Cardiovascular and Pulmonary Late Effects

27

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27.1 Cardiovascular Toxicity

Radiotherapy and chemotherapy for Hodgkin lymphoma may both cause cardiovascular toxicity. Cardiovascular toxicity following radiotherapy is usually not observed until more than 5 years after therapy, whereas anthracycline-related toxicity is observed at varying intervals after therapy. This chapter mainly focuses on late effects. Tables 27.1 and 27.2 show detailed information on standardized mortality rates and standardized incidence rates of several cardiovascular diseases following treatment for Hodgkin lymphoma including the absolute excess risks, mainly from cohorts treated using historical treatment techniques. A population-based cohort study from Sweden [1] demonstrated that excess mortality from circulatory disease has decreased continuously since the 1980s, and it is expected to decrease further with more modern treatment techniques.

27.1.1 Chemotherapy-Associated Cardiotoxicity

27.1.1.1 General Aspects of Chemotherapy-Associated Cardiotoxicity

The most relevant cardiotoxic chemotherapeutic agents used in treatment of Hodgkin lymphoma patients are anthracyclines, specifically doxorubicin and epirubicin. Anthracycline-associated toxicity may occur at different intervals after therapy. Cardiotoxicity may present as electrocardiographic changes and arrhythmias or as cardiomyopathy leading to congestive heart failure. Anthracycline-associated cardiotoxicity is mainly caused by direct damage to the myocardium, but anthracyclines are also recognized to cause vascular endothelial dysfunction which may increase cardiovascular risk. Several risk factors for anthracycline-associated cardiotoxicity have been identified (see Table 27.3). The occurrence of acute anthracycline-associated cardiotoxicity is dose dependent [13] and increases dramatically with cumulative doses higher than 500 mg/m^2 doxorubicin [14]. The total dose of anthracyclines during first-line therapy for Hodgkin lymphoma does usually not exceed 300 mg/m^2. For example, the cumulative dose of six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is 300 mg/m^2 and of eight cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP) is 280 mg/m^2. However, it is now recognized that there is no risk-free dose of anthracyclines, and particularly younger patients have experienced cardiac damage at doses of <250 mg/m^2 [13, 15].

Whether toxicity following chemotherapy and radiotherapy is additive or synergistic remains unclear. Clinical studies have shown that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders by two- to threefold compared to radiotherapy alone [20]. This effect may be more than additive [21]. A British study also demonstrated that an increased risk of death from myocardial infarction was related to anthracycline and vincristine treatment as well as supradiaphragmatic radiotherapy; the risk of death from myocardial infarction was increased for patients who did not receive supradiaphragmatic radiotherapy but had received vincristine (standardized mortality ratio (SMR) = 2.2,

Table 27.1 Risk of death from cardiac diseases in large cohorts of patients treated for Hodgkin lymphoma

Authors	Treatment period	No. in cohort	Age range at treatment in years	Follow-up in years (range)	Type of treatment	Endpoint	SMR[a]	(95% CI) SMR[a]	AER[b]
Boivin [2]	1940–1985	4665	All ages[c]	Mean 7 (–)	Mediastinal RT ± CT	MI	4.1	(1.5–10.9)	–
Hancock [3] and Hoppe [4]	1960–1991	2232	1–82 (mean 29)	Mean 9.5 (–)	89% including mediastinal RT	MI	3.2	(2.3–4.0)	17.8
King [5]	1954–1989	326	5–72 (mean 25.6)	Mean 13.3 (3–37)	Mantle RT ± CT	MI	2.8	(0.7–4.9)	10.4[d]
Glanzmann [6]	1964–1992	352	4.0–81 (mean 33.8)	Mean 11.2 (1.0–31.5)	Mediastinal RT ± CT	MI	4.2	(1.8–8.3)	–
Brierley [7]	1973–1984	611	17–90 (median 31)	Median 11.0 (0.7–18.0)	97% RT ± CT	MI	1.5	(0.7–3.0)	5.4
Ng [8]	1969–1997	1080	3–50 (median 25)	Median 12	96% RT ± CT	Cardiac death	3.2	(1.9–5.2)	9.0
Aleman [9]	1965–1987	1261	Median 26	Median 17.8	97% RT ± CT; 84% mediastinal RT	MI	4	(2.3–6.5)	5.6
Swerdlow [10]	1976–2000	7033	All ages	Median 11.1	72% RT ± CT; 34% including mediastinal RT	MI	2.5	(2.1–2.9)	12.6

SMR standardized mortality ratio, *CI* confidence interval, *AER* absolute excess risk, *RT* radiotherapy, *CT* chemotherapy, *MI* myocardial infarction

[a]Standardized mortality ratio (SMR) as the ratio of the observed (O) and expected (E) numbers of cardiovascular events in the cohort. The expected numbers are calculated based on general population rates

[b]Absolute excess risk (AER) per 10,000 person-years as O minus E, divided by the number of person-years at risk, multiplied by 10,000

[c]62% <40 years

[d]Calculated from the data in the paper: (observed [7] – expected (2.5)/person-years at risk (4335)) × 10,000

Table 27.2 Standardized incidence ratio and absolute excess risks of coronary heart disease as first event, congestive heart failure as first event, stroke, and transient ischemic attack by sex, age at start of treatment, follow-up interval, attained age, and treatment in patient treated for Hodgkin lymphoma[a]

