Heart, Coronary Arteries, Aorta and Great Vessels, Arteries and Veins, Microcirculation

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Contents

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Abstract

- Radiotherapy can cause injury to any of the substructures of the heart, including the pericardium, valves, myocardium, and arteries.
- Myocardial injury appears to occur secondary to the vascular events.
- Coronary artery disease often occurs years to decades post-radiotherapy, and is associated with an increased risk of MI and cardiac death.
- Subclinical evidence of cardiovascular disease consistent with microvascular injury can be detected within months of completion of radiotherapy, and the clinical significance of this is unclear.
- Valves have been generally considered to be unaffected by radiotherapy, but recent data suggest that valvular injury is relatively common following radiotherapy.
- The risk of pericarditis following radiotherapy has a strong volume dependence.
- A variety of chemotherapy agents (alone and in combination with radiotherapy) are associated with heart disease.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
AV	Atrioventricular
NT-proBNP	Brain natriuretic peptide and N-terminal fragment
CAC	Coronary artery calcification
EBCTCG	Early breast cancer trialists' collaborative group

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EGFR	Epidermal growth factor receptor
HR	Hazard ratios
HER2	Human epidermal growth factor receptor 2
LAD	Left anterior descending artery
LCX	Left circumflex artery
LSS	Life span study
MR	Magnetic resonance
NTCP	Normal tissue complication probability
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
RT	Radiation treatment
RCA	Right coronary artery
RMA	Right marginal artery
SE	Standard error
SIR	Standardized incidence ratios
SEER	Surveillance, epidemiology and end-results cancer registries
VEGF	Vascular endothelial growth factor

1 Introduction

Circulatory diseases are major causes of morbidity and mortality, accounting for 30–50 % of all deaths in most developed countries. Both radiotherapy and chemotherapy used to treat patients with for malignant diseases may cause early and late cardiovascular toxicity. Whereas cardiovascular disease following radiotherapy is usually observed from 5 to 10 years of follow-up onwards, chemotherapy-related toxicity occurs with a more variable timecourse. Because of the improved prognosis of many patients treated for malignancies, cardiovascular disease is becoming an increasingly important late event that must be understood in order to develop effective interventions. The Biocontinuum of adverse and late effects of the heart is shown in Fig. 1.

2 Anatomy and Physiology: The Functional Unit

2.1 Anatomy

The cardiovascular system consists of the heart, arteries, and veins.

The heart is a hollow, muscular organ lying within a two-layered sac, the pericardium. It is a four-chamber pump consisting of two atria and two ventricles. The heart valves maintain the unidirectional flow of blood in the heart by opening and closing depending on the difference in pressure on each side. The valves between the atria and ventricles prevent backflow of blood from the ventricles to the atria during systole. In addition, the semilunar valves between the heart and the aorta and the heart and the pulmonary arteries prevent backflow from the aorta and the pulmonary arteries into the ventricles during diastole. The heart valves do not have a blood supply, but they are covered with a specific type of endothelium.

Although the heart is filled with blood, the heart muscle requires its own blood supply, namely the coronary arteries. There are two main coronary arteries, the left and right. Both of these arteries originate from the root of the aorta, immediately above the aortic valve. The left main coronary artery (or left main trunk) branches into the circumflex artery (LCX) and the left anterior descending artery (LAD), and the right coronary artery (RCA) branches into right marginal artery (RMA) and the posterior descending artery (PDA). The circumflex artery supplies the left atrium, the side, and back of the left ventricle. The left anterior descending artery supplies the front and bottom of the left

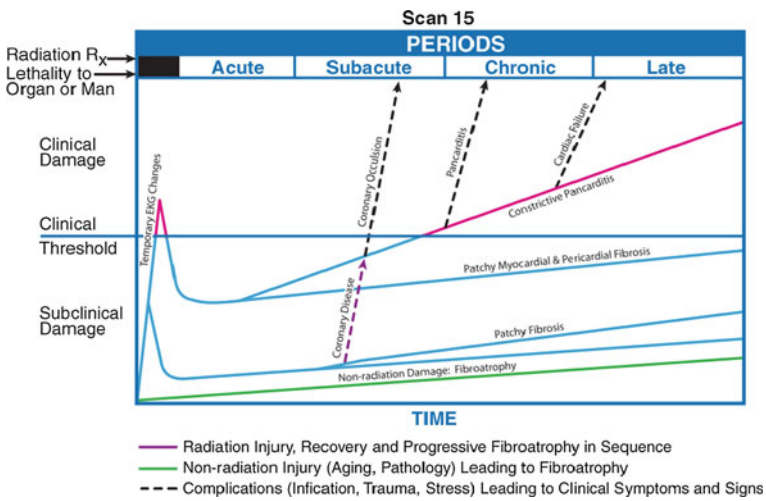

Fig. 1 The biocontinuum of RT-induced heart injury (Published with kind permission of Saunders: Rubin Casarett: Clinical Radiation Pathology, 1968)

ventricle and the front of the septum. The right coronary artery supplies the right atrium, the right ventricle and the bottom portion of both ventricles and the back of the septum (see Fig. 2).

2.2 Histology and Functional Subunit

The major part of the heart, the myocardium, is constituted of cardiac muscle. The inner surface of the myocardium is lined with endocardium, and the outer surface with epicardium. The epicardium is the inner visceral layer of the pericardium. The outer part of the epicardium is lined with mesothelium. Large blood vessels and nerves are found in the epicardium.

All arteries possess three coats: a tunica intima, a tunica media, and a tunica adventitia. The tunica intima is composed of a smooth layer of thin endothelial cells based upon a delicate basement membrane that penetrates between the subendothelial connective tissue and the underlying smooth muscle cells. The tunica media consists of smooth muscle cells and an elastic network. The tunica adventitia is a poorly defined layer of connective tissue in which elastic and nerve fibers and in case of large arteries, small, thin-walled nutrient vessels, and the vasa vasorum, are dispersed.

The three separate layers generally seen in arteries are not well defined in veins. Veins are in general thin-walled with relatively large lumina.

The essential function of the heart is to pump blood to various parts of the body. De-oxygenated blood from the body enters the right atrium, passes into the right ventricle and is pumped by the right ventricle to the pulmonary artery into the lungs. Oxygenated blood returns from the lungs to the heart into the left atrium, passes into the left ventricle and is pumped into the body through the aorta. Throughout the body, blood delivers oxygen and nutrients, picks up waste materials, and flows back to the heart again. The muscle wall from the ventricles is thicker and stronger than the muscle wall from the atria.

