Radiotherapy: Clinical Aspects and Cardiotoxicity

Chiara Lestuzzi, Anju Nohria, Riccardo Asteggiano, and Paola Vallerio

C. Lestuzzi et al. (eds.), *Manual of Cardio-oncology*, DOI 10.1007/978-3-319-40236-9_12

12.1 Pathophysiology

Radiation therapy (RT) causes inflammation, activation of pro-fibrotic cytokines, and endothelial and microvascular damage. Radiation increases oxidative stress through free radical production and results in recruitment of matrix metalloproteinases and pro-inflammatory mediators such as IL-4, IL-13, and TGF-β. After myofibroblasts have been activated, collagen deposition and fibroblast differentiation can continue independent of TGF-β signaling via autocrine induction. These changes may lead to acute toxicity (evident during or shortly after radiotherapy) and start a chronic process leading to delayed dysfunction that is evident several years later. Acute changes largely result from direct radiation damage and the immediate inflammatory response, while long-term changes are due to stem cell loss and late and persistent tissue fibrosis. Thus, chronic radiation-induced damage is irreversible and can affect multiple cardiac structures including the coronary arteries, myocardium, pericardium, cardiac valves, and the conduction system [1] (Table 12.1).

Table 12.1 Reproduced with permission from [74]

	Echo-cardiography	Cardiac CMR	Cardiac CT	Stress echo-cardiography	ERNA/SPECT perfusion
Pericardial disease					
Effusion—screening and positive diagnosis	++++	+	+	–	+/–
Effusion—follow-up	++++	–	–	–	+/–
Constriction—screening and positive diagnosis	++++	++++	++	–	+/–
Myocardial disease					
LV systolic dysfunction	++++ (first-line imaging, contrast echocardiography if poor acoustic window)	++++	+	++++ (contractile reserve assessment)	++++/++++ (used when both function and perfusion are to be analyzed)
LV diastolic dysfunction	++++	+	–	–	++/+
LV dysfunction—follow-up	++++ (first-line imaging, contrast echocardiography if poor acoustic window)	+	–	++ (contractile reserve assessment)	++/++
Myocardial fibrosis	–	++++	+	–	–

Table 12.1 (continued)

Valve disease					
Positive diagnosis and severity assessment	++++	++	–	++	+/–
Follow-up	++++	–	–	++	+/–
Coronary artery disease					
Positive diagnosis	+ (if resting wall-motion abnormalities)	++++ (stress CMRb)	++ (CT angioa)	++++ (exercise or dobutamine)	+/++++
Follow-up	+	+	–	++++ (first-line imaging)	+/++

12.2 Acute Toxicity

12.2.1 Acute Pericarditis

The most common acute toxicity is **acute pericarditis**. It is seen mostly in patients treated with high-dose RT for mediastinal Hodgkin (HL) or non-Hodgkin (NHL) lymphoma, esophageal cancer, lung cancer, and thymoma. It is a consequence of (1) increased production of pericardial fluid due to the increased vascular permeability and (2) impaired drainage due to fibrosis of the lymphatic vessels.

- The incidence of acute pericarditis has decreased over time from 20 % to 2.5 % with modern radiation techniques
- Small, asymptomatic pericardial effusions are the most frequent complication but are usually self-limited and disappear within weeks without requiring any specific therapy [2].

Small pericardial effusions (due probably to impaired lymphatic drainage) are frequently present *before* radiotherapy in patients with lymphoma and large mediastinal masses and should not be considered a complication of RT.

- Acute pericarditis with chest pain, ECG changes, and/or pericardial friction rubs may be observed in some patients during or in the first months after RT over the esophagus or lung cancer. Pericardial effusion is usually mild to moderate or even absent.
- Therapy is the same as for acute viral or idiopathic pericarditis, i.e., nonsteroidal anti-inflammatory drugs. Colchicine may also be considered in refractory cases.

12.2.2 Ventricular Dysfunction

Ventricular dysfunction is a rare event. It is more frequent when an anthracycline or high-dose chemotherapy is administered concurrently, or shortly before RT, since radiation interacts synergistically to induce myocardial damage [3, 4].

- The dysfunction is usually both systolic and diastolic, and a restrictive pattern is usually seen.

12.2.3 Cardiac Ischemia

Cardiac ischemia may also be observed in the first months after RT, especially with radiation fields very close to the heart. In one prospective study, volume-dependent perfusion defects were observed in approximately 40 % of patients within 2 years of RT [5]. Patients with early perfusion defects might have a high incidence of cardiac events at long-term follow-up [6].

12.3 Late Toxicity

Delayed radiation-induced heart disease (RIHD) is a significant problem, especially in long-term survivors of lymphoma and breast cancer. The median time from RT to appearance of clinically significant RIHD is 15 years, with the incidence increasing progressively over time [7–11].

12.3.1 Coronary Artery Disease (CAD)

Coronary Artery Disease (CAD) is the most frequent and relevant form of RIHD. The risk of death due to acute myocardial infarction (AMI) is two- to fourfold higher in patients treated for Hodgkin lymphoma compared with age-matched controls, but can be increased sevenfold or higher in some subgroups [12]. Animal models of radiation-induced atherosclerosis have shown that radiation accelerates the development of atherosclerotic plaques and predisposes to an inflammatory phenotype prone to hemorrhage, as well as increasing the total plaque burden relative to age-matched animals.

- The most relevant risk factors for CAD after chest RT are:
  - Total radiation exposure of the heart: treatments delivered without heart shielding, higher cumulative dose (≥30 Gy), fractional dose ≥ 2 Gy, left vs right chest RT (in breast cancer)
  - Younger age (≤25 years) at the time of RT
  - High blood cholesterol, active cigarette smoking, and other cardiovascular risk factors
- The mechanism involved in plaque formation is thought to mirror spontaneous atherosclerosis; however, plaques in irradiated patients have been found to be more fibrous with decreased lipid content, and the lesions are consistently more proximal, smoother, concentric, tubular, and longer.
- Typically, CAD develops mostly within the radiation field.
  - Ostial stenoses are typical of mediastinal RT. Macroscopically, there is a significantly higher incidence of left main disease, followed by ostial right coronary artery and left anterior descending artery stenoses.
  - After left chest irradiation for breast cancer, the apical segments are more involved; in these patients, there is a damage of the microvasculature, leading to kinetics abnormalities rather than acute myocardial infarction in most cases [13].
- Radiation-induced CAD is often clinically silent and AMI may be the first presenting event (Fig. 12.1). Both silent ischemia and false-negative stress tests have been documented [14]. In our experience, 75 % of patients with inducible ischemia on screening stress tests are asymptomatic.

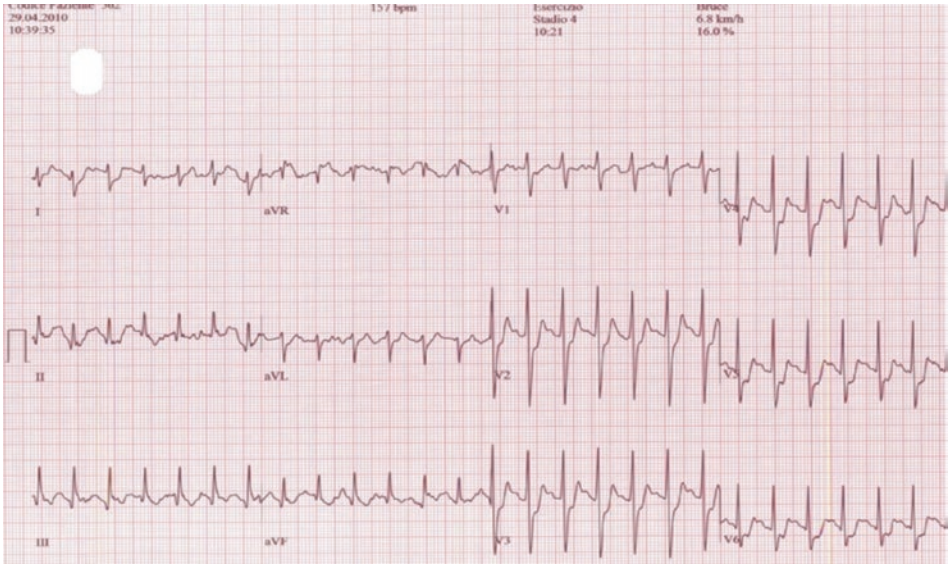

Fig. 12.1 Silent ischemia at stress test in an asymptomatic 48-year-old man, without any cardiovascular risk factor, 22 years after mediastinal radiotherapy. Coronary angiography revealed a stenosis of main left coronary artery, which was successfully treated with percutaneous angioplasty

- The probable explanation is that radiation damages the cardiac nerves, leading to a functionally denervated heart.
- Therefore, screening of patients at risk for radiation-induced CAD should be based on functional and/or imaging techniques rather than on symptoms alone.