	CHD		CHF		Stroke		TIA	
	SIR	AER	SIR	AER	SIR	AER	SIR	AER
Total cohort	3.3	70	5.1	30	2.2	12	3.1	9
Sex								
Male	1.4	25	4.1	28	2.0	10	2.7	8
Female	6.2	114	6.4	33	2.4	14	3.8	11
Age at treatment (years)								
<18 MI and CHF, ≤20 stroke and TIA	7.1	46	26.5	25	3.8	7	7.6	5
18–30 MI and CHF, 21–30 stroke and TIA	3.9	63	11.0	32.5	3.1	14	4.2	7
31–40	2.8	91	4.1	30	2.0	15	3.1	13
41–50	2.0	98	2.0	29	1.4[b]	11	2.1[b]	18
Follow-up period (years)								
5–9	2.9	30	4.9	11	2.1[b]	5	2.3	3
10–14	3.1	51	6.2	22	2.3	10	3.3	8
15–19	3.6	94	6.1	32	2.6	18	4.4	17
20–24	3.1	108	6.4	55	2.1[b]	17	2.5[b]	11
25–29	2.8	132	5.0	58	1.9[b]	26	2.8	23
30–34	2.3	122	2.2	24				
≥ 35	1.8	124	1.9	59				
Attained age (years)								
Age at treatment 25–34 years								
Attained age <45 years	4.2	41	9.3	17				
Attained age 45–59 years	3.8	131	5.5	34				
Attained age ≥60 years	2.7[b]	64	1.1[b]	3				
Age at treatment <51 years								
Attained age <51					2.5	7	3.2	4
Attained age ≥51					2.0	29	3.1	30
Treatment								
No mediastinal RT, no anthracyclines	1.5	17	1.4	4				
Anthracyclines, no mediastinal RT	3.0	54	4.6	20				
Mediastinal RT, no anthracyclines	3.1	82	4.8	30				
Mediastinal RT and anthracyclines	4.7	79	16.0	53				
Treatment								
Radiotherapy alone					2.0	11	3.4	12
Chemotherapy alone					0.4[b]	−6	–	–
Radiotherapy/chemotherapy					2.6	15	3.4	10

CHD coronary heart disease, includes both myocardial infarction and angina pectoris, *CHF* congestive heart failure, *TIA* transient ischemic attack, *SIR* standardized incidence ratio, *AER* absolute excess risk, *RT* radiotherapy

[a]Adapted from Van Nimwegen et al. [11] and De Bruin and Dorresteijn et al. [12]. CHD and CHF data from cohort of 2524 Dutch patients diagnosed as having HL at age younger than 51 years (median age, 27.3 years) who had been treated between 1965 and 1995 and had survived for 5 years since their diagnosis and stroke and TIA data from cohort of 2201 5-year survivors of Hodgkin lymphoma treated before the age of 51 between 1965 and 1995

[b]Not statistically significant

95% CI = 1.6–3.0) and anthracyclines (SMR = 3.2, 95% CI = 1.9–5.2), especially those who were treated with the ABVD regimen (SMR = 7.8, 95% CI = 1.6–22.7) [10].

The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity including congestive heart failure is beginning to be elucidated. A growing number of studies in humans have provided evidence that genetic susceptibility may play a role in the risk of anthracycline-associated cardiotoxicity. Patients with particular genetic profiles, leading to higher levels of

Table 27.3 Risk factors for anthracycline-associated cardiotoxicity

Risk factor	Features
Total cumulative dose	Most significant predictor for abnormal cardiac function
Age	For comparable cumulative doses, younger age predisposes to a greater relative risk of cardiotoxicity
Length of follow-up	Longer follow-up results in higher prevalence of myocardial impairment
Gender	Females more vulnerable than males for comparable doses perhaps due to a greater fat percentage of body mass [16]
Race	Those of black race possibly more susceptible [17]
Mediastinal irradiation	Enhanced toxicity; not clear whether additive or synergistic
Genetic susceptibility	Patients with particular genetic profiles are more prone to develop chemotherapy-related cardiac dysfunction [18]

Adapted from Table 10.4 of Chap. 10, "Cardiovascular Effects of Cancer Therapy," by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [19]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer

reactive oxygen species and topoisomerase 2β, increased accumulation of cardiotoxic anthracycline metabolites, and poorer sarcomere function, are more prone to develop chemotherapy-related cardiac dysfunction [18].

27.1.1.2 Prevention of Chemotherapy-Associated Cardiotoxicity

The obvious measure to prevent cardiotoxicity is to limit both cardiotoxic chemotherapy (especially anthracyclines) and radiation volume and dose as much as possible [22, 23]. The evidence on the effectiveness of other approaches to reduce or prevent anthracycline-associated cardiotoxicity is limited in terms of quantity and quality [24]. Early studies suggested that limiting the peak serum concentration of anthracyclines administered by continuous infusion could limit cardiotoxicity [25], but this has not been confirmed by subsequent studies, mainly in children. Anthracyclines release free radicals that damage cardiac myocytes, which are especially susceptible to such damage because of their highly oxidative metabolism and poor antioxidant defenses. Dexrazoxane, a free-radical-savaging, iron-chelating agent, has been demonstrated to reduce cardiotoxicity [26, 27]. Liposomal doxorubicin, an alternative preparation where the drug is encapsulated in an enclosed lipid sphere, has demonstrated efficacy with a reduced risk of cardiotoxicity [28]. A recent meta-analysis ($n = 633$) of randomised trials carvedilol for the primary prevention of anthracycline-induced cardiotoxicity demonstrated that prophylactic administration may reduce the early onset of left ventricular dysfunction compared with placebo [29]. Furthermore, there are some indications of a possible beneficial effect of angiotensin-converting enzyme (ACE) inhibitors after cardiotoxic chemotherapy [30]. Several other agents including L-carnitine have also been investigated [31] with some promising results. However, these studies have so far not been conclusive.

27.1.1.3 Surveillance for and Management of Chemotherapy-Associated Cardiotoxicity

Guidelines published by the International Late Effects of Childhood Cancer Guideline Harmonization Group [32] recommended regular echocardiographic surveillance for cardiomyopathy in children treated with anthracycline doses of >250 mg/m^2 or lower doses (>100 mg/m^2) in combination with moderate doses of chest radiation (>15 Gy). However, owing to the absence of high-quality evidence in other patient groups, guidelines from different organizations in North America and Europe do not agree on the need for surveillance in survivors of adult cancers with either imaging or other cardiac biomarkers [33]. Whether patients are offered routine surveillance may therefore vary from country to country and by the clinician's assessment of an individual's risk based on the factors outlined in Table 27.3.