Cardiac contraction is generated by the myocytes. Myocytes are highly differentiated cells rich in mitochondria. Adjacent myocytes are separated by intercalated disks and they form a network of branching fibers with the ability to carry forward an action potential. Myocytes contract spontaneously and continuously, under regulation of electrical impulses. The electrical impulse initiates in the sinoatrial node (pacemaker), at the junction between right atrium and superior vena cava, and is propagated to the atrioventricular (AV) node, located between the atria and the ventricles. The distal part of the AV node, the bundle of His, splits into two branches to activate the left and right ventricle, respectively. Norepinephrine and its receptors regulate heart rate and the force of contraction.

3 Pathophysiology

3.1 Pathophysiology of Radiation-Related Toxicity

All structures of the heart and major arteries can be damaged by ionizing radiation. See for summary on risk factors Table 1.

3.1.1 Heart Muscle

The normal adult heart is a slow turnover organ, with low proliferative activity. Previously, it was thought that cardiomyocytes were terminally differentiated, without the capacity for cell division. In order for the myocardium to maintain its vital role, it was assumed that loss of myocytes as a result of injury or aging was compensated by hypertrophy of remaining myocytes or by fibrosis. Recent studies have shown that the mammalian heart has the inherent ability to replace its cardiomyocytes through the activation of a pool of resident primitive cells or the recruitment of hematopoietic stem cells (Anversa et al. 2007).

In addition, there is new evidence that circulating mononuclear cells, including progenitor endothelial cells, can home to sites of ischemic damage in the heart and contribute to new vessel formation by transdifferentiation into endothelial cells and secretion of angiogenic cytokines (Caplice and Doyle 2005).

3.1.2 Arteries

Radiation may damage the endothelium of blood vessels. In large arteries this damage may lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism (Stewart et al. 1995; Veinot and Edwards 1996; Adams and Lipshultz 2005). Experimental data showed that early inflammatory changes in the endothelial cells of irradiated large vessels may lead to monocyte adhesion and trans-migration into the subendothelial space. In the presence of elevated cholesterol levels, these invading monocytes transform into activated macrophages, which ingest lipids and form fatty streaks in the intima, thereby initiating and accelerating the process of atherosclerosis. Proliferation of myofibroblasts is then stimulated by the production of inflammatory cytokines, resulting in a reduction of the arterial lumen (Vos et al. 1983; Tribble et al. 1999; Stewart et al. 2006). Animal studies have shown that radiation predisposes to the formation of macrophage rich, unstable plaque, rather than stable collagenous plaque (Stewart et al. 2006; Pakala et al. 2003). Such lesions are more likely to rupture and cause a fatal heart attack or stroke (Stewart et al. 2010) (see Fig. 3 for histopathology, and Fig. 4 for pathogenesis of vessel injury).

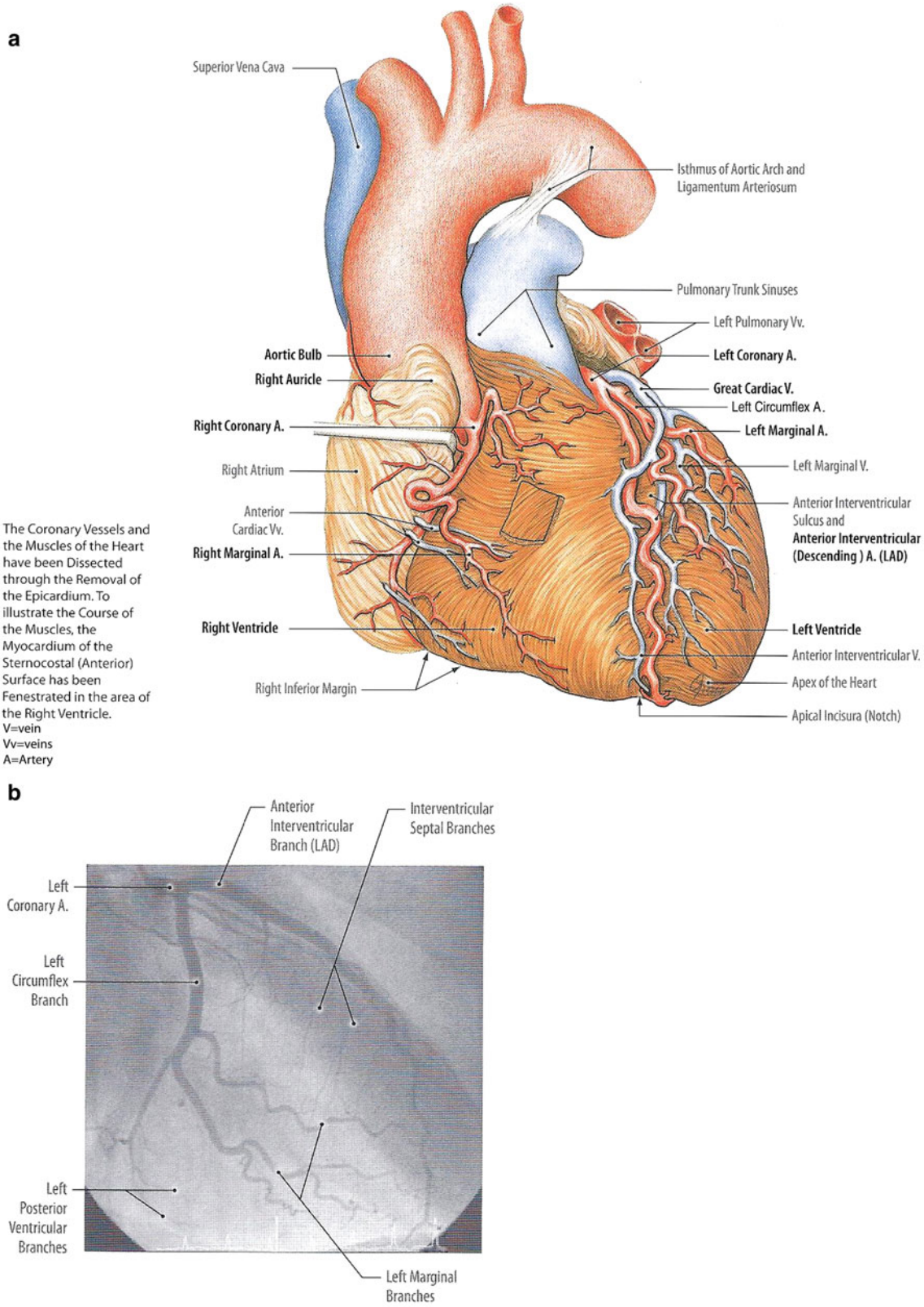

Fig. 2 **a** Gross anatomy of the heart with an emphasis on depiction of coronary arteries. **b** Selective coronary angiogram using an anteroposterior projection demonstrating the left coronary arteries and interventricular branches (with permission from Tillman 2007)