12.3.2 Left Ventricular (LV) Dysfunction

Left ventricular (LV) dysfunction is a frequent complication of chest RT

- it can occur due to one or more of the following mechanisms:
  - Macroscopic CAD leading to chronic ischemia and myocardial hibernation, stunning, and/or necrosis (Fig. 12.2).
  - Decrease in capillary density resulting in myocyte hypoxia
  - Direct myocyte damage and necrosis, more evident in synergy with anthracycline cardiotoxicity (in the patients treated also with CHOP-like and ABVD chemotherapy), with progressive fibrosis replacing viable myocardial tissue.
  - Increase in type I collagen rather than type III collagen, leading to reduced myocardial distensibility.

The cardiovascular system responds differently to RT-related myocardial damage compared with ischemia-related ventricular dysfunction. Left ventricular dilatation is often limited.

- Strain deformation parameters may be significantly altered before any relevant systolic or diastolic dysfunction (Fig. 12.3).
- Left ventricular diastolic dysfunction is usually predominant, with evolution towards a restrictive cardiomyopathy in most severe cases [15].

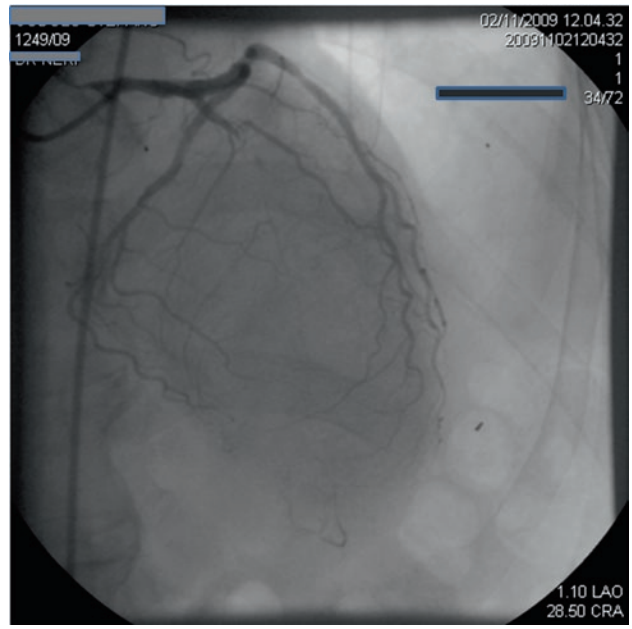

Fig. 12.2 Coronary angiography of a 53-year-old male, former smoker, with high blood pressure and cholesterol. This patient underwent chemoradiotherapy for Non-Hodgkin Lymphoma in 2006. In 2009, a drop of ejection fraction (EF) from 61% before treatment to 49% was observed. Coronary angiography revealed a 100% stenosis of left anterior descending artery, which was treated by angioplasty. Two years later EF had raised to 59%

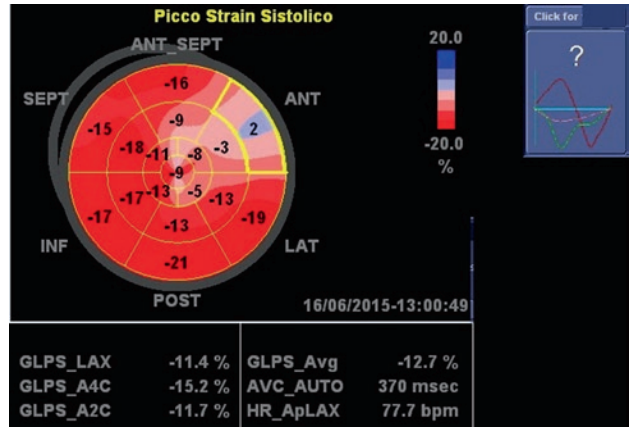

Fig. 12.3 Female patient, age 43, treated by mediastinal radiotherapy for Hodgkin lymphoma at age 17, followed by chemotherapy including doxorubicin at age 18. Ten years later she underwent breast surgery and chemotherapy with epidoxorubicin for radiation-induced breast carcinoma. Ejection fraction is normal (63%) and diastolic function mildly altered (E/A ratio 0.83, E/E' 13), but the global strain is reduced (−13%), with abnormalities most evident at the level of anterior wall

12.3.3 Valvular Heart Disease (VHD)

Valvular heart disease (VHD) ranges from sclerosis to severe, often calcific, valvular stenosis and/or regurgitation. It is more common after mediastinal RT in comparison to chest wall RT for breast cancer. Among breast cancer patients, it is more common after left-sided RT in comparison to right-sided RT [16].

- Screening studies in HL survivors have reported that 32 % of those given mediastinal irradiation developed asymptomatic valvular defects after six years [17].
- In Hodgkin lymphoma patients, the prevalence is 25–40 %, 20 to 30 years after cancer diagnosis (Fig. 12.4).
- The median time between RT and detection of significant valvular heart disease is approximately 20 years, and >50 % of patients require surgery in the following years. Usually the first finding is regurgitation, and stenosis develops years after [18] (Fig. 12.5).
- Aortic valve regurgitation and stenosis is the more frequent finding, followed by mitral valve regurgitation and/or stenosis [19].
- Cardiac doses ≥30 Gy increase the risk of VHD, while at lower doses the increase per Gy is smaller and there may be a threshold dose below which there is no risk.
- The main risk factors include age < 20 years at the time of RT, obesity at HL diagnosis, and hyperlipidemia at the end of follow-up [20, 21] (Fig. 12.1).
- Other potential risk factors include splenectomy at the time of HL diagnosis and hypertension at follow-up (21).
- The use of chemotherapy was not found to be an independent risk factor.

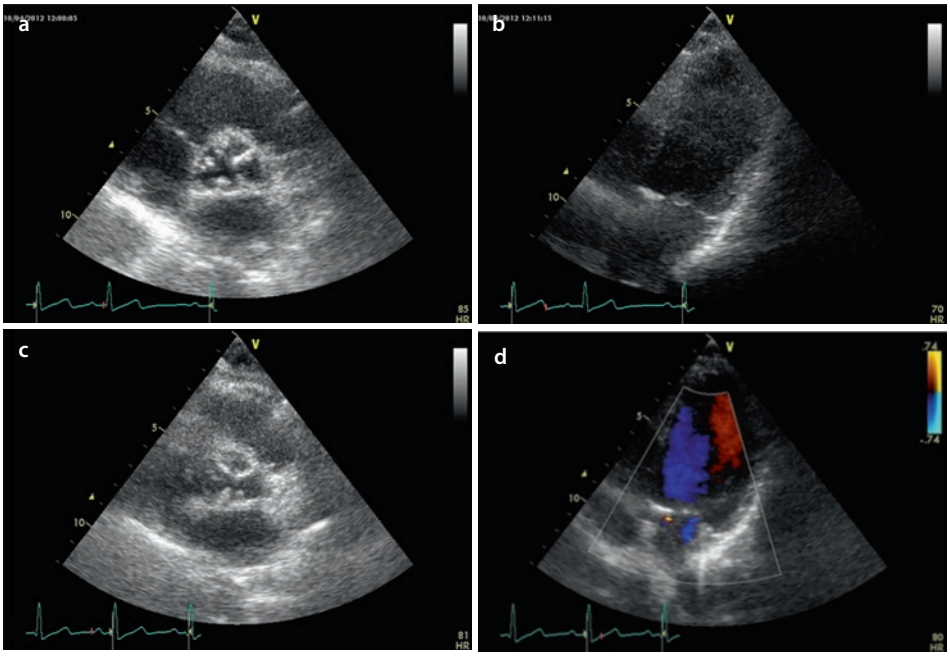

Fig. 12.4 Same patient of Fig. 12.3: (**a** and **b**): At age 41, the aortic valve leaflets are thickened and mildly calcific, with mild stenosis and regurgitation. Mitral annulus is thickened, with normal leaflets. (**c** and **d**): Three years later, the aortic valve disease is stable, but mitral valve leaflets and mitral annulus are more thickened, with mild regurgitation

