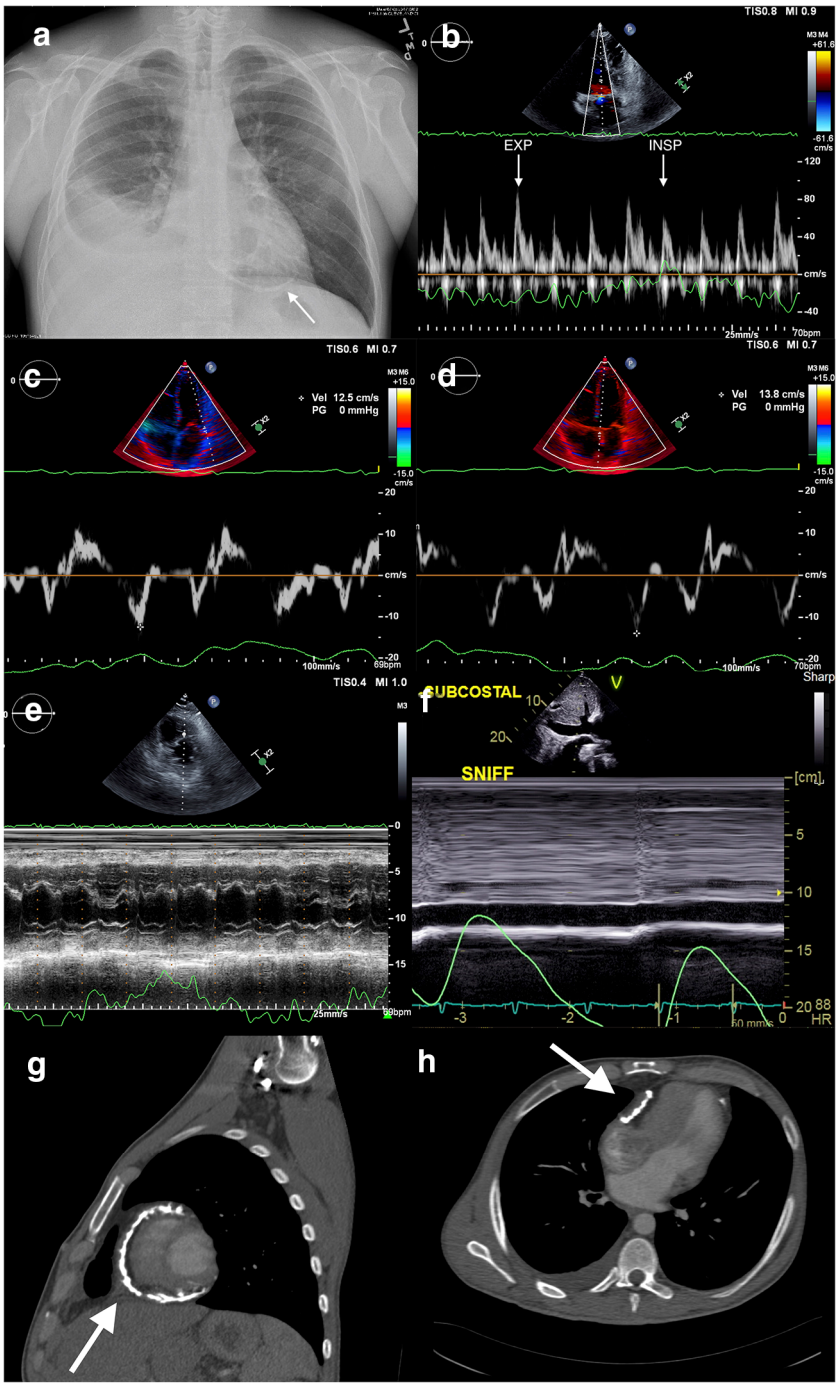

Fig. 2 A 44-year-old gentleman with history of Hodgkin's lymphoma presenting with constrictive pericarditis. **a** Chest X-ray illustrates pericardial calcification along the inferior border (*arrow*). **b** Apical window with pulsed-wave Doppler at the mitral valve leaflet tips shows expiratory (EXP) increase and inspiratory (INSP) decrease in early inflow velocity. **c**,**d** Four-chamber apical window with lateral mitral annular diastolic tissue velocity of 12.5 cm/s (**c**), which is reduced compared to medial mitral annular diastolic tissue velocity (**d**) signifying annulus reversus suggestive of pericardial tethering. **e** Subcostal short-axis view with M-mode across mid-ventricular septum demonstrates respirophasic shift and septal diastolic shudder. **f** Subcostal view with M-mode of the plethoric inferior vena cava, indicative of increased right heart pressures. **g**,**h** Computed tomography shows extensive pericardial calcification predominantly along the right ventricle and right atrium (*arrows*)

should be considered with caution and reserved for patients refractory to conservative measures.