Table 1 Risk factors for the different manifestations of radiation-associated heart disease

Risk factor	Pericarditis	Cardiomyopathy	Coronary artery disease	Arrhythmia	Valvular disease	All causes cardiac death	References
Total dose; (>30–35 Gy)	X	X	X	X	X	X	Schultz-Hector and Trott (2007), Heidenreich et al. (2003), Moser et al. (2006)
Dose per fraction (≥2.0 Gy/day)	X	X	X	Likely	Likely	X	Cosset et al. (1988)
Volume of heart exposed	X	X	X	Likely	Likely	X	Schultz-Hector and Trott (2007), Hancock et al. (1993a)
Younger age at exposure Increased	–	X	X	Likely	Likely	X	Aleman et al. (2007)
Increased time since exposure	–	X	X	X	X	X	Aleman et al. (2007)
Use of adjuvant cardiotoxic chemotherapy	–	X	–	X	X	X	Aleman et al. (2007), Myrehaug et al. (2008), Moser et al. (2006)
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	X	–	–	X	Aleman et al. (2007), Glanzmann et al. (1998)

Modified with permission from Table 10.5 from "BioPediatric Complexities of Growth and Development" Cardiovascular Effects of Cancer Therapy by Adams, Constine, Duffy and Lipshultz (and from Simbre et al. Curr Treat Options Cardiovasc Med 2001) in Survivors of Childhood and Adolescent Cancer (second edition) published by Springer

The anterior location of the heart in the chest, and the relative anterior location of the coronary arteries (in particular the LAD) within the heart, has been suggested to explain the increased risk of radiation-associated heart disease that is observed when thoracic radiation treatment is "weighted" to be preferentially delivered from the anterior direction (Stewart et al. 1995; Byhardt et al. 1975; Morton et al. 1973).

3.1.3 Valves

Since valves do not have blood vessels, radiation-related valvular disease cannot be explained by (micro) vascular damage. However, possibly this damage is consequential to late injury of the surrounding myocardial endothelium leading to fibrosis (Veinot and Edwards 1996).

Valvular leakage could also be secondary to dilated cardiomyopathy. Cardiomyopathy is usually caused by chemotherapy (especially anthracyclines) but may also be seen after radiotherapy probably secondary to vascular damage.

3.1.4 Pericardium

In experimental studies in dogs, rabbits, or rats a single dose of greater than or equal to 15 Gy has been shown to lead to a reversible exudative pericarditis, occurring at around 100 days (Schultz-Hector 1992). Edematous swelling, fibrotic thickening, and adhesions of epicardium and pericardium may develop (Schultz-Hector and Trott 2007; Lauk et al. 1985).

In mammals, the encasement of the heart by a rigid nonpliable pericardium results in characteristic pathophysiologic effects, including impaired diastolic filling of the ventricles, exaggerated ventricular interdependence, and dissociation of intracardiac and intrathoracic pressures during respiration.

In humans, acute pericarditis/pericardial effusion may be observed following irradiation including a considerable part of the heart (Carmel and Kaplan 1976; Cosset et al. 1988). Pericardial effusions may resolve spontaneously. However, constrictive pericarditis does develop in a minority of patients and surgery may be needed (see below).

3.2 Pathophysiology of Chemotherapy-Induced Cardiotoxicity

The mechanisms of cardiotoxicity vary widely among different chemotherapeutics (Kang 2001). The cardiovascular

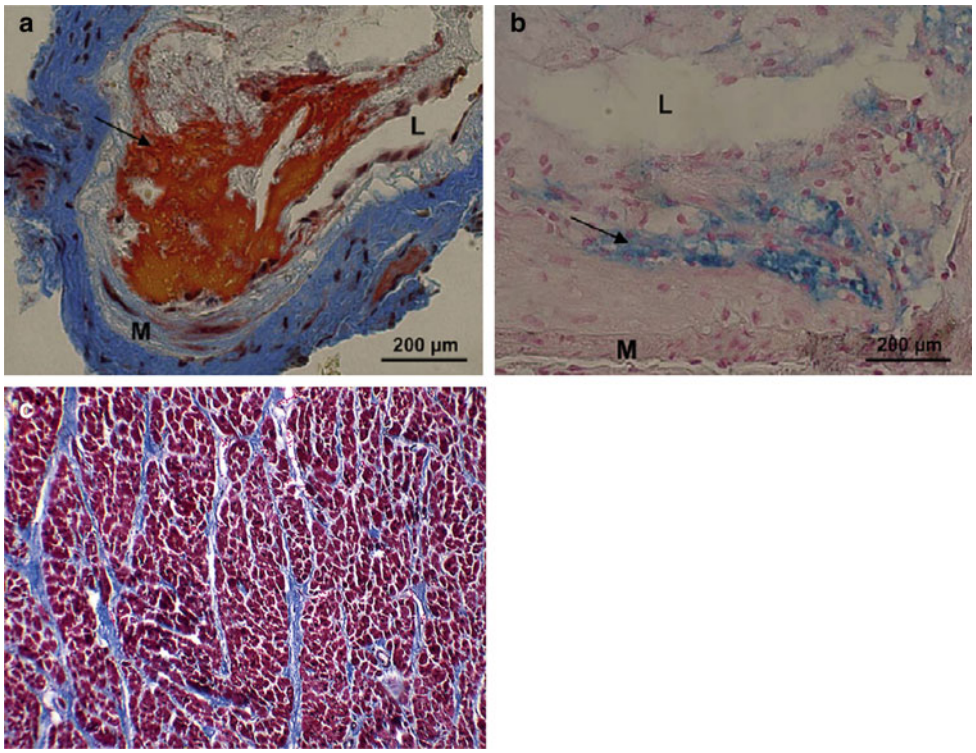

Fig. 3 Pathology. Examples of thrombotic phenotypes of carotid lesions in irradiated ApoE -/- mice. **a** Martius-scarlet-blue staining of lesions 30 weeks after 14 Gy, in which fibrin deposits are stained red (arrow). **b** Perl staining in which iron is stained blue (arrow) in lesions 34 weeks after 20 Gy × 2.0 Gy. L = lumen; M = media. (From Hoving et al. 2008). **c** Example of myocardial fibrosis (fatal) in a patient many years after irradiation for Hodgkin Lymphoma. Whereas normally there should be very little collagen among the dark red myocytes, this heart muscle is criss-crossed by multiple bands of blue collagen. Gomori trichrome stain (with permission from Darby et al. 2010)