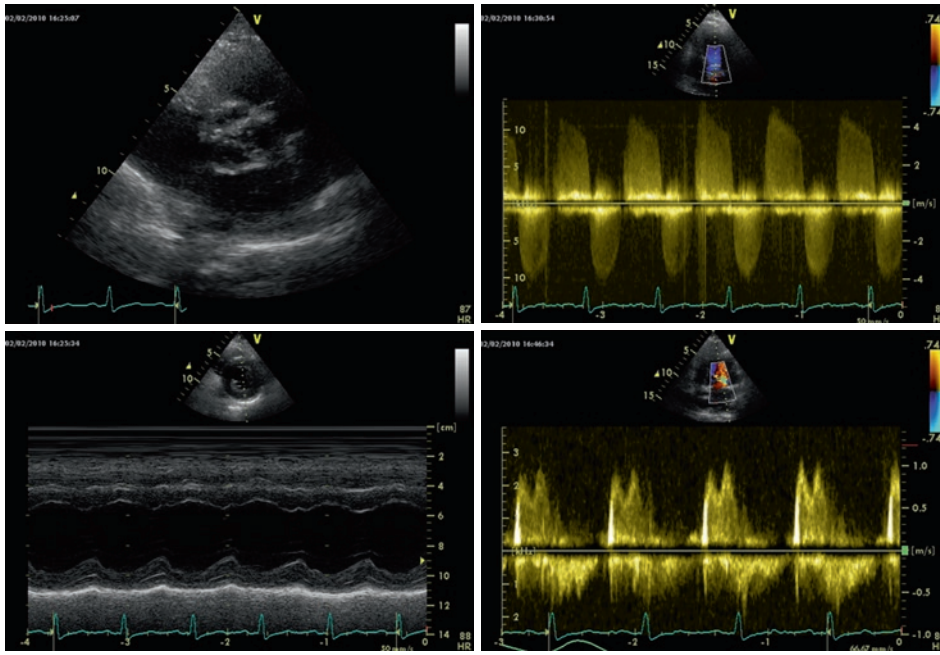

Fig. 12.5 Female patient, 60-year-old, treated with mantle field radiotherapy for Hodgkin lymphoma at age 27. Calcific aortic stenosis (peak gradient 71 mmHg, mean gradient 46 mmHg, area 0.7 cm^2) and moderate regurgitation. Ejection fraction 52%. NYHA class 2. Pericardium and mitral flow are normal

12.3.4 Chronic Pericarditis

Chronic pericarditis may develop as a consequence of acute pericarditis seen during or shortly after RT and as a delayed complication.

- The pericardium is often thickened and may be calcific.
- The most common clinical presentation is constrictive pericarditis
- Some patients have thickened pericardium with mild to moderate effusion and may become symptomatic when the effusion increases (effusive-constrictive pericarditis).
- Signs and symptoms of pericarditis may be subtle and may change with blood volume.
  - Most patients have a combination of restrictive and constrictive disease and pericardial stripping does not afford similar benefits in RT patients compared to those with constriction due to other causes.

If a constrictive pericarditis is suspected, the intravenous infusion of 300–500 ml of saline is useful to reveal the hemodynamic pattern of constriction.

12.3.5 Arrhythmias

Both brady- and tachyarrhythmias can be seen as a consequence of RT, may be both hyperkinetic and hypokinetic.

- **Inappropriate sinus tachycardia**, both at rest and during effort, is common after thoracic RT and is felt to be a consequence of autonomic dysfunction [22].
- Direct damage and eventually fibrosis of critical structures such as the sinoatrial or atrioventricular nodes may lead to a variety of arrhythmias including all degrees of **atrioventricular block,** including complete heart block, and sick sinus syndrome [23, 24]

Right and left bundle branch blocks may also be observed and are likely due to microvascular damage and ischemia.

12.4 Clinical Presentation

- The clinical presentation differs according to the predominant pathologic change. However, it should be noted that:
  - Pathologies often coexist, thus confounding symptoms. The finding of a severe valvular heart disease in a dyspneic patient may lead to underdiagnosis of an associated pericardial constriction (Fig. 12.6).
  - Patients with RIHD may be asymptomatic for years, even in the presence of significant anatomic changes [25]. This is true mostly for CAD, as stated before.

If a specific RIHD is suspected, a thorough evaluation to rule out any associated pathology affecting other cardiac structures is of outmost importance.

Tip

In patients presenting with symptoms of dyspnea, fatigue, and reduced exercise tolerance, it is important to consider other organs that may be affected by RT or chemotherapy **in the differential diagnosis.**

- **Acute radiation pneumonitis** occurs in the majority of cases between 6 and 12 weeks after the end of thoracic RT. It is characterized by interstitial edema, inflammatory infiltrates, and pneumocyte proliferation. There are often no symptoms or clinical signs appreciated. In some patients, dyspnea and wheezing may occur, sometimes accompanied by a nonproductive cough, and crackles on auscultation. In about half of the cases, chest radiography shows confluent alveolar and interstitial infiltrates in the irradiated field. Rare cases may progress to the development of acute respiratory distress syndrome (ARDS). Rarely, one may observe findings consistent with *bronchiolitis obliterans* with organizing pneumonia (BOOP). The clinical picture is that of a nonspecific pneumonitis, presenting immediately after RT. Imaging depicts sparse and migratory alveolar opacities. Steroid therapy is useful, but relapses have been described after steroid discontinuation [26]. Concomitant chemotherapy with gemcitabine (such as in lung cancer) increases radiosensitivity of the lungs and the incidence of pneumonitis. In breast cancer patients, both paclitaxel and tamoxifen have been reported to increase the rate of pneumonitis.

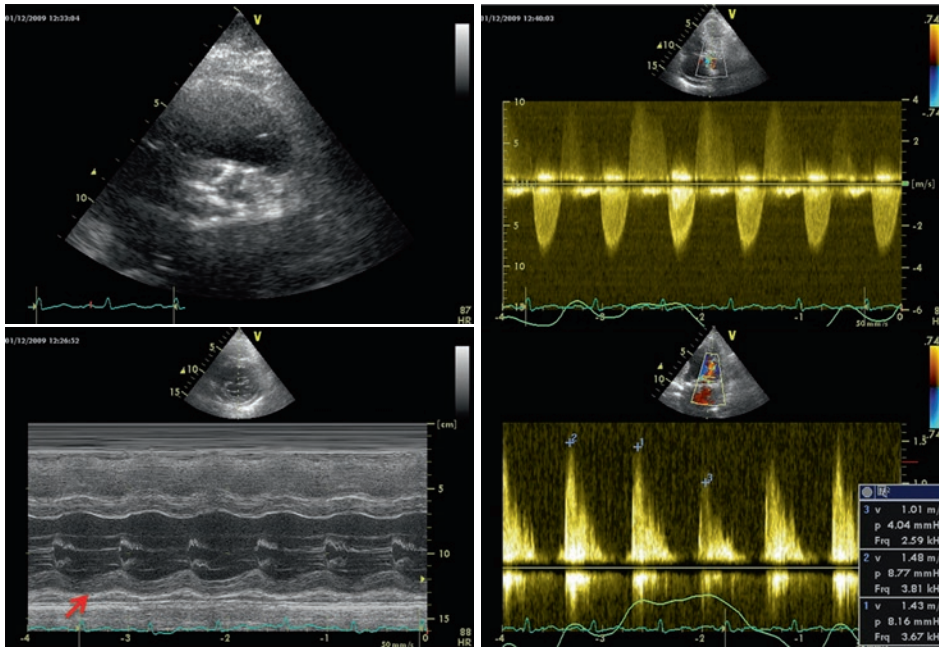

Fig. 12.6 Female patient, 65-year-old, treated with mediastinum radiotherapy for Hodgkin lymphoma at age 35. Calcific aortic stenosis (peak gradient 55 mmHg, mean gradient 30 mmHg, area 0.6 cm^2) and moderate regurgitation. Ejection fraction 51 %. NYHA class 3, with engorged jugular veins, enlarged liver, and ankle edema. The pericardium is thickened (*red arrow*); the diastolic mitral flow is reduced during inspiration (*bottom right*). These findings suggest the presence of constrictive pericarditis