Currently, there are no indications that the management of anthracycline-associated congestive heart failure should differ from that due to other causes [34]. Treatment generally focuses on correcting underlying physiological abnormalities such as increased afterload and decreased

contractility frequently including treatment with ACE inhibitors and/or beta-blockers [35]. Several guidelines developed for treating patients with asymptomatic left ventricular dysfunction or heart failure (not specifically after cancer treatment) include beta-blockers, ACE inhibitors, and diuretics [36, 37].

27.1.2 Radiation-Associated Cardiotoxicity

27.1.2.1 General Aspects of Radiation-Associated Cardiotoxicity

Radiation-associated heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities [38, 39] (see Fig. 27.1). Pericarditis is sometimes observed early after radiation, although it is rare with modern doses and techniques of Hodgkin lymphoma radiotherapy. Delayed pericarditis may occur months to years after radiation and usually resolves spontaneously although it may develop into chronic and/or constrictive pericarditis [40, 41]. Radiation-associated heart diseases other than pericarditis usually present 10–15 years after exposure, although, recently, a significantly increased risk of ischemic heart disease has been reported within 5 years following radiotherapy for breast cancer. Non-symptomatic abnormalities may develop much earlier on cardiac imaging.

Radiation causes both increased mortality, mainly fatal myocardial infarction (MI), and increased morbidity (see Tables 27.1 and 27.2).

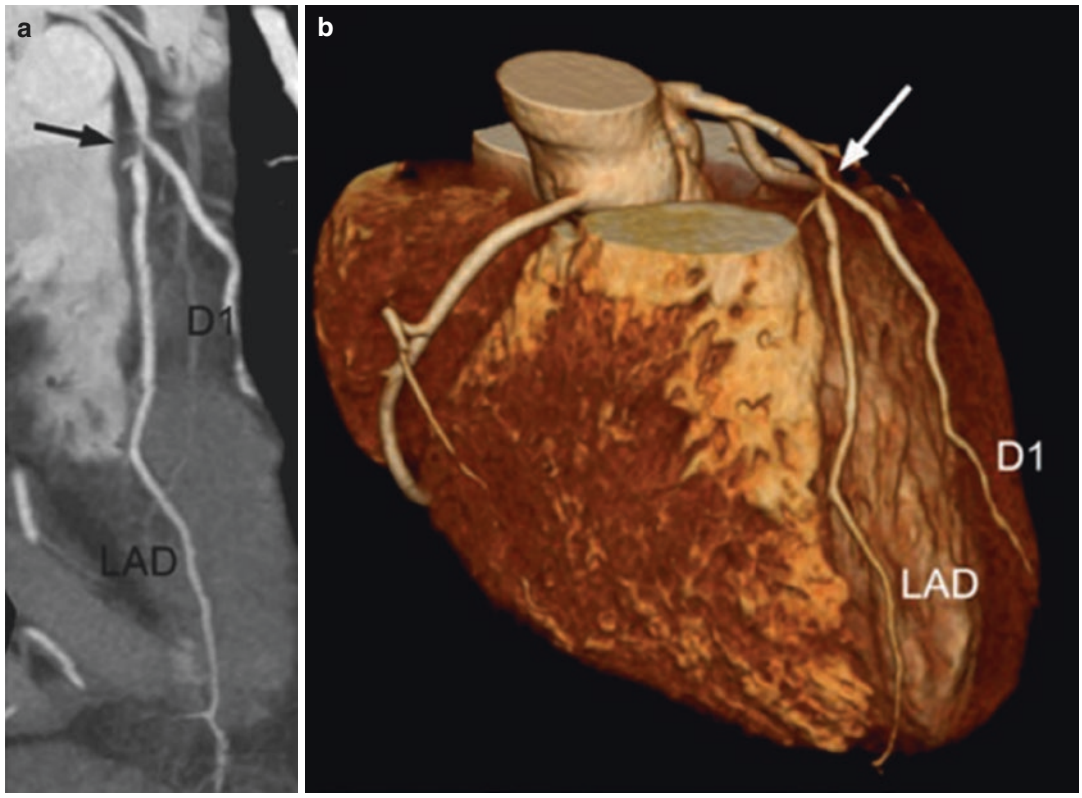

Fig. 27.1 Cardiac CT. Coronary artery disease: a 41-year-old man with severe obstructive coronary disease of the left anterior—diagonal bifurcation (arrow) only a few years after mediastinal radiation therapy because of Hodgkin lymphoma by angiographic (**a**) and cardiac CT (**b**) imaging (from Lancellotti et al. [42])

Table 27.4 Risk factors for the different manifestations of radiation-associated cardiotoxicity

Risk factor	Pericarditis	CM	CAD	Arrhythmia	Valvular disease	All causes of CD	References
Total dose (>30–35 Gy)	✓	✓	✓	✓	✓	✓	[41, 48–51]
Dose per fraction (≥2.0 Gy/day)	✓	✓	✓	✓	✓	✓	[41]
Volume of the heart exposed	✓	✓	✓	✓	✓	✓	[40, 52]
Younger age at exposure	–	✓	✓	✓	✓	✓	[20, 52]
Increased time since exposure	–	✓	✓	✓	✓	✓	[20]
Use of adjuvant cardiotoxic chemotherapy	–	✓	–	✓	✓	✓	[20, 21, 48]
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	✓	–	–	✓	[6, 20]

Adapted from Table 10.5 of Chap. 10, "Cardiovascular Effects of Cancer Therapy," by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [19]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer
CM cardiomyopathy, *CAD* coronary artery disease, *CD* cardiac death

Epidemiological studies on Hodgkin lymphoma survivors show relative risk estimates for MI and cardiac death in the range of two- to fourfold in adults. This risk varies with age at treatment (increased relative risks for irradiation at a young age), the radiation therapy methods used, and the follow-up time [38, 39, 43]. In a Dutch study of Hodgkin lymphoma patients treated before the age of 51 years, even after 35 years or more, four- to sixfold increased standardized incidence ratios (SIR) for coronary heart disease and heart failure were observed, corresponding to 857 excess events per 10,000 person-years [11]. The persistence of increased relative risk over prolonged follow-up is of concern because this implies an increase in absolute excess risks over time, due to the rising incidence of cardiovascular disease with age.