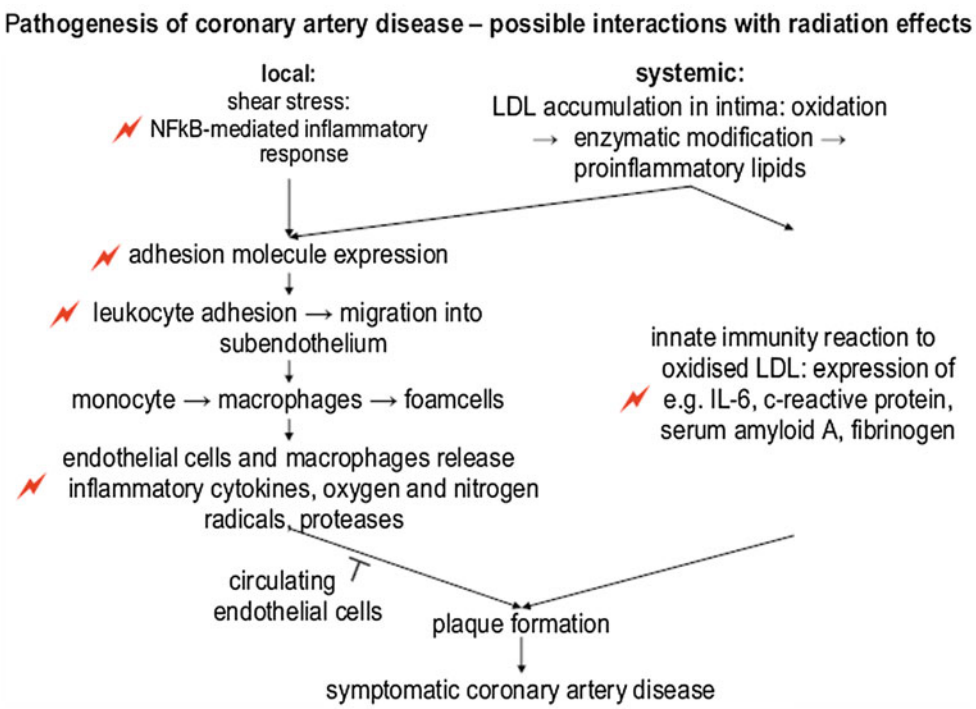

Fig. 4 Schematic representation of the most important steps of pathogenesis of coronary artery disease. Events that have also been observed after radiation are indicated by flashes (with permission from Schultz-Hector and Trott 2007)

Table 2 Potential mechanisms of cardiovascular damage induced by anticancer treatments. A summary of probable mechanisms of cardiotoxicity induced by a range of chemotherapeutic and chemoprevention agents[a] from Albini et al. JNCI 2010 (Albini et al. 2010)

		Effects						
		Systemic-macroenvironment						
		Mitochondrial				Local-microenvironment		
Examples of chemotherapeutics	Possible cardiovascular damage	DNA damage	ATP block	Apoptotic protein release	ROS generation	Endothelial cell damage/ spasms	Cell signaling/ survival block	ADCC
Anthracyclines and anthraquinolones	CHF, LVD, acute myocarditis, and arrhythmia	+	+	+	+	−	−	−
Capecitabine, 5-fluorouracil, cytarabine	Ischemia, pericarditis, CHF, and cardiogenic shock	+	+	+	+	+	−	−
Paclitaxel, vinca alkaloids	Sinus bradicardia, ventricular tachycardia, atrioventricular block, hypotension, CHF, and ischemia	+	?	?	?	?	−	−
Cyclophosphamide	Neurohumoral activation, mitral regurgitation	+	?	?	?	+	−	−
Imatinib	Arrythmias, CHF, angioedema, and LVD	−	+	+	−	<>	<>	−
Sorafenib	Hypertension, arrhythmias	−	?	?	−	<>	<>	−
Sunitinib	Hypertension, arrhythmias	−	+	?	−	<>	<>	−
SERMs	LDL/HDL modulation, thromboembolism	−	−	−	−	−	−	−
Trastuzumab	Arrhythmias, CHF, angioedema, and LVD	−	−	−	−	<>	<>	+
Bevacizumab	Hypertension, thromboembolism, and GI tract bleeding	−	−	−	−	<>	<>	−
COX-2–specific inhibitors	Thromboembolism	−	−	−	−	<>	−	−
Thorax irradiation	Myocardial fibrosis, valvular heart disease, and LVD	+	−	<>	+	+	−	−

[a] + = likely; − = unlikely; ? = unknown; <> = probable. *ADCC* antibody-dependent cellular cytotoxicity; *CHF* congestive heart failure; *COX-2* cyclooxygenase 2; *GI* gastrointestinal tract; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *LVD* left ventricular dysfunction; *ROS* reactive oxygen species; *SERMs* selective estrogen receptor modulators. For references, see text

system has numerous different targets that can be subject to damage (Albini et al. 2010). Some drugs directly damage cardiomyocytes or cause inflammation of the pericardium. Some drugs damage the intima of blood vessels and thereby engage the coagulation system, promoting blood clotting in the vessels predisposing to thromboembolic events and consequent cardiovascular and cerebrovascular ischemia. Some drugs cause hypertension with acute and long-term effects on cardiac hypertrophy and insufficiency. See for summary on potential mechanisms and risk factors Tables 2 and 3.

3.2.1 Anthracyclines

Anthracycline-induced cardiotoxicity has been divided into acute, occurring immediately after infusion of the drug, early onset chronic progressive, occurring during or within a year after treatment, and late-onset chronic progressive, occurring more than a year after treatment with anthracycline.

Several different biochemical changes are seen in cellular and animal studies after exposure, and the cardiotoxicity after exposure is likely to be the result of several biochemical insults (Barry et al. 2007; Giantris et al. 1998; Herman et al. 1999; Wouters et al. 2005). Iron-mediated free radical formation leading to apoptosis seems to be important for acute cardiotoxicity (Minotti et al. 2004). However, chronic cardiomyopathy seems to develop due to a combination of diverse processes as follows: increased membrane lipid peroxidation; inhibition of nucleic acid and protein synthesis; release of vasoactive amines; changes in

Table 3 Risk factors for Anthracycline-induced cardiotoxicity in decreasing order of importance

Risk factor	Features
Total cumulative dose	Most significant predictor of abnormal cardiac function
Age	For comparable cumulative doses, younger age predisposes to greater cardiotoxicity
Length of follow-up	Longer follow-up results in higher prevalence of myocardial impairment
Gender	Females more vulnerable than males for comparable doses
Concomitant mediastinal irradiation	Enhanced toxicity; not clear whether additive or synergistic

Modified with permission from Table 10.4 from "BioPediatric Complexities of Growth and Development" Cardiovascular Effects of Cancer Therapy by Adams, Constine, Duffy and Lipshultz (and from Simbre et al. Curr Treat Options Cardiovasc Med 2001) in Survivors of Childhood and Adolescent Cancer (second edition) published by Springer

adrenergic function and adenylate cyclase; abnormalities in the handling of Ca^{2+}; reduced expression of specific genes possibly caused by altered expression and function of anthracycline sensitive transcriptional regulatory proteins; impairment of membrane binding, assembly, and enzymatic activity of mitochondrial creatine kinase; induction of nitric oxide synthase, leading to nitric oxide and peroxinitrite formation and to inactivation of myofibrillar creatine kinase or activation of metalloproteinases (Wouters et al. 2005; Minotti et al. 2004). Whether and how these processes contribute to the development of chronic cardiotoxicity is still not clear. Moreover, it is not clear how iron and reactive oxygen species interact with these processes.