- **Late radiation pneumonitis** occurs approximately 6 months after the end of thoracic RT, even in the absence of acute pneumonia. It is a virtually constant radiological feature which stabilizes two years after the end of treatment. From a pathological point of view, the inflammatory infiltrate is replaced by fibrosis and obliteration of the capillaries, causing chronic ischemia. This fibrosis may lead to chronic restrictive respiratory failure, a rare occurrence.
- **Recall pneumonitis** corresponds to pneumonia in a previously irradiated territory following subsequent chemotherapy (anthracyclines, gemcitabine, etoposide, vinorelbine, taxanes) or after exposure to some targeted therapies [27, 28].
- **Chemotherapy-induced lung disease** may be observed with several agents [29]. Bleomycin, in particular, can cause pulmonary toxicity (from acute pneumonitis to late fibrosis) in 20–40 % of patients [30]. Of note, Bleomycin is part of the ABVD and VEPEB chemotherapy protocols used in lymphomas.
- **Hypothyroidism.** Radiation fields including the neck (such as mantle field used for HL) may cause thyroid dysfunction. The actuarial risk of any thyroid disease is about 67 % at 26 years after therapy for Hodgkin lymphoma that includes irradiation of the thyroid gland. Hypothyroidism, Graves' disease (relative risk, 7.2–20.4), thyroiditis, thyroid nodularity, and thyroid cancer are among the commonly observed thyroid effects of RT [31]. The most frequent effect is hypothyroidism, which may be clinically overt, characterized by low free T4 and high TSH, or subclinical (biochemical or compensated) hypothyroidism with normal free T4 and high TSH. In the majority

of cases, subclinical hypothyroidism evolves to overt hypothyroidism, although up to 20 % of patients experience spontaneous return of TSH to normal levels, or substantial improvement [32].

12.5 Diagnosis of RIHD

Electrocardiography (ECG) and echocardiography are the most widely used tools to screening for RIHD. ECG may be normal or show conduction system and/or repolarization abnormalities. Echocardiography can detect structural cardiac abnormalities (including valvular heart disease and pericardial disease) and measure LV function. Several echocardiographic approaches (M-mode, Doppler, two-/three-dimensional (2D/3D) transthoracic or transesophageal, contrast, or stress echocardiography) can be used according to the clinical indication. **Computed Tomography** (CT) is useful to image the pericardium and coronary arteries and in recognizing cardiac calcifications. **Magnetic Resonance Imaging** (MRI) is the ideal complement to echocardiography: using contrast-enhanced images and dark-blood and bright-blood sequences, it may both give anatomic information and detect signs of inflammation; real-time cine imaging is of great value to assess functional abnormalities. Among the noninvasive tests, standard exercise stress tests, cardiopulmonary stress tests, and pulmonary function tests (for the differential diagnosis between cardiac and lung radiation disease) are also routinely used for screening after RT. **Cardiac catheterization** is useful in assessing CAD and can be used to confirm/distinguish constrictive and restrictive physiologies [33, 34]. See ◘ Table 12.1.

12.5.1 Coronary Artery Disease

- Echocardiography may show segmental abnormalities which suggest the presence of CAD. However, a hypokinetic ventricular region is not necessarily specific for the presence of CAD, but could reflect a myocardial disease process. A stress-induced wall-motion abnormality is a reliable indicator of transient myocardial ischemia and is highly sensitive and specific for angiographically assessed epicardial coronary artery disease. Either dobutamine or exercise echocardiography can be used, but exercise testing is recommended in patients who are able to exercise. In a study enrolling 294 asymptomatic patients with Hodgkin disease treated with mediastinal RT, stress echocardiography had predictive values of 80 and 87 % for detecting ≥70 and 50 % coronary stenoses, respectively. In this study, after a median follow-up of 6.5 years, 23 patients developed symptomatic CAD, including 10 who sustained an acute myocardial infarction. The risk of a cardiac event after screening was related to, among other things, the presence of resting wall-motion abnormalities on echocardiography and ischemia on stress testing [35].
- A cardiac **CT scan** is a noninvasive way to obtain information about the location and extent of calcified plaques in the coronary arteries. In the general population, the presence of coronary calcium is associated with adverse outcomes and can be useful for risk stratification. As with other groups of patients, obstructive CAD is unlikely to be present in the absence of detectable coronary calcium in RT survivors. Thus, **coronary calcium scores using cardiac CT can be used to rule out CAD**. Impaired image

quality and excessive calcification (combined with residual motion artifacts) can lead to overestimation of the severity of obstructive disease. Coronary CT has been used for follow-up in small groups of patients after RT for Hodgkin disease. These studies have demonstrated advanced coronary calcification and obstructive CAD (often requiring revascularization) in relatively young patients, even in the absence of any symptom and with normal stress test [14, 36].

- **MRI** is able to directly image epicardial coronary arteries, microvasculature on myocardial perfusion, ventricular function, and viability. Reversible myocardial ischemia can be assessed through stress-induced myocardial perfusion and/or function. In the last decade, CMR has emerged as the gold standard to evaluate myocardial infarction in both acute and chronic settings [37, 38]. In a recent CMR study of 20-year survivors of Hodgkin disease, perfusion defects were found in 68 % and late myocardial enhancement in 29 % of patients [39].
- **Radionuclide imaging** (SPECT and PET) is an accurate and robust technique to assess myocardial perfusion. The prevalence of myocardial perfusion defects among long-term survivors of chest RT varies widely, depending on the volume of the LV in the radiation field, age and timing of screening, and scintigraphic method used. In a prospective study, the prevalence of stress-induced perfusion abnormalities increased from 5 % to 11 % and 20 % in 2–10 years, 11–20 years, and >20 years after RT, respectively. In this study, myocardial ischemia on SPECT was shown to be associated with a higher risk for subsequent coronary events and prompted myocardial revascularization in a substantial proportion of patients [40].

Tip

There are often discrepancies between imaging techniques and functional studies: no single tool has 100 % sensitivity and specificity in detecting CAD and inducible ischemia after RT [41]**.** There are limited data comparing the accuracy of different imaging modalities to detect CAD in patients after mediastinal RT. In one head-to-head comparison, SPECT had the highest sensitivity compared with stress echocardiography and exercise stress testing (65 vs. 59 %), albeit at the cost of a higher false-positive rate (89 vs. 11 %). Many of these false-positive findings may actually be caused by microvascular disease, endothelial dysfunction, or vascular spasm [34].

12.5.2 LV Systolic and Diastolic Dysfunction

- LV ejection fraction assessment by **echocardiography** can be regarded as the standard in global systolic function assessment during and after RT. However, subtle changes, particularly due to early treatment effects, may be missed due to measurement variability. Deformation parameters derived by strain imaging can detect subtle changes that may be missed by standard echocardiographic techniques (Fig. 12.3). LV diastolic function is commonly evaluated by conventional Doppler (mitral inflow, pulmonary venous flow) and tissue Doppler techniques (applied to mitral annulus motion). However, it is important to note that diastolic parameters are highly sensitive to any change in loading conditions.

- **MRI** is an adequate alternative technique to assess LV function in patients with poor acoustic windows. Bright-blood cine imaging using the SSFP technique is an accurate and reproducible method to assess ventricular volumes, mass, and systolic function longitudinally. The same set of images can be used to assess regional contractility and contractile patterns [42]. MRI assessment of diastolic function with phase contrast is similar to Doppler echocardiography [43].
- **Radionuclide ventriculography** (RNV), either by the gated-equilibrium or first-pass methods, is an accurate tool to assess and quantify LV systolic and diastolic function at rest and during conditions of stress (for the gated-equilibrium method). The advantage of RNV is the ability to quantify ventricular volumes from total radioactive count density without the need for calculating volumes from 2D slices using assumptions about LV geometry. Diastolic function can be assessed by acquiring data with high temporal resolution and by calculating the peak filling rate and time-to-peak filling rate [44]. The disadvantage is the cost and the radiation burden.