Prospective screening studies demonstrate that clinically significant cardiovascular abnormalities such as coronary artery stenosis [44], reduced left ventricular dimensions, and valvular and conduction defects are very common even in asymptomatic Hodgkin survivors [45]. Hodgkin lymphoma survivors also have a significantly higher risk (SIR 8.4) of requiring valve surgery or revascularization procedures 15–20 years after radiotherapy [46]. Furthermore, an increased risk of restenosis after coronary artery stenting has been reported in patients treated with thoracic radiation for lymphoma [47].

There are several risk factors for radiation-associated cardiotoxicity (see Table 27.4). Cardiotoxicity is evidently related to both total radiation dose and dose per fraction to the heart [41].

27.1.2.2 Dose-Response Relationships for Radiation-Associated Cardiotoxicity

The heart volume included in the radiation field influences the risk of cardiotoxicity [41, 53], although there are still uncertainties regarding dose-effect and volume-effect relationships. A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction was reported 30 years ago in Hodgkin lymphoma patients treated after partial shielding of the heart and restriction of the total fractionated mediastinal dose to less than 30 Gy [3]. More recently, relationships between different cardiac radiotherapy dose parameters and several radiation-related heart diseases have been demonstrated following treatment for childhood cancer [53], breast cancer [54], and Hodgkin lymphoma [13, 49–51, 55]. These dose-effect relationships can be used to predict CVD risks for patients with newly diagnosed Hodgkin

lymphoma and Hodgkin lymphoma survivors. A linear dose-effect relationship between risk of cardiac disease and mean whole heart dose was found in a large study based on data from randomized trials performed by the EORTC between 1964 and 2004 in Hodgkin lymphoma patients [13]. Furthermore, a series of case-control studies nested in a large cohort of Hodgkin lymphoma patients treated in the Netherlands between 1965 and 1995 showed the following relationships:

- A nonlinear relationship between risk of valvular heart disease and dose to the affected cardiac valve [49] (Fig. 27.2a).
- A linear dose relationship between risk of coronary heart disease and mean dose to the whole heart [50] (Fig. 27.2b).
- A nonlinear dose relationship between risk of heart failure and mean dose to the whole heart (Fig. 27.2c) and a linear relationship between risk of heart failure and mean left ventricular dose [51].

With modern treatment techniques, 20–30 Gy of involved site or involved node radiotherapy can be applied to the mediastinum while keeping the mean heart dose between 5 and 10 Gy. Doses in this range are not expected to cause a significantly increased risk of heart failure or valvular heart disease and only lead to a 1.4–1.7-fold increased risk of coronary heart disease. More data are however needed to validate these dose-effects, to determine dose-volume relationships more precisely for individual cardiac substructures, and to disentangle radiation and chemotherapy effects.

27.1.2.3 Other Risk Factors for Radiation-Associated Cardiotoxicity

The risk for cardiovascular disease may also increase through indirect effects of radiotherapy; irradiation of the left kidney during para-aortic and spleen radiotherapy, for example, may lead to hypertension [56].

General risk factors for cardiovascular diseases such as hypertension, diabetes, hypercholesterolemia, obesity, and smoking [57–59] will also contribute to the risk for cardiovascular disease in patients treated for Hodgkin lymphoma [20, 60]. Whether the cardiovascular risk factor profile in these patients differs from that of the general population is unknown. The joint effects of anthracyclines, radiotherapy, and conventional cardiovascular risk factors (e.g., hypertension, smoking, physical inactivity) appear to be additive [11, 50, 51, 61].

27.1.2.4 Imaging of and Screening for Radiation-Associated Cardiotoxicity

Several studies, mainly in breast cancer, using single-positron emission computed tomography and Doppler echocardiography have revealed subclinical abnormalities [62] less than 2 years after radiotherapy. There is some evidence of a volume effect with such studies demonstrating that the extent of the left ventricle irradiation is predictive of observed imaging abnormalities [63, 64]. Although a relationship between these subclinical abnormalities and subsequent clinical heart disease may be expected, this has not yet been proven [41, 63–65]. However, one study in Hodgkin lymphoma survivors did demonstrate that diastolic dysfunction detected by Doppler echocardiography in asymptomatic patients was associated with stress-induced myocardial ischemia and an increased risk of subsequent cardiac events [66]. Several studies are ongoing looking at the utility of various imaging modalities including cardiovascular magnetic resonance. Conventional and novel blood biomarkers might detect early signs of radiation-associated cardiotoxicity. In the future, we hope to be able to identify survivor groups at high risk of late adverse effects (based on treatment, imaging/blood biomarkers, and/or genotype) for which screening should be recommended and/or intervention trials could be designed. Currently, screening for cardiovascular diseases following thoracic radiotherapy is still a matter of debate [67, 68]. There are uncertainties about the most effective screening modalities. Stress testing may identify asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death [69], but this is not yet common practice.