Compared with the cells of other organs, cardiac cells are more susceptible to free radical damage because of the highly oxidative metabolism and relatively poor antioxidant defenses (Doroshow et al. 1980). Additionally, anthracyclines have a high affinity for cardiolipin present in the inner mitochondrial membrane leading to accumulation of anthracyclines in cardiomyocytes (Goormaghtigh et al. 1990).

The anthracycline damage to cardiomyocytes causes apoptosis, thereby decreasing the number of myocardial cells (Arola et al. 2000). The wall of the left ventricle becomes thinner, and the contractility of the myocardium decreases, leading to depressed overall function of the left ventricle (Lipshultz et al. 1991; Giantris et al. 1998; Sorensen et al. 1995).

Recent research indicates that anthracyclines cause damage to the cardiac progenitor cells in particular, causing massive apoptotic death, thus reducing the reserve of functionally competent cardiac progenitor cells. This process may contribute to the development of anthracycline-mediated cardiomyopathy in children. In adults, decrease in cardiac stem cells may impair cardiac response to injury. The cumulative effects of anthracyclines on various types of cardiac tissue are summarized in Fig. 5 (Chen et al. 2011). In the future, cardiac progenitor cells may have a potential role in ameliorating cardiotoxicity of cancer therapy. A recent study in rats suggested that it might be possible to prevent cardiomyopathy caused by chemotherapy by obtaining cardiac progenitor cells before initiating cardiotoxic treatment and using them for prevention or management of heart failure (De Angelis et al. 2010).

A number of different drugs have cardioprotective properties against anthracycline cardiotoxicity (Wouters et al. 2005). However, due to the risk that these drugs may also reduce the anti-tumor activity of the anthracyclines, they have not gained acceptance except for very special clinical situations.

3.2.2 Alkylating Agents

Cyclophosphamide cardiotoxicity is characterized by hemorrhagic myocarditis in the acute phase. The precise mechanism is unknown, but it is hypothesized that cyclophosphamide causes direct endothelial injury leading to extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema (Goldberg et al. 1986; Gottdiener et al. 1981; Morandi et al. 2005; Pai and Nahata 2000). Microemboli in cardiac capillaries may develop, giving rise to ischemic myocardial damage (Gottdiener et al. 1981; Morandi et al. 2005). Coronary vasospasm is another possible mechanism (Pai and Nahata 2000).

Ifosfamide cardiotoxicity may possibly cause myocardial damage by the same mechanisms as cyclophosphamide, but hemorrhagic myocarditis has not been described, so other unknown mechanisms may be at play (Quezado et al. 1993).

3.2.3 Antimetabolites

Fluorouracil and its prodrug capecitabine may cause cardiotoxicity by mechanisms which are as yet not fully elucidated. Coronary vasospasms have been proposed (Akhtar et al. 1993; de Forni et al. 1992; Kosmas et al. 2008; Luwaert et al. 1991; Shoemaker and Arora 2004; Sudhoff et al. 2004; Wacker et al. 2003). However, there is also evidence for a direct effect on the metabolism of the cardiomyocytes (de Forni et al. 1992; Kohne et al. 1998; Sasson et al. 1994). Symptoms usually start several hours after repeated administrations of the drug. In view of the short half-life of fluorouracil, it seems likely that cardiotoxicity is caused by metabolites which accumulate. Evidence points to metabolites formed by dihydro-pyrimidine