Screening

The European Association of Cardiovascular Imaging and the American Society of Echocardiography published joint guidelines in 2013 regarding screening and surveillance of all forms of radiation-induced heart disease [18]. The European Society of Cardiology has likewise released a position paper on cancer treatment-related cardiotoxicity [50]. These guidelines encourage performing a baseline echocardiogram prior to the initiation of radiotherapy. In patients who develop pericardial effusion, surveillance echocardiography is the imaging modality of choice for monitoring size and resolution. Subsequent annual routine follow-up comprising of a comprehensive history and physical examination to screen for radiation-induced heart disease is a fundamental component to survivorship care. The interval development of cardiac

symptoms or evidence of decompensated heart failure on examination should trigger an echocardiogram and subsequent cardiology consultation based on findings. The frequency of longitudinal screening with imaging is not clear and is based on expert opinion. In asymptomatic individuals with no baseline cardiac abnormalities, transthoracic echocardiogram at 10 years after radiation therapy is advised given the possibility of subclinical cardiac disease. Afterwards, the time interval for screening is abbreviated to every 5 years. High-risk patients, as defined by the risk factors described previously, may require additional attention via more frequent screening. As such, guidelines recommend initiation of echocardiographic screening at 5 years post-radiation [18]. At this time, there is no data to support the use of CT or MRI in screening for radiation-induced heart disease.

Prevention

Modern radiation techniques have evolved to provide more tailored delivery of radiation to malignant tissue and avoid inadvertent toxicity to healthy adjacent structures. In 2017, the American Society of Oncology published recommendations for prevention of cardiac dysfunction in survivors of adult cancers [51]. Many of the sophisticated strategies suggested are executed during the planning stages of radiation, and their purpose is to reduce radiation field or volume. For Hodgkin's disease patients, involved-site radiotherapy and involved-node radiotherapy incorporate pre-chemotherapy positron-emission tomography to target only diseased lymph nodes rather than indiscriminately irradiating entire lymphatic networks [52]. Maraldo et al. estimated that compared to traditional mantle therapy, involved-node radiotherapy decreased the mean doses to the heart from 36 to 7.7 Gy, thereby reducing the 25-year excess cardiovascular risk from 9.1% (95% CI 5.5–16.6) to 1.4% (95% CI 0.4–5.1) [53•]. Other techniques include intensity-modulated radiotherapy, which varies radiation energy while treatment is delivered in order to meticulously contour tumor edges, and three-dimensional conformal radiotherapy, which creates multi-dimensional reconstructions that allow for more individualized selection of radiation beam direction and intensity [54].

In special circumstances, dose reduction can be considered. One randomized trial reported that in early-stage and low-risk Hodgkin's lymphoma, dose reduction of radiotherapy from 30 to 20 Gy did not compromise survival rates [55]. Because of the recent nature of this study, it remains to be seen whether this also results in a cardiovascular benefit. Dose reduction is an area of ongoing investigation given the strong association between mean heart dose and risk of cardiac toxicity [12].

There are also relatively simple maneuvers that mitigate cardiac radiation. In breast cancer patients, prone positioning reduces cardiotoxicity while maintaining therapeutic efficacy [56•]. One study that demonstrated this approach was associated with a reduction of 85.7% in heart volume radiation in patients with left-sided breast cancer [57]. Respiratory gating is another technique. The heart location is slightly variable as a result of respiratory motion, and deep inspiration breath hold in patients with breast and mediastinal malignancies has been shown to avoid radiation to normal tissue [58]. The successes of these newer methods with respect to long-term cardiovascular and pericardial outcomes have yet to be ascertained.

Conclusions

In comparison to other forms of post-radiation cardiotoxicity, the realm of pericardial disease is overlooked. To date, pericardial complications have been neglected in survivorship studies, and, as a result, understanding of risk factors and post-treatment surveillance is unclear. Fortunately, radiation-related cardiotoxicity is receiving increasingly more attention. Moving forward, studies regarding the long-term effects of modern radiotherapy techniques are needed to assess risk to the pericardium. In light of the improved mortality from breast cancer and Hodgkin's disease in recent decades, such knowledge is paramount to the care of cancer survivors in the future.

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Compliance with Ethical Standards

Conflict of Interest Natalie Szpakowski and Milind Y. Desai declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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