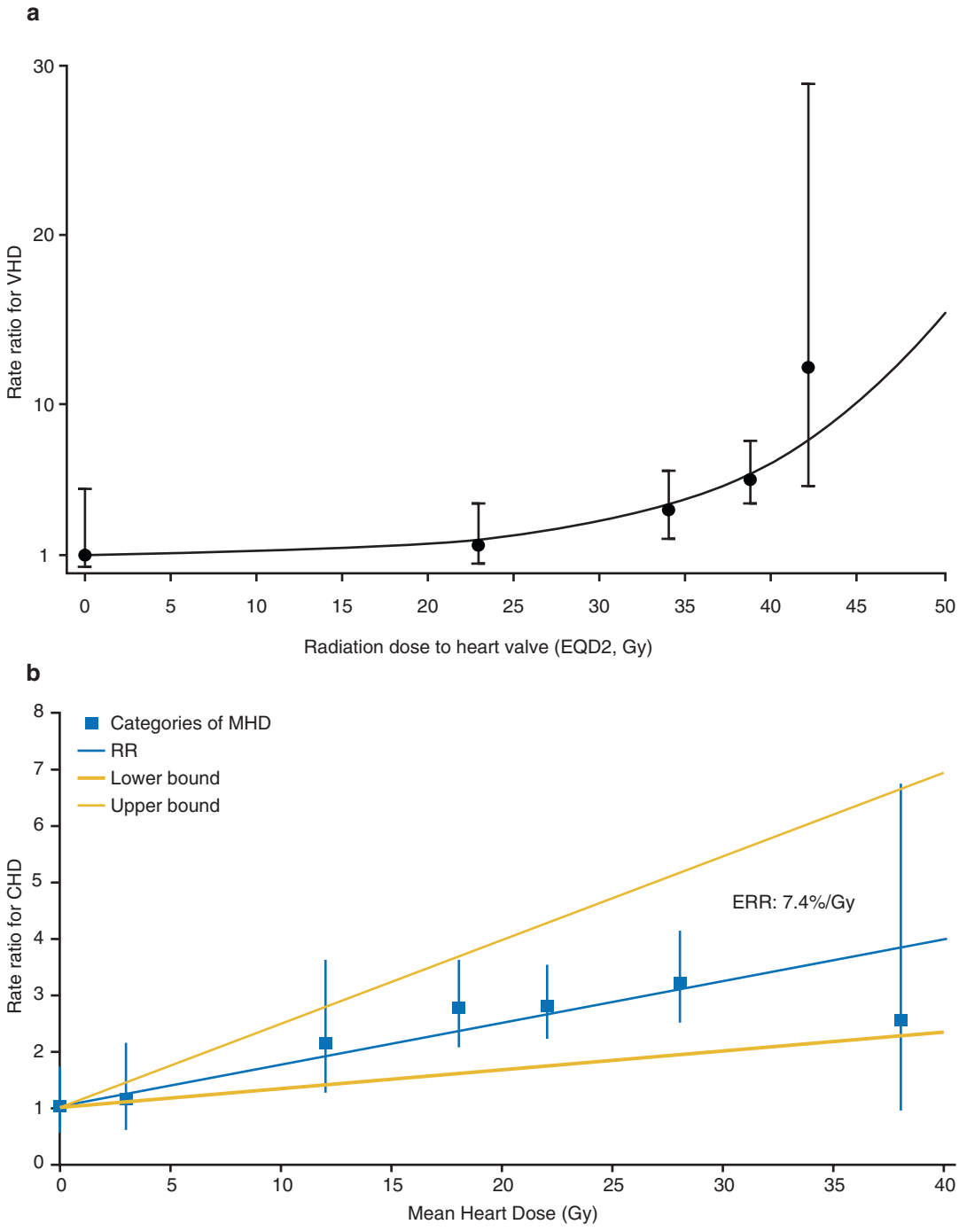

Fig. 27.2 Rate ratios (RR) for valular heart disease (VHD) (**a**) [48], coronary heart disease (CHD) (**b**) [49], and heart failure (HF) (**c**) [50] following radiotherapy for Hodgkin lymphoma by radiation dose to affected heart valve (**a**) and mean heart dose (MHD) (**b**), **c**) measured in Gray (Gy)

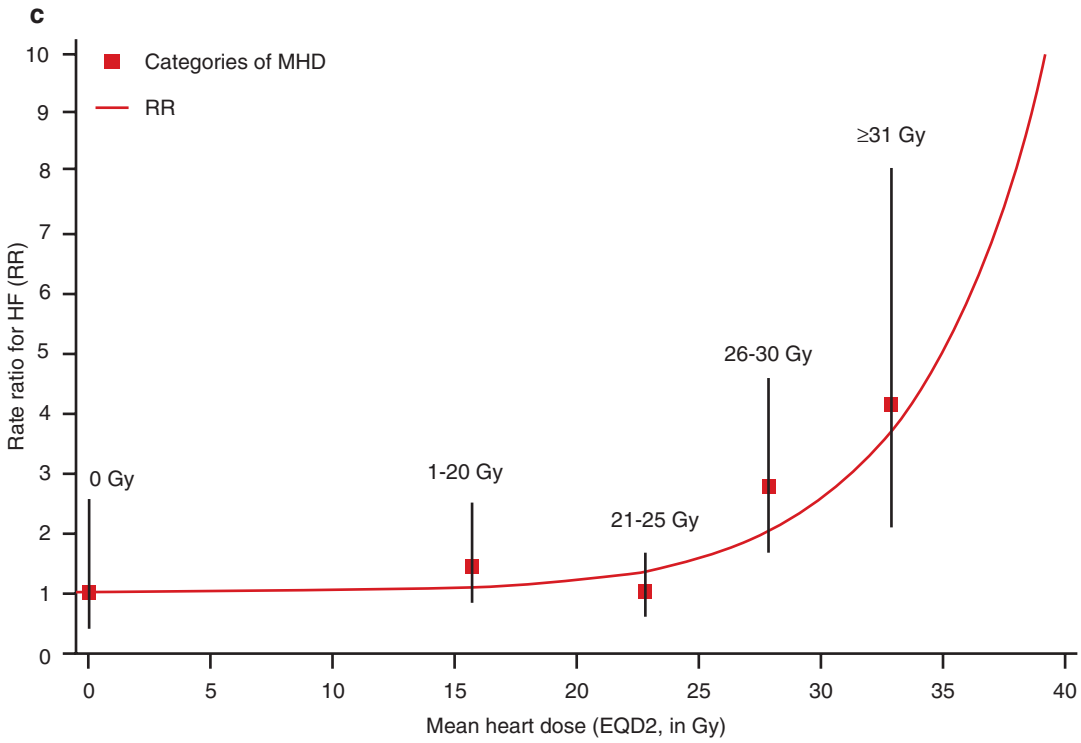

Fig. 27.2 (continued)

27.1.2.5 Prevention and Management of Radiation-Associated Cardiotoxicity

With respect to radiation, it is important to use conventionally fractionated radiation and to limit both radiation dose and volume [22]. Modern radiation techniques such as intensity-modified radiotherapy and radiotherapy during deep inspiration [70] allow radiation with lower exposure of the heart without compromising the radiation dose in the target volume. Proton beam therapy may also allow effective treatment of the mediastinum with reduced radiation doses to the heart and cardiac substructures [71]. Ongoing research is expected to provide more information regarding which structures are most critical and whether it is less harmful to expose a slightly larger volume to a low dose or a smaller volume to a slightly higher dose. Optimization of treatment regimens, including whether to omit radiotherapy entirely in individual cases, is still an important subject of study.