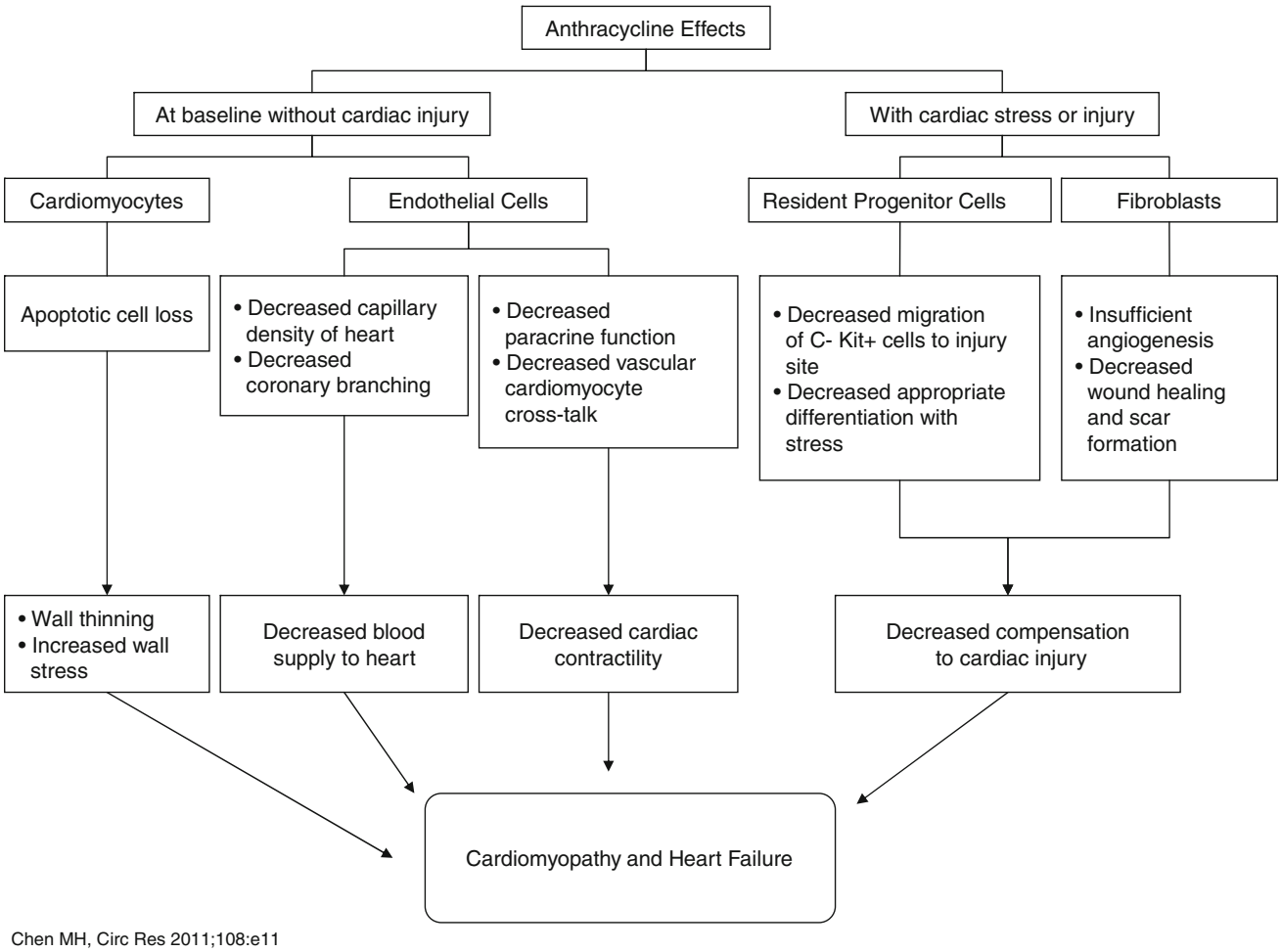

Fig. 5 Anthracycline effects on different cardiac tissues (including myocytes and stems cells) and how it results in heart failure (with permission Chen et al. 2011)

dehydrogenase degradation of fluorouracil (Di Paolo et al. 2001; Van Kuilenburg et al. 2002).

3.2.4 Antimicrotubule Agents

Myocardial ischemia and infarction have been associated with paclitaxel and docetaxel administration. The etiology is thought to be multifactorial, including histamine release by the cremophor of the paclitaxel formulation (Rowinsky et al. 1991). Paclitaxel may also cause arrhythmias, possibly via direct effects on the Purkinje system or extracardiac autonomic control (McGuire et al. 1989), but also via histamine release by the cremophor (Rowinsky et al. 1991; Arbuck et al. 1993).

Vinca alkaloids can also cause arrhythmias, ischemia, and congestive heart failure (Yeh et al. 2004).

3.2.5 Monoclonal Antibodies

Monoclonal antibodies used in cancer therapy typically target growth factors or their receptors thereby inhibiting the tyrosine kinases normally activated through interaction between the growth factor and the corresponding receptor.

3.2.5.1 Bevacizumab

Arterial thrombotic events, including myocardial infarction, are associated with treatment with bevacizumab. The mechanism is unclear, but it is thought that anti-vascular endothelial growth factor (VEGF) therapy may decrease the capability of endothelial cells to regenerate in response to trauma, leading to defects in the interior vascular lining with exposure of subendothelial collagen, increasing the risk of thrombotic events (Kamba and McDonald 2007; Kilickap et al. 2003).

Furthermore, antiangiogenic therapy is known to cause hypertension by mechanisms which are not fully understood. It is possibly related to VEGF inhibition, which decreases nitric oxide production in the arterioles (Kamba and McDonald 2007). Nitric oxide is a natural vasodilator,

and blocking its production leads to increased peripheral vascular resistance and blood pressure. Angiogenesis is an important component of the normal adaptive response to pressure load, and inhibition of VEGF signaling may be even more serious in hypertensive patients (Izumiya et al. 2006; Shiojima et al. 2005).

3.2.5.2 Trastuzumab

Human epidermal growth factor receptor 2 (HER2) has an essential role in the development of the embryonic heart (Erickson et al. 1997; Lee et al. 1995a), and HER2 is expressed on adult myocardiocytes (Strasser et al. 2001; Zhao et al. 1998). Preclinical experiments have shown that activation of the HER2 receptor induced by its ligand neuregulin promotes cardiomyocyte survival (Zhao et al. 1998). Cardiotoxicity of trastuzumab is most likely secondary to inhibition of HER2 receptor on cardiomyocytes, thereby interfering with their normal growth and repair, whereas there is little evidence of cell death in the adult myocardium due to HER2 inhibition, which may explain the reversibility of trastuzumab cardiotoxicity (Crone et al. 2002; Ewer and O'Shaughnessy 2007; Ozcelik et al. 2002; Suter et al. 2007). However, other mechanisms not involving HER2 signaling may also be operating (Guglin et al. 2008).

3.2.5.3 Cetuximab and Panitumumab

These antibodies target the epidermal growth factor receptor (EGFR), and no cardiotoxicity has been reported with these two drugs.

3.2.6 Small Molecule Tyrosine Kinase Inhibitors

Cardiotoxicity of tyrosine kinase inhibitors falls into two categories (Chen et al. 2008). The first relates to the tyrosine kinase target for cancer therapy having an important role in normal cardiomyocyte survival. Inhibition therefore causes myocardial dysfunction. The second is characterized by inhibition of a kinase which is not the intended target of the drug but which is important in normal cardiomyocytes. This situation is more likely the broader the range of targets for the tyrosine kinase inhibitor in question.

With the growing number of tyrosine kinase inhibitors being developed and approved, the likelihood will increase that some of them inhibit novel kinase targets for which little clinical data exist on associations with cardiotoxicity (Chen et al. 2008; Chen 2009; Cheng and Force 2010).

3.2.6.1 Lapatinib

Lapatinib cardiotoxicity is likely related to HER2 inhibition, as mentioned previously for trastuzumab. However, the risk associated with lapatinib is smaller. The difference may be due to the fact that monoclonal antibodies cause antibody dependent cellular and complement-dependent cytoxicity which could augment cardiotoxicity (Imai and Takaoka 2006). Moreover, differential inhibition and/or activation by lapatinib compared to trastuzumab of downstream signaling pathways may also be responsible (Spector et al. 2007).

3.2.6.2 Imatinib

Animal studies have shown cardiotoxicity in cardiomyocytes. Cardiotoxicity is most likely due to Abl inhibition in cardiomyocytes (Force et al. 2007; Kerkela et al. 2006). This seems to lead to induction of endoplasmic reticulum stress response, although the mechanisms are not clear. The endoplasmic reticulum stress response leads to cellular apoptosis. Imatinib-induced cardiotoxicity in patients is still an issue of debate (Breccia 2011).