12.5.3 Restrictive Cardiomyopathy

- On ***echocardiography***, classical restrictive cardiomyopathy is characterized by increased stiffness of the myocardium and a small LV with an increased left atrial size. This causes an early rapid rise in LV pressure during LV filling. Systolic function assessed by traditional echocardiographic techniques is usually normal. Doppler measurements of the transmitral flow reveal a typical pattern consisting of a short mitral E deceleration duration and a low A wave velocity resulting in a high E/A ratio [45]. The E′-wave by tissue Doppler imaging is usually decreased. A combined occurrence of constrictive pericarditis and restrictive cardiomyopathy may lead to a more difficult interpretation of the transmitral LV filling pattern.
- **MRI** may add useful information. Restrictive cardiomyopathy occurs as a result of diffuse myocardial fibrosis. *T*1 mapping by MRI may depict diffuse myocardial fibrosis. *T*1 mapping can be used to quantify the concentration of gadolinium-based extracellular contrast agents in the myocardium and in the blood pool. However, the diagnostic power is still limited [46].
- **CTscan and nuclear cardiology** are of little or no value in the diagnosis of restrictive cardiomyopathy.

12.5.4 Valve Disease

- ***Echocardiographic* characteristics** of radiation-induced valve disease include fibrosis and calcification of the aortic root, aortic valve annulus, aortic valve leaflets, aortic-mitral inter-valvular fibrosis, mitral valve annulus, and the base and mid-portions of the mitral valve leaflets (5-8). Typically, these changes spare the mitral valve tips and commissures, which is **the main distinguishing feature between radiation-induced valve disease and rheumatic heart disease**. 3D echocardiography is particularly useful for the assessment of the presence or absence of commissural fusion.

- **Pitfalls in evaluating valve disease severity:** Planimetry of the mitral valve area at the leaflet tips may underestimate the severity of stenosis since the leaflet tips are spared and there is no commissural fusion. The presence of restrictive cardiomyopathy with significant underlying diastolic dysfunction may lead to shortened pressure half-time and overestimation of the mitral valve area. In addition, increased LV end-diastolic pressure may lead to an elevated mitral E-wave resulting in an elevated velocity–time integral of the mitral inflow CW Doppler signal, which will result in an elevated mean diastolic Doppler gradient tracing. The aortic stenosis gradient may be underestimated in these patients because of significant LV systolic dysfunction. Of note, a low-flow state can also be observed in patients with preserved LV function. When the LV ejection fraction is reduced, dobutamine stress echocardiography can help differentiate pseudo- and fixed severe aortic stenosis. The assessment of the severity of mitral valve regurgitation can be difficult in the presence of significant mitral annular calcification because of acoustic shadowing and difficulties with measuring the diameter of the mitral annulus. Transesophageal echocardiography can be particularly useful in the assessment of mitral valve disease when there is significant mitral valve annular calcification.

- **MRI** provides both anatomic and dynamic evaluation of the diseased valves, including information on the number of leaflets, valve thickness, valve structure, leaflet mobility, and valve orifice. Valvular dysfunction can be quantified by measuring the degree of valvular stenosis (the measurement of transvalvular gradients, assessment of aortic valve area) and/or valvular regurgitation (the measurement of regurgitant volumes and fraction) and by assessing its impact on cardiac chamber size and function [38, 39].

12

12.5.5 Pericardial Disease

- Echocardiography is the first-line imaging modality in patients with suspected or confirmed pericardial disease. **Pericardial effusion** is visualized as an echo-free space, external to the myocardial wall. **Pericardial thickening** appears as increased echogenicity of the pericardium on 2D echocardiography and as multiple parallel reflections posterior to the LV on M-mode recordings. However, the distinction between the normal and thickened pericardium may be difficult. Characteristic echocardiographic findings of **constrictive pericarditis** include:
  - Thickened pericardium.
  - Prominent respirophasic diastolic bounce of the inter-ventricular septum.
  - Restrictive diastolic filling pattern (E/A ratio of >2 and deceleration time of the mitral E-velocity of <140 ms).
  - Significant inspiratory variation of the mitral E-wave velocity (>25 %) (Fig. 12.6).
  - Diastolic flattening of the LV posterior wall.
  - Inferior vena cava plethora.
  - Expiratory diastolic flow reversal in the hepatic veins.

- Tissue Doppler interrogation of the medial mitral annulus reveals a normal or increased velocity that can be higher than the lateral annulus velocity.
- The systolic pulmonary pressures are not significantly elevated.

Constrictive pericarditis may be differentiated from restrictive cardiomyopathy (also a complication of radiation) by the presence of normal mitral tissue Doppler velocities and a systolic pulmonary artery pressure <50 mmHg.

- **MRI** allows the detection of indirect signs of constrictive pericarditis, such as unilateral or bilateral atrial enlargement, conical deformity of the ventricles, dilatation of caval/hepatic veins, pleural effusion, and ascites. In pericarditis, the pericardium is typically thickened. Acute, but not chronic, pericarditis is associated with delayed enhancement following contrast administration and this differentiation can have therapeutic implications [47, 48]. **Real-time cine imaging** can be of great value in assessing the impact of respiration on inter-ventricular septal motion, allowing easy detection of pathological (increased) ventricular interdependence [49]. Furthermore, tagged sequencing allows detection of pericardial adhesions. Recently, real-time phase-contrast imaging has been proposed to assess the effects of respiration on cardiac filling [50].
- The pericardial cavity and membranes can be recognized on cardiac **CT** images even without injection of contrast media. Normal pericardium is usually < 3 mm in thickness. Thickening of the pericardium may be difficult to distinguish from small pericardial effusions. **Pericardial calcifications** as well as larger pericardial effusions are also readily identified on non-enhanced CT images. Constrictive pericarditis is not an anatomical diagnosis, although certain CT characteristics such as pericardial calcification, pericardial thickening (>4 mm), narrowing or tubular deformation of the RV, as well as manifestations of venous congestion can be present. Pericardial abnormalities may be regional.

12.6 Prevention Strategies in Subjects Treated By RT

RIHD is the most common nonmalignant cause of death in HL and breast cancer patients treated with RT. Among cured HL patients, it accounts for 25 % of mortality, with myocardial infarction as the most common cause of death. Patients with breast cancer also have an increased cardiovascular mortality if treated with RT, mostly those with left breast cancer [34].

- The first step of prevention is responsibility of the radiation oncologist, who can use radiation techniques (as conformational radiation fields, heart shielding…) at the time of treatment [51]. With modern radiation techniques, probably the problem of RIHD will be reduced in the future.

Many of the patients currently aged 40 or more have been treated in the past, before the introduction of new RT techniques, and should be object of an active program of prevention and follow-up. Usually, the HL and breast cancer patients who achieved complete remission are dismissed by the oncological follow-up after 5–10 years. Few patients have the opportunity to be included in a cancer survivor clinic for long-term follow-up of treatment-related disease. The general practitioners and the cardiologists should take care of this problem.