There are currently no indications that radiation-associated ischemic heart disease or other radiation-associated heart diseases need management approaches that are substantially different from the treatment used for heart diseases due to conventional causes. However, if cardiovascular surgery is needed, operating surgeons should be aware of increased risks due to radiation-induced fibrosis [72].

It is recognized that conventional risk factors for cardiovascular disease (e.g., smoking, obesity, hypertension, diabetes, and hypercholesterolemia) can further increase risks in addition to the risks associated with radiation exposure. It is therefore important that these factors are managed appropriately. Lifestyle advice should be offered so that patients should be advised to refrain from smoking from the start of treatment of Hodgkin lymphoma, maintain a healthy body weight, and exercise regularly. Vigorous exercise (i.e., exercise or sports for at least 20 min that made people sweat or breathe hard) has been shown to be associated with substantial reduc-

tions in the risk of major cardiovascular events in a large population of adult survivors of childhood HL even after controlling for important clinical covariates such as cardiovascular risk factors, treatment exposures, and other chronic health conditions [61]. It is quite likely that subgroups of Hodgkin lymphoma survivors can be identified that have risks similar to patients with recognized risk factors like diabetes for whom pharmacological primary prevention should be considered. In many countries, guidelines have been developed for primary and secondary prevention of cardiovascular diseases [73–75].

27.1.3 Radiation-Associated Cerebrovascular Toxicity

27.1.3.1 Radiation-Associated Stroke and Transient Ischemic Attack

As well as coronary artery toxicity, other blood vessels may be damaged by radiation treatment for Hodgkin lymphoma. Damage to the carotid arteries is of particular importance. Significantly increased risks of transient ischemic attack (TIA) and stroke have been described in patients previously treated with radiotherapy for Hodgkin lymphoma [12, 60].

The Childhood Cancer Survivor Study (CCSS) published a self-reported incidence and risk factors for stroke among childhood Hodgkin lymphoma survivors [76]. Twenty-four late-occurring strokes were observed in a cohort of 1926 survivors of childhood Hodgkin lymphoma (RR = 4.32, 95% CI = 2.01–9.29). A Dutch retrospective cohort study among 2201 5-year Hodgkin lymphoma survivors treated before the age of 51 between 1965 and 1995 showed a substantially increased risk for stroke and TIA that was associated with radiation to the neck and mediastinum [12]. The standardized incidence ratio for stroke was 2.2 (95% CI = 1.7–2.8) and 3.1 for TIA (95% CI = 2.2–4.2). Compared with the general population, these risks remained elevated after prolonged follow-up. The cumulative incidence of ischemic stroke or TIA 30 years after Hodgkin lymphoma treatment was 7% (95% CI = 5–8%) in this historical cohort.

27.1.3.2 Prevention and Screening for Radiation Damage to Carotid Arteries

Reduction of the prescribed radiation doses, the use of smaller target volumes, and radiation techniques that allow homogeneous dose distributions now allow the delivery of effective radiotherapy with a lower incidental radiation dose to the carotid arteries. With current concepts used in radiation therapy for patients with Hodgkin lymphoma (involved-node or involved-site radiation rather than involved-field radiation) [22], it is predicted that the risk of radiation-related damage to the carotids in patients treated for Hodgkin lymphoma will diminish [77].

There is no proof for the value of screening for radiation effects on the carotid arteries. Intervention studies are difficult to perform because of the relatively low number of patients treated for Hodgkin lymphoma and the prolonged latency and low absolute numbers of clinical events. Surrogate endpoints including measurement of intima-media thickness of the carotid arteries could be used, but due to lack of evidence for benefit, such screening is not generally recommended.

As for cardiotoxicity, the general risk factors for cardiovascular disease should be monitored and treated as necessary. Lifestyle advice should also be given, i.e., patients should be advised to refrain from smoking (from the start of treatment of Hodgkin lymphoma), maintain a healthy body weight, and exercise regularly [78].

27.1.3.3 Management of Radiation-Associated Carotid Artery Damage

The management of radiation-associated carotid artery disease should be as for that due to other causes. Experience shows that intervention for carotid artery stenosis as for non-radiation-associated disease can be successful. Both open endarterectomy [79] and angioplasty with stenting [80] have been used. There may be particular challenges with an open surgical approach following radiotherapy including fibrosis and

poor healing of irradiated tissue. Additionally, the disease may be situated more proximally in the carotid artery, and restenosis has been reported to be more common [81]. As such it could be recommended that radiation-associated disease is best managed by vascular surgeons with experience of the condition.

27.1.4 Radiation-Associated Damage to Other Major Arteries

Other major arteries are also susceptible to damage from doses of radiation above 30 Gy, including the subclavian and axillary arteries following supradiaphragmatic irradiation [46] and renal, mesenteric, and iliac vessels following subdiaphragmatic irradiation [82]. The clinical manifestations depend on the site and severity of the disease. Due to the potential for complications caused by radiation-induced fibrosis, management of radiation-associated vascular disease is best decided by a vascular surgeon with particular experience. As for other forms of radiation-related cardiovascular disease, good control of cardiovascular risk factors (e.g., smoking cessation, treatment of hypertension and hypercholesterolemia) should be maintained and antiplatelet therapy considered based on the severity of disease.

27.2 Late Pulmonary Toxicity

Both chemotherapeutic agents and radiation exposure of the lungs may lead to pulmonary morbidity and mortality. Significant mortality may be seen in the first months up to 1 year after chemotherapy [83]. During long-term follow-up, the mortality from second pulmonary neoplasms is significantly increased (see Chap. 26, Hodgson DC et al.), but not from other pulmonary diseases [8, 9]. Longer-term increased morbidity from pulmonary toxicity, as suggested by an increased risk of hospital admissions due to respiratory conditions, has also been observed among Hodgkin lymphoma survivors [84].