3.2.6.3 Dasatinib

Like imatinib, dasatinib inhibits Abl, and the mechanism of cardiotoxicity may be similar. However, dasatinib inhibits a number of other kinases, which may be involved in the cardiotoxicity (Chen et al. 2008).

3.2.6.4 Nilotinib

Nilotinib, like imatinib and dasatinib, inhibits Abl. However, it seems to have a favorable toxicity profile, and the only cardiotoxicity reported is QT prolongation.

3.2.6.5 Sunitinib

Sunitinib is a multi-target tyrosine kinase inhibitor. It has been shown in human and animal studies to cause mitochondrial damage in cardiomyocytes (Chu et al. 2007) (see Fig. 6), with ensuing heart failure and cardiomyopathy in a minority of patients. These symptoms improve with discontinuation of the agent and are responsive to heart failure therapy. Animal studies suggest that sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase (Kerkela et al. 2009). Further work has also suggested that sunitinib cardiotoxicity is caused by inhibition of ribosomal kinase leading to activation of the intrinsic apoptotic pathway (Force et al. 2007). Hypertension may also play a role (Chu et al. 2007; Khakoo et al. 2008).

3.2.6.6 Sorafenib

Sorafenib is also a multi-target tyrosine kinase inhibitor, and it may cause cardiac damage by the same mechanisms as sunitinib. However, sorafenib also causes inhibition of the Raf kinases which may lead to enhanced cardiomyocyte apoptosis and fibrosis of the heart (Yamaguchi et al. 2004).

3.2.6.7 Gefitinib and erlotinib

These drugs target the EGFR tyrosine kinase, and no cardiotoxicity has been reported with these two drugs.

Endomyocardial Biopsy from Patients who Developed Sunitinib-induced Heart Failure

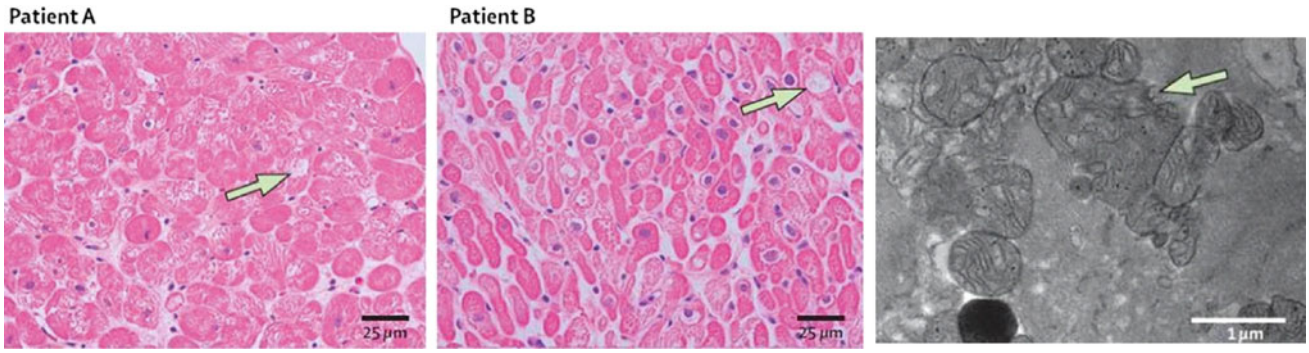

Fig. 6 Endomyocardial biopsy from patients who developed sunitinib-induced heart failure. Representative light photomicrographs from patients A and B (*left+middle panels*) showed cardiomyocyte hypertrophy with mild degenerative changes and diffuse, and moderate myocyte vacuolization (*arrows*). There was no edema, interstitial or replacement fibrosis, regional infarct or focal cell necrosis, myocarditis, or inflammation. Transmission election micrograph from patient A (*right*) showed swollen, abnormal mitochondrial configurations (*arrow*) with effaced cristae (with permission from Chu et al. 2007)

3.2.7 Proteasome Inhibitors

Bortezomib is associated with the development of heart failure, but the mechanism is unknown. It has been proposed that the inhibition of proteasomes in the myocytes is the direct cause of cardiotoxicity (Voortman and Giaccone 2006). In patients with chronic (even subclinical) cardiomyopathy, the ubiquitin–proteasome system is activated, which may be an adaptive mechanism for maintaining a normal stroke volume. In this situation, proteasome inhibition may cause manifest heart failure.

3.2.8 Angiogenesis Inhibitors

With regard to monoclonal antibodies and tyrosine kinase inhibitors acting via the VEGF pathway (bevacizumab, sunitinib), see above.

3.2.8.1 Thalidomide

Thalidomide is associated with the development of bradycardia. The mechanism remains unclear. It has been suggested to be due to the central sedative effects of the drug or to vasovagal activation. Thalidomide reduces the level of TNF-alpha which causes inhibition of the dorsal motor neurons including the nucleus of the vagus nerve. This could conceivably lead to over-reactivity of the parasympathetic nervous system leading to bradycardia. In some patients, thalidomide may cause hypothyroidism which may also lead to bradycardia (Fahdi et al. 2004; Kaur et al. 2003).

3.2.9 Histone Deacetylase Inhibitors

Vorinostat has been associated with QT prolongation. The mechanism is unknown.

3.2.10 Arsenic Trioxide

Arsenic trioxide has been associated with QT prolongation, and the mechanism is unknown.

4 Clinical Syndromes: Radiation Versus Chemotherapy and Interactions

The heart is a complex organ composed of distinct anatomic components that work in synchrony for effective global function. Injury to any one component of the organ can compromise function or render the entire organ dysfunctional. Conversely, the heart also has tremendous reserve, and can sustain a moderate degree of injury that remains subclinical. We will discuss the effects of radiotherapy and systemic therapy on several anatomical parts of the cardiovascular system.