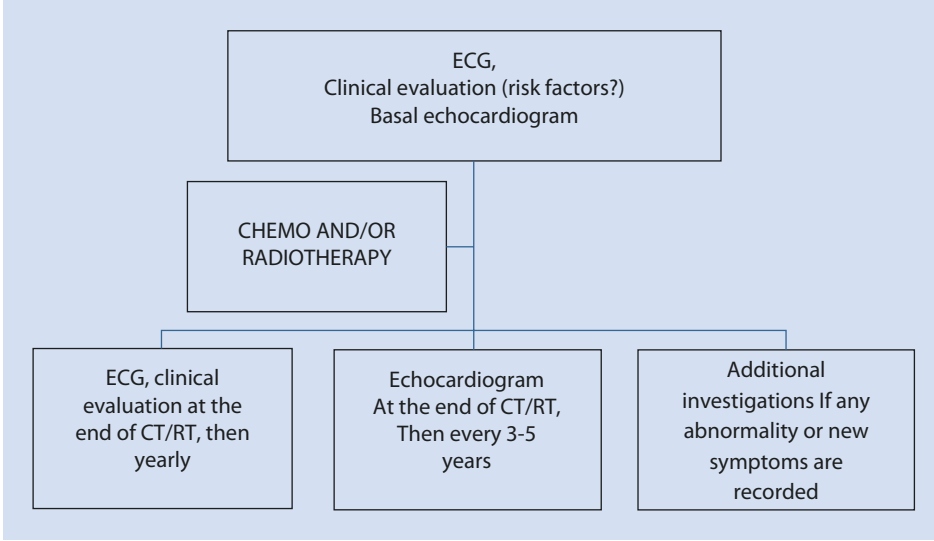

Fig. 12.7 Suggested pretreatment evaluation and short-medium term follow-up for patients without cardiac disease or symptoms undergoing RT

- The group at highest risk is represented by childhood cancer survivors, and this problem has been addressed in Chap. 16 (Cardiotoxicity in children). We will consider here the patients treated in their adulthood. There are no official guidelines about the optimal method and frequency of screening in this group of patients. The following suggestions have been obtained by the synthesis of published recommendations and by the personal experience of the authors.
- **Primary prevention** includes the common strategies for CAD: subjects treated by chest RT should be encouraged to avoid smoking, have a healthy lifestyle (including diet and regular physical activity), and maintain optimal body weight.
- Check regularly patient's blood pressure, blood glucose, and cholesterol, and start appropriate dietary or pharmacological interventions as soon as necessary
  - **Start a cardiac screening** with yearly ECG and clinical visits soon after the end of radiation treatment, and echocardiogram every 3–5 years (Fig. 12.7).
  - The echocardiographic follow-up should be more strict if cardiotoxic chemotherapy was also given.
  - Additional investigations may be planned according to the clinical findings
  - The data about the possible role of biomarkers (natriuretic peptides, troponins), in detecting RT-induced cardiac injury are scarce and conflicting [52].
- **Ten years after RT, noninvasive tests to detect CAD or ischemic heart disease are necessary and should be repeated every 2–3 years thereafter.**
  - In patients with additional risk factors (younger age at RT treatment, other CAD risk factors), the screening should be anticipated (5 years after RT).
- **In the following years, echocardiograms should be performed every 3 years and more often if cardiac valve abnormalities are observed** (Fig. 12.8)
- **The follow-up should last lifelong.**

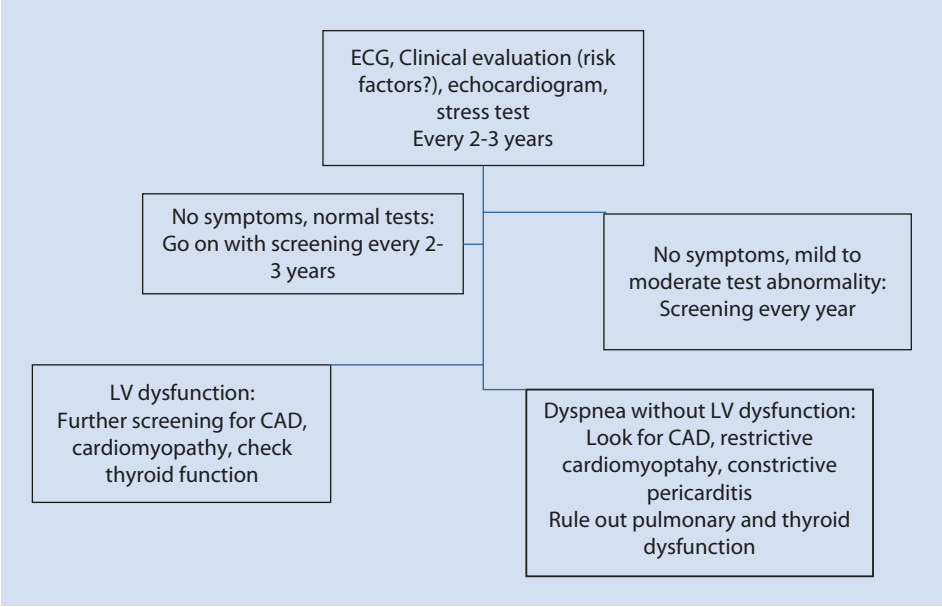

Fig. 12.8 Suggested long-term follow-up for patients without cardiac disease or symptoms. Start after 5 years after RT if the patient has a high cardiovascular risk, after 10 years if he/she haven't

12.7 Therapy

Some particular aspects of RIHD should be considered when planning therapy:

- **Both tachy- and bradyarrhythmias** may affect RT survivors. For advanced atrioventricular block, permanent pacemaker implantation may be necessary. The most common problem, however, is inappropriate sinus tachycardia. Beta blockers are indicated, but often require cautious titration in order to avoid symptomatic hypotension. Ivabradine may be a useful alternative and better tolerated by some patients (Fig. 12.9).
- **Percutaneous angioplasty** (PTCA) for CAD may be technically difficult and followed by early re-stenosis in comparison to non-RT-induced CAD [53].
- **Coronary bypass surgery** may be more difficult or associated with poorer outcomes because the internal mammary arteries may be also be affected by RT, because of poor distal arterial runoff caused by radiation damage [54], or due to the postoperative complications related to RT-induced lung disease and impaired lymphatic drainage.
- **Pericardiectomy** is usually associated with poorer outcomes in RT patients compared to those with non-RT-related causes of pericarditis. This is due to the observation that many RT patients have concomitant myocardial restriction that persists despite pericardiectomy. Pericardial stripping may also be difficult because the visceral pericardium is usually adherent to the epicardium. Pericardiectomy has the highest perioperative and long-term mortality if RT was the underlying cause [55, 56].
- **Cardiac valve repair** is difficult and is associated with suboptimal long-term results compared to **valve replacement**. However, the involvement of multiple valves, pres-

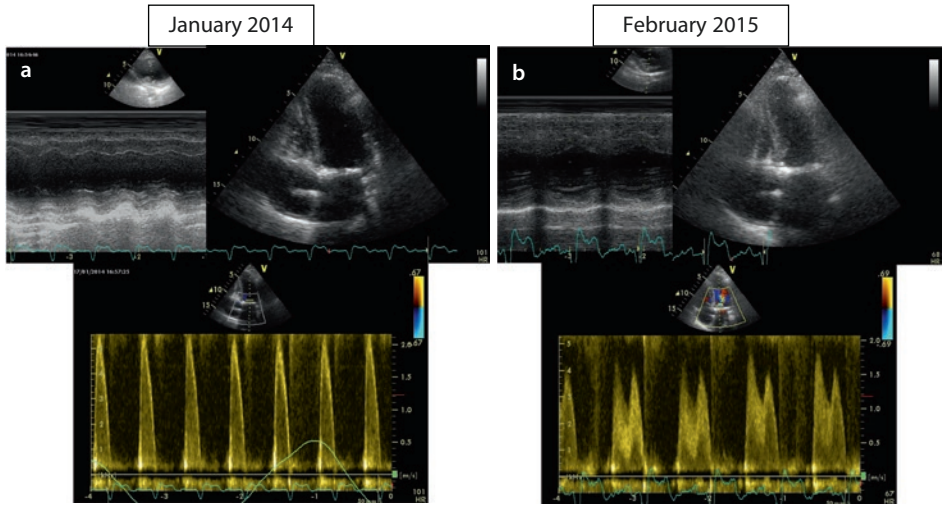

Fig. 12.9 Female patient, treated by mediastinal radiotherapy in 1981, at age 24, for Hodgkin lymphoma. In the following years, she had: thyroidectomy for cancer (2000); acute myocardial infarction (inferior wall and right ventricle) with 95 % ostial stenosis of the right coronary artery (2008) treated with angioplasty; recurring pneumonia; complete atrioventricular block treated by pacemaker (2012); transcatheter aortic valve replacement for severe stenosis (2013); occlusion of the right coronary artery (2013). (**a**) Systolic four-chamber view, ventricular M-Mode, and diastolic mitral Doppler flow in January 2014: an extensive calcification of the mitral annulus is evident; heart rate 101, ejection fraction 57 %, and restrictive pattern at Doppler. (**b**) One year later, after adding to therapy bisoprolol 2.5 mg and Ivabradine 10 mg the heart rate is reduced to 68, the ejection fraction increased to 62 %, mitral flow has improved, and symptoms have improved from NYHA 3 to NYHA 2

12

ence of concomitant coronary artery disease, restrictive myocardial disease, aortic abnormalities, and mediastinal fibrosis can increase the length and complexity of the surgery, leading to adverse outcomes. Evolving trans-catheter approaches to valve replacement may be particularly suited to RT patients [19, 57].