27.2.1 Chemotherapy-Associated Pulmonary Toxicity

27.2.1.1 General Aspects of Chemotherapy-Associated Pulmonary Toxicity

Several frequently used chemotherapeutic agents may cause pulmonary toxicity. Bleomycin is the most frequently used agent in treatment of patients with Hodgkin lymphoma that causes pulmonary toxicity.

27.2.1.2 Bleomycin

The pulmonary toxicity of bleomycin has been recognized since it was used in clinical trials in the 1960s for testicular cancer. Acute pulmonary toxicity following bleomycin-containing chemotherapy usually presents with dyspnea, dry cough, and fever. Long-term pulmonary toxicity is predominantly fibrotic and may be associated with pulmonary impairment and a dry cough. The classic radiographic pattern of bleomycin-induced interstitial fibrosis on chest X-ray is bibasilar reticular or fine nodular infiltrates. On CT scans, infiltrative changes, nodules, and patchy ground-glass opacities may be seen (see Fig. 27.3). Nowadays, FDG-PET can identify early bleomycin-related pulmonary toxicity, and it may also be used for follow-up of this toxicity. Conventional CT scanning is not able to distinguish between residual changes and active

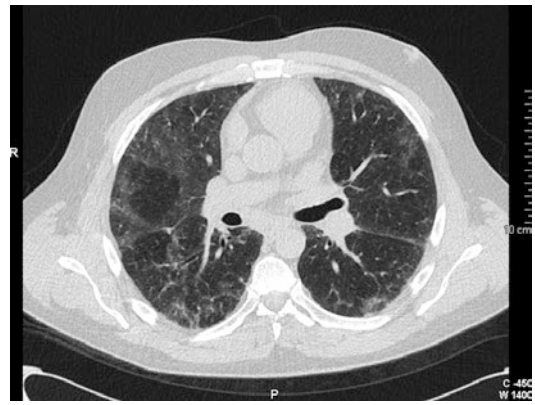

Fig. 27.3 CT scan of the chest showing interstitial pulmonary changes attributed to bleomycin

inflammation. Thus, PET represents a useful diagnostic tool and, independently of CT, indicates the resolution of disease activity, even in the presence of residual pulmonary scarring [85].

The severity of bleomycin toxicity may vary. Martin et al. [83] reported a bleomycin pulmonary toxicity incidence rate of 18% in patients treated with ABVD (25 of 141 patients), and one-quarter of the patients with bleomycin pulmonary toxicity died from pulmonary toxicity within 9 months of their Hodgkin lymphoma diagnosis. Risk factors for bleomycin toxicity included age >40 years, smoking, previous lung or renal impairment, thoracic radiotherapy, and G-CSF treatment. A detrimental impact on 5-year overall survival rates in Hodgkin lymphoma patients who developed bleomycin pulmonary toxicity was observed; the 5-year overall survival was 90% in unaffected patients and 63% in patients with bleomycin pulmonary toxicity ($p = 0.001$). In patients who survived the pulmonary toxicity, bleomycin pulmonary toxicity had no effect on outcome.

The BEACOPP regimen, which contains lower doses of bleomycin and higher steroid doses, has a lower incidence of pulmonary toxicity [86]. The recently reported RATHL trial in advanced Hodgkin lymphoma randomized omission of bleomycin from subsequent cycles if a complete metabolic response was obtained on FDG-PET following two cycles of ABVD. The pulmonary toxicity of continued ABVD was greater than AVD, with more grade 3 or 4 respiratory events and a larger reduction in the diffusing capacity of the lung for carbon monoxide (DLco) [87]. Importantly, the omission of bleomycin from cycles 3 to 6 did not result in significantly lower treatment efficacy.

27.2.1.3 Other Agents Leading to Pulmonary Toxicity

Carmustine is used in high-dose regimens, such as in combination with etoposide, cytarabine, and melphalan (BEAM), and may also induce pulmonary toxicity. The toxic reaction in the lung caused by carmustine usually manifests as chronic interstitial fibrosis that occurs after prolonged treatment and high cumulative doses.

The substitution of etoposide for gemcitabine in the escalated BEACOPP regimen was reported as non-feasible due to severe acute pulmonary toxicity. This increased toxicity was probably related to the concomitant application of gemcitabine and bleomycin [88]. No long-term follow-up is available for this treatment yet. In the same patient population [89], no increased toxicity was observed following radiation treatment. The authors therefore concluded that integration of radiotherapy in gemcitabine-containing regimens for Hodgkin lymphoma is feasible provided there is an interval of at least 4 weeks between the two modalities and that radiotherapy follows chemotherapy.

Brentuximab vedotin (BV) is an antibody-drug conjugate composed of a CD30-targeted chimeric monoclonal antibody covalently linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). BV is associated with acute pulmonary toxicity which, although rare, can be potentially fatal. In 2015, on the basis of improved progression-free survival results in the phase III AETHERA trial, BV was approved for consolidation therapy after autologous transplant in patients deemed to be of high risk of relapse. The rate of pulmonary toxicity in this study was reported as 5% [90]; however due to heavy pretreatment, this likely represents a high-risk group. Small studies using BV as first-line treatment have reported no pulmonary toxicity [91]. BV should not be given in combination with bleomycin because this leads to a high risk of pulmonary toxicity [92].

27.2.1.4 Prevention of Chemotherapy-Associated Pulmonary Toxicity

Information on how to prevent long-term toxicity is scarce. High inspired concentrations of oxygen after prior treatment with bleomycin have been reported to be toxic [93]. The best strategy to avoid chemotherapy-associated pulmonary toxicity may simply be minimization of the use of these agents as demonstrated by the RATHL trial [87].

27.2.1.5 Management of Chemotherapy-Associated Pulmonary Toxicity

There is no accepted standard treatment for acute bleomycin toxicity. Corticosteroids, withholding bleomycin from subsequent chemotherapy, and proceeding with a regimen not containing bleomycin, if possible, are the most common approach [83]. Long-term corticosteroid treatment may be necessary to avoid recall pneumonitis.

27.2.2 Radiation-Associated Pulmonary Toxicity

27.2.2.1 General Aspects of Radiation-Associated Pulmonary Toxicity

Radiation may damage both the lung and the pleura leading to different clinical symptoms. Lung irradiation can cause subacute pneumonitis resulting in a dry cough and shortness of breath 2–3 months following treatment. Corresponding changes on chest X-rays and CT scans of the thorax may be observed (see Fig. 27.4). In the longer term, this may progress to chronic pulmonary fibrosis.

The risk for radiation pneumonitis is related to both the radiation dose and irradiated volume. Generally accepted clinical parameters related to radiation pneumonitis within 1 year after treatment include mean lung dose (MLD) and the volume of lung tissue receiving at least 20 Gy (V20). Koh et al. reported that a V20 ≥ 36% and an MLD of ≥14.2 Gy predicted a risk of RTOG grade 2 or greater that would be considered clinically significant (10–25% vs. 3% overall) [94]. Fox et al. reported similar cutoffs (V20 ≥ 33.5% and MLD ≥ 13.5 Gy) and also noted that those treated with mediastinal radiotherapy for relapsed Hodgkin lymphoma pretransplant had a higher risk of RP than those treated post transplant (57% vs. 0%, $p = 0.015$) [95]. More recently, Pinnix et al. reported predictors of radiation pneumonitis in patients receiving intensity-modulated radiotherapy (IMRT) [96]. Similar to the previous studies, an MLD > 13.5Gy and a V20 > 30% was predicted for radiation pneumonitis, but of note, the strongest predictor was for the volume of lung tissue receiving at least 5 Gy (V5) with a cutoff of V5 > 55%.

A Dutch study on breast cancer and Hodgkin lymphoma patients reported a partial recovery from early local perfusion, ventilation, and density changes that were seen between 3 and 18 months after radiotherapy. In lymphoma patients, local lung function did not further improve after 18 months [97].

Although minor radiological and pulmonary function abnormalities may be seen regularly

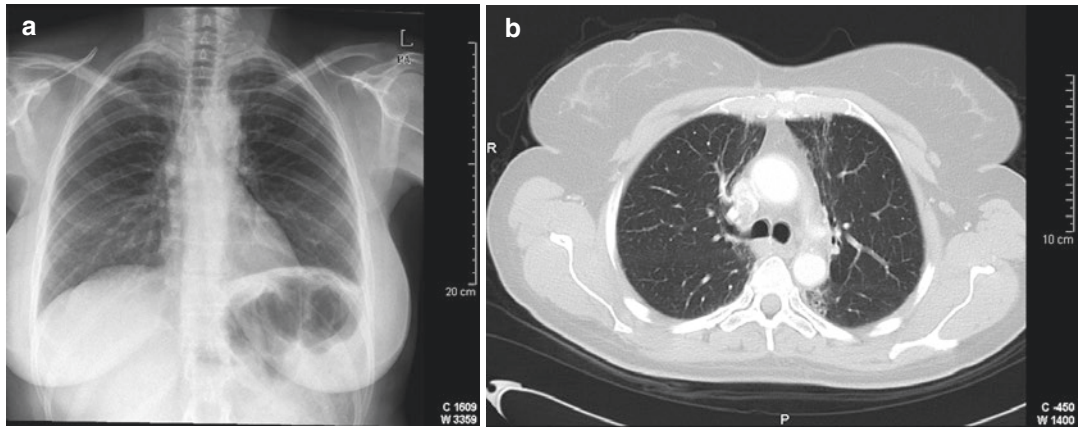

Fig. 27.4 (**a**) Chest X-ray 11 years after mediastinal radiation showing paramediastinal radiation fibrosis. (**b**) CT scan of the chest of the same patient also 11 years after mediastinal radiation showing interstitial pulmonary changes limited to the mediastinal radiation field

following radiation therapy for Hodgkin lymphoma, clinically significant symptoms are rare.

27.2.2.2 Prevention of Radiation-Associated Pulmonary Toxicity

The best way to minimize the risk of radiation-associated pulmonary toxicity is to minimize incidental radiation dose to the normal lung. The mean lung dose and V20 should be kept as low as possible, ideally well below recognized levels that are associated with increased risk [96]. This can be achieved by utilizing modern concepts of target volume definition and advanced treatment planning and delivery techniques where appropriate. IMRT can help reduce the higher radiation dose to the lungs, but care must be taken to limit the low dose received by the lung particularly in patients with non-modifiable risk factors for radiation pneumonitis such as bulky mediastinal disease and use of salvage treatment. Deep-inspiration breath-hold techniques may be particularly useful in these circumstances [98]. Proton beam therapy can also help reduce lung doses particularly for large mediastinal target volumes. Patients should be advised to refrain from smoking as this may increase the risk of acute and late pulmonary effects.

27.2.2.3 Management of Radiation-Associated Pulmonary Toxicity

Treatment of symptomatic radiation pneumonitis, occurring within the first year following treatment, generally consists of high-dose corticosteroids given for at least 2 weeks and then tapered over 3–12 weeks dependent on response. In the long term, no specific treatment is currently available, and pulmonary fibrosis following radiation is generally irreversible.

27.2.2.4 Combined Toxicity

Combined modality treatment is frequently used in patients with Hodgkin lymphoma. As the pulmonary toxicity of bleomycin and radiotherapy may interact, bleomycin dose modification may be required [99], and radiotherapy may have to be similarly adapted.

27.3 Conclusion

The cure rate of Hodgkin lymphoma patients today exceeds 80% with risk-adapted treatment using modern chemotherapy and radiotherapy regimens. Effective chemotherapy combinations have been developed, and ability to manage acute toxicities has improved significantly. Much of the knowledge regarding long-term cardiovascular and pulmonary toxicities relates to historical treatment regimens that are no longer applied. By utilizing the data available on toxicity and delivering patient-tailored treatment, we expect to observe lower risks of cardiovascular and pulmonary toxicity in the future for patients being treated today. However, it is important that treating physicians and patients remain aware of these possible late effects following cure.

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