- Technical problems during **cardiac operations of any kind** include dense scarring of the mediastinum from radiation-induced mediastinitis and impaired wound healing due to skin changes [58].
- **Due to the multiple cardiac complications seen with RT, patients with RIHD often require repeat cardiac surgery and may even require cardiac transplantation.** However, in two small series published, secondary malignancies, kidney injury, and respiratory failure contribute to significant postoperative morbidity and death [59, 60].

According to two large studies, patients with radiation heart disease undergoing cardiothoracic surgery have greater short-term and long-term mortality compared with age- and sex-matched comparison group patients undergoing similar surgeries in the same time frame. Perioperative morbidity and mortality are high mostly because of respiratory dysfunction and multiorgan failure [61, 62].

- In radiation heart disease patients undergoing cardiac surgery, the prediction of mortality risk based solely on standard preoperative scores is suboptimal; the extent of exposure is also relevant.

The presence of radiation-induced lung fibrosis is a significant predictor of worse long-term mortality independent of euroSCORE.

It is important to carefully evaluate patients being considered for cardiac surgery using clinical (including detailed pulmonary function testing) and multimodality imaging (echocardiography, multidetector computed tomography, and in select cases, carotid ultrasound) to fully understand the extent of their cardiovascular involvement prior to surgery [63].

12.8 Vascular RT Complications

- The risk from RT has been best characterized in patients with breast cancer or Non-Hodgkin lymphoma. Theoretically, however, any vascular location that is in the radiation field is at increased risk for early atherosclerosis. This is particularly relevant among patients with head and neck cancer because neck RT is a major risk factor for significant carotid disease. In fact, the risk of stroke is increased after mediastinal, cervical, or cranial RT. [64, 65].
- The pathophysiological effects of human cerebrovascular radiation have been shown in vitro or in animal models using non-fractionated, supra-therapeutic radiation [66]. The histological and cellular modifications of the human cerebral vascularization to radiotherapy can be characterized in relation to vessel diameter and time from treatment. Inflammatory response, endothelial damage, intima proliferation, and thrombus formation may occur after irradiation in the cerebral smallest arteries, arterioles, and capillaries, with increased permeability of the blood–brain barrier [67]. Large vessels, carotid arteries, and the circle of Willis are more resistant, but advanced atherosclerosis may occur.
- In the first year after neck irradiation, a certain degree of increase in the thickness of the carotid wall may be shown. In medium and large vessels, vasa-vasorum occlusions with medial necrosis followed by fibrosis, adventitial fibrosis, and accelerated atherosclerosis have been described [68].
  - These alterations lead to increased stiffness and advanced atherosclerosis of carotid arteries also after long time (>10 years after RT) [69].
  - Radiation-induced carotid disease produces carotid lesions that are more extensive than the traditional bifurcation stenosis and often involves atypical areas such as long segments of the carotid artery [70].
  - The global risk of cerebrovascular events is increased and the common atherosclerosis risk factors and preexisting atherosclerotic lesions are exacerbating factors [71]. Thus, a radiation-related increase in vascular disease risk has been confirmed and a dose–response relationship based on individual patient characteristics.
  - Hypertension is a cause and, at the same time, a long-term consequence of the stiffening process that may follow the atherosclerotic disease due to RT.
  - Hypertension can be enhanced by many cancer therapies, including both chemotherapy and targeted agents, should the patient undergo antineoplastic treatments after RT (for a relapsing or a second cancer).
- Similar consequences are reported on the aorta and other peripheral arteries, including subclavian and ilio-femoral arteries, with ischemic limb symptoms [72].

- Frequently, there are no symptoms attributable to carotid disease in patients previously treated with RT. Therefore, clinicians should be proactive about age-appropriate cardiovascular screening for potentially significant yet asymptomatic disease in these patients [73].
  - For patients at risk for carotid artery disease, ultrasound is the safest and most effective screening tool and must be used for follow-up of atherosclerotic damage.
  - During the last years, increasing interest has been placed on methods for assessment of vascular function, such as pulse wave analysis, arterial stiffness, and endothelial dysfunction, able to detect a very early vascular damage, but their role is still debated for the interference with coexisting risk factors.
- It's mandatory to make an estimation of global cardiovascular risk combined with subclinical targeted organ damage, taking into account the increased cardiovascular risk due to the effects of the concomitant oncologic treatment.

Operative Protocol

- In symptomatic patients for stroke/TIA or in the presence of carotid murmurs, it is indicated to perform a study with Doppler ultrasound integrated by MRI angiography or CT angiography.
- These surveys are also indicated for asymptomatic patients who have other manifestations of vascular disease and who have a moderate-to-high cardiovascular risk or for patients exposed to RT by at least 10 years. In the case of proven carotid disease is indicated to carry on an annual survey, otherwise, just a follow-up every 5 years.

References

1. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. Front Oncol. 2015;5:39.
2. Murthy SC, Rozas MS, Adelstein DJ, et al. Induction chemoradiotherapy increases pleural and pericardial complications after esophagectomy for cancer. J Thorac Oncol. 2009;4:395–403.
3. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977-1997. Bone Marrow Transplant. 2001;28:283–7.
4. de Ville de Goyet M, Brichard B, et al. Prospective cardiac MRI for the analysis of biventricular function in children undergoing cancer treatments. Pediatr Blood Cancer. 2015;62:867–74.
5. Marks LB, Yu X, Prosnitz RG, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys. 2005;63(1):214–23.
6. Gayed I, Gohar S, Liao Z, et al. The clinical implications of myocardial perfusion abnormalities in patients with esophageal or lung cancer after chemoradiation therapy. Int J Cardiovasc Imaging. 2009;25:487–95.
7. Galper SL, Yu JB, Mauch PM, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. Blood. 2011;117:412–8.
8. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–98.
9. Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 2003;45:55–75. Review.
10. Gaya AM, Ashford RF. Cardiac complications of radiation therapy. Clin Oncol (R Coll Radiol). 2005;17:153–9. Review.
11. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med. 2015;175:1007–17.

12. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Inst. 2007;99:206–14.
13. Duma MN, Molls M, Trott KR. From heart to heart for breast cancer patients-cardiovascular toxicities in breast cancer radiotherapy. Strahlenther Onkol. 2014;190:5–7.
14. Daniëls LA, Krol AD, de Graaf MA, et al. Screening for coronary artery disease after mediastinal irradiation in Hodgkin lymphoma survivors: phase II study of indication and acceptance†. Ann Oncol. 2014;25:1198–203.
15. Heidenreich PA, Hancock SL, Vagelos RH, et al. Diastolic dysfunction after mediastinal irradiation. Am Heart J. 2005;150:977–82.
16. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol. 2011;100:167–75.
17. Cella L, Liuzzi R, Conson M, et al. Dosimetric predictors of asymptomatic heart valvular dysfunction following mediastinal irradiation for Hodgkin's lymphoma. Radiother Oncol. 2011;101:316–32.
18. Wethal T, Lund MB, Edvardsen T, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer. 2009;101:575–81.
19. Handa N, McGregor CG, Danielson GK, et al. Valvular heart operation in patients with previous mediastinal radiation therapy. Ann Thorac Surg. 2001;71:1880–4.
20. Schellong G, Riepenhausen M, Bruch C, et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer. 2010;55:1145–52.
21. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst. 2015;107(4)
22. Groarke JD, Tanguturi VK, Hainer J, et al. Abnormal exercise response in long-term survivors of hodgkin lymphoma treated with thoracic irradiation: evidence of cardiac autonomic dysfunction and impact on outcomes. J Am Coll Cardiol. 2015;65:573–83.
23. Slama MS, Le Guludec D, Sebag C, et al. Complete atrioventricular block following mediastinal irradiation: a report of six cases. Pacing Clin Electrophysiol. 1991;14:1112–8.
24. Orzan F, Brusca A, Gaita F, et al. Associated cardiac lesions in patients with radiation-induced complete heart block. Int J Cardiol. 1993;39:151–6.
25. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003;42:743–9.
26. Chargari C, Riet F, Mazevet M, et al. Complications of thoracic radiotherapy. Presse Med. 2013;42:e342–51.
27. Ding X, Ji W, Li J, Zhang X, Wang L. Radiation recall pneumonitis induced by chemotherapy after thoracic radiotherapy for lung cancer. Radiat Oncol. 2011;6:24.
28. Levy A, Hollebecque A, Bourgier C, et al. Targeted therapy-induced radiation recall. Eur J Cancer. 2013;49:1662–8.
29. Limper AH. Chemotherapy-induced lung disease. Clin Chest Med. 2004;25:53–64.
30. Della Latta V, Cecchettini A, Del Ry S, Morales MA. Bleomycin in the setting of lung fibrosis induction: From biological mechanisms to counteractions. Pharmacol Res. 2015;97:122–30.
31. Hancock SL, Cox RS, McDougall IR. Thyroid Diseases after Treatment of Hodgkin's Disease. N Engl J Med. 1991;325:599–605.
32. Jereczek-Fossa BA, Alterio D, Jassem J, et al. Radiotherapy-induced thyroid disorders. Cancer Treat Rev. 2004;30:369–84. Review.
33. Lancellotti P, Nkomo VT, Badano LP, et al.; European Society of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance; American Society of Nuclear Cardiology; Society for Cardiovascular Magnetic Resonance; Society of Cardiovascular Computed Tomography. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2013;14:721–40.
34. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013;61:2319–28.
35. Heidenreich P, Schnittger I, Strauss H, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol. 2007;25:43–9.
36. Kupeli S, Hazirolan T, Varan A, et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. J Clin Oncol. 2010;28:1025–30.

37. Schwitter J, Arai AE. Assessment of cardiac ischaemia and viability: role of cardiovascular magnetic resonance. Eur Heart J. 2011;32:799–809.
38. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012;379:453–60.
39. Machann W, Beer M, Breunig M, et al. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys. 2011;79:1117–23.
40. Pierga J, Maunoury C, Valette H, et al. Follow-up thallium-201 scintigraphy after mantle field radiotherapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1993;25:871–6.
41. Mulrooney DA, Nunnery SE, Armstrong GT, et al. Coronary artery disease detected by coronary computed tomography angiography in adult survivors of childhood Hodgkin lymphoma. Cancer. 2014;120:3536–44.
42. Grothues F, Smith G, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90:29–34.
43. Caudron J, Fares J, Bauer F, Dacher JN. Evaluation of left ventricular diastolic function with cardiac MR imaging. Radiographics. 2011;31:239–59.
44. Brouwer C, Postma A, Vonk J, et al. Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. Eur J Cancer. 2011;47:2453–62.
45. Nagueh S, Appleton C, Gillebert T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10:165–93.
46. Dickerson JA, Raman SV, Baker PM, Leier CV. Relationship of cardiac magnetic resonance imaging and myocardial biopsy in the evaluation of nonischemic cardiomyopathy. Congest Heart Fail. 2013;19:29–38.
47. Zurick A, Bolen M, Kwon D, et al. Pericardial delayed hyperenhancement with CMR imaging in patients with constrictive pericarditis undergoing surgical pericardiectomy: a case series with histopathological correlation. JACC Cardiovasc Imaging. 2011;4:1180–91.
48. Feng D, Glockner J, Kim K, et al. Cardiac magnetic resonance imaging pericardial late gadolinium enhancement and elevated inflammatory markers can predict the reversibility of constrictive pericarditis after antiinflammatory medical therapy: a pilot study. Circulation. 2011;124:1830–7.
49. Francone M, Dymarkowski S, Kalantzi M, et al. Assessment of ventricular coupling with real-time cine MRI and its value to differentiate constrictive pericarditis from restrictive cardiomyopathy. Eur Radiol. 2006;16:944–51.
50. Thavendiranathan P, Verhaert D, Walls M, et al. Simultaneous right and left heart real-time, free-breathing CMR flow quantification identifies constrictive physiology. JACC Cardiovasc Imaging. 2012;5:15–24.
51. Johansen S, Tjessem KH, Fosså K, et al. Dose Distribution in the Heart and Cardiac Chambers Following 4-field Radiation Therapy of Breast Cancer: a Retrospective Study. Breast Cancer (Auckl). 2013;7:41–9.
52. Tian S, Hirshfield KM, Jabbour SK, et al. Serum biomarkers for the detection of cardiac toxicity after chemotherapy and radiation therapy in breast cancer patients. Front Oncol. 2014;4:277.
53. Schömig K, Ndrepepa G, Mehilli J, et al. Thoracic radiotherapy in patients with lymphoma and restenosis after coronary stent placement. Catheter Cardiovasc Interv. 2007;70:359–65.
54. Brown ML, Schaff HV, Sundt TM. Conduit choice for coronary artery bypass grafting after mediastinal radiation. J Thorac Cardiovasc Surg. 2008;136:1167–71.
55. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation. 1999;100:1380–6.
56. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause specific survival after pericardiectomy. J Am Coll Cardiol. 2004;43:1445–52.
57. Crestanello JA, McGregor CG, Danielson GK, et al. Mitral and tricuspid valve repair in patients with previous mediastinal radiation therapy. Ann Thorac Surg. 2004;78:826–31.
58. Handa N, McGregor CG, Danielson GK, et al. Coronary artery bypass grafting in patients with previous mediastinal radiation therapy. J Thorac Cardiovasc Surg. 1999;117:1136–42.
59. Uriel N, Vainrib A, Jorde UP, et al. Mediastinal radiation and adverse outcomes after heart transplantation. J Heart Lung Transplant. 2010;29(3):378–81.
60. Saxena P, Joyce LD, Daly RC, et al. Cardiac transplantation for radiation-induced cardiomyopathy: the Mayo Clinic experience. Ann Thorac Surg. 2014;98:2115–21.
61. Chang AS, Smedira NG, Chang CL, et al. Cardiac surgery after mediastinal radiation: extent of exposure influences outcome. J Thorac Cardiovasc Surg. 2007;133:404–13.

62. Wu W, Masri A. Popovic ZBet al. Long-term survival of patients with radiation heart disease undergoing cardiac surgery: a cohort study. Circulation. 2013;127:1476–85.
63. Desai MY, Karunakaravel K, Wu W, et al. Pulmonary fibrosis on multidetector computed tomography and mortality in patients with radiation-associated cardiac disease undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2014;148:475.e3–81.
64. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transientischemic attack in 5-year survivors of Hodgkin lymphoma. J Natl Cancer Inst. 2009;101(13):928–37.
65. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transientischemic attack after head and neck radiotherapy: a review. Stroke. 2011;42:2410–8.
66. Acker JC. Serial in vivo observation of cerebral vasculature after treatment with a large single fraction of radiation. Radiat Res. 1998;149:350.
67. Ye J, Rong X, Xiang Y, et al. A study of radiation-induced cerebral vascular injury in nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis. PLoS One. 2012;7(8), e42890.
68. Louis EL, McLoughlin MJ, Wortzman G. Chronic damage to medium and large arteries following irradiation. J Can Assoc Radiol. 1974;25(2):94–104.
69. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA. 2003;290:2831–7.
70. Cheng SW. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg. 2000;126:517.
71. Steele SR, Martin MJ, Mullenix PS, et al. Focused high-risk population screening for carotid arterial stenosis after radiation therapy for head and neck cancer. Am J Surg. 2004;187:594–8.
72. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. Catheter Cardiovasc Interv. 2008;72:563–8.
73. Zagar TM, Marks LB. Breast cancer radiotherapy and coronary artery stenosis: location, location, location. J Clin Oncol. 2012;30:350.
74. Mousavi N, Nohria A. Radiation-induced cardiovascular disease. Curr Treat Opt Cardiovasc Med. 2013; 15:507–17.