4.1 The Heart

4.1.1 Effects of Radiation on the Heart

4.1.1.1 Radiation-Associated Heart Disease: Epidemiological Data

Radiation-associated heart disease includes a wide spectrum of cardiac disease, and combined disease of the coronary arteries, the heart valves, the myocardium, and the conductive system may occur (Adams et al. 2003; Aleman et al. 2007). These conditions usually only become symptomatic 10–15 years after exposure of the heart to irradiation, leading to an increased risk of (fatal) cardiovascular events

Table 4 Endpoints related to radiation-induced heart disease

	Focal	Global
Subclinical (usually objective)	Abnormalities in regional perfusion or wall motion via SPECT/MRI Valvular abnormalities via ECHO Asymptomatic coronary lesions Pericardial thickening on imaging or a pericardial rub heard on exam EKG abnormalities	Global imaging abnormality (e.g. diffuse hypocontractility) Asymptomatic reduced EF
Clinical (usually subjective)	Coronary artery disease Myocardial infarction Valvular disease	Congestive heart failure Pericarditis/pericardial effusion Arrhythmia Autonomic dysfunction

after for instance mediastinal irradiation for Hodgkin lymphoma and after irradiation for left-sided breast cancer; symptomatic abnormalities may develop much earlier. (Hancock et al. 1993a; Stewart et al. 1995; Adams et al. 2004; Boivin et al. 1992; Carlson et al. 1991; Clarke et al. 2005; Darby et al. 2003, 2005; Giordano et al. 2005; Glanzmann et al. 1998; Gustavsson et al. 1990; Hojris et al. 1999; Lee et al. 2000; Lipshultz and Sallan 1993; Lund et al. 1996; Paszat et al. 1998; Piovaccari et al. 1995; Rutqvist and Johansson 1990; Swerdlow et al. 2007; Taylor et al. 2006). The reported incidence of injury is thus clearly related to the endpoints being considered. It is often useful to stratify the various endpoints (albeit somewhat imperfectly) into categories as shown in Table 4.

The long delay before expression of serious damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

Information on mortality from cardiovascular diseases (CVDs) has been available in many countries for quite some time, whereas the information of incidence rates of CVD has been scarce. Gradually, incidence rates of several CVDs have become available. In addition, incidence rates of hospitalization for ischemic heart disease (Reinders et al. 1999) and of utilization of valve surgery, percutaneous interventions, and coronary bypass graft surgery among patients with HL (Hull et al. 2003) compared with general population rates, have been used as surrogate markers for CVD incidence.

Epidemiological studies on survivors of Hodgkin lymphoma show relative risk estimates for cardiac deaths in the range of 2–7, depending on the age of the patients (increased risks for irradiation at young age), the radiation therapy methods used, and the follow-up time (Hancock et al. 1993a; Adams et al. 2003; Boivin et al. 1992; Swerdlow et al. 2007; Aleman et al. 2003). In a Dutch study 3- to 5-fold increased standardized incidence ratios (SIR) of various heart diseases were observed in patients treated for Hodgkin lymphoma before the age of 41 years relative to the general population, even after a follow-up of more than 20 years (Aleman et al. 2007). The 25-year cumulative incidence of heart failure or cardiomyopathy with death from any cause as competing risk following mediastinal radiotherapy only was 6.8 %. The persistence of increased risk over prolonged follow-up time is of concern because this implies increasing absolute excess risks over time, due to the rising incidence of cardiovascular diseases with age.

Increased morbidity from cardiac diseases has been widely reported after treatment for breast cancer, especially using older radiotherapy techniques (Adams et al. 2003; Verheij et al. 1994; Gaya and Ashford 2005; Senkus-Konefka and Jassem 2007). The early breast cancer trialists'collaborative group (EBCTCG) evaluated the effects of local treatment on death from breast cancer and other causes in a collaborative meta analysis evaluating 42,000 women. This study showed a clear benefit of radiotherapy for local control and risk of death from breast cancer. However, there was, at least with some of the older radiotherapy regimens, a significant excess of nonbreast-cancer mortality in irradiated women [rate ratio 1.12; standard error (SE) 0.04] mainly from heart disease (rate ratio 1.27; SE 0.07) (Clarke et al. 2005).

The SEER database (surveillance, epidemiology, and end-results cancer registries) analysis also provides evidence of increased risk of myocardial infarction due to radiotherapy (Darby et al. 2005; Paszat et al. 1998). In a cohort of 308,861 women treated for early breast cancer, tumor laterality had no influence on subsequent mortality for women who did not receive radiotherapy. However, for women irradiated in the period of 1973–1982, there was a significant increase in cardiac mortality for left versus right-sided tumor (1.2 at <10 years, 1.42 at 10–14 years and 1.58 at >15 years). For women irradiated between 1983 and 1992, these risks had decreased to 1.04 at <10 years and 1.27 at >10 years.

Another large study ($n > 4{,}000$) investigated treatment-specific incidence of cardiovascular diseases in 10-year survivors of breast cancer treated from 1970 to 1986 in the Netherlands (Hooning et al. 2007). When comparing breast cancer patients who did or did not receive radiotherapy, radiation to the internal mammary chain was associated with significantly increased risk of cardiovascular disease (estimated mean, fractionated dose to the heart 6–15 Gy), while for breast irradiation alone no increased risk was

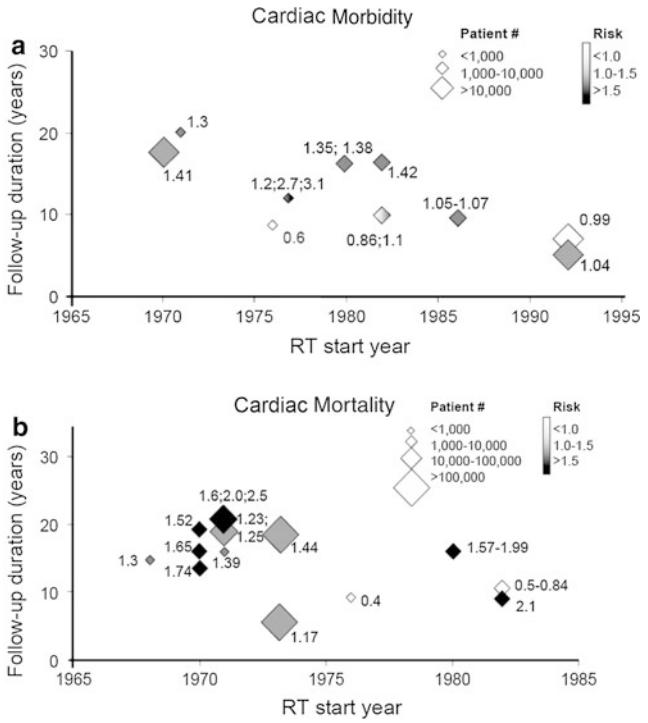

Fig. 7 The interaction of treatment era (based on patient accrual start-year) *and* follow-up duration on cardiac morbidity (panel **a**) and mortality (panel **b**) risk. The number (s) beside each point is the reported 'risk (s)' of cardiac morbidity/mortality in the published trial. The size of the diamonds represents trial sample size, and the shading represents the risk of cardiac morbidity (*black*: >1.5, *gray*: 1–1.5, and *white* as ≤1) From Demirci IJROBP 2009

observed (estimated mean, fractionated dose to the heart <7 Gy). For patients treated before 1979, radiation was associated with hazard ratios (HR) of 2.6 and 1.7 for myocardial infarct and congestive heart failure, respectively. For patients irradiated after 1979, the risk of myocardial infarct declined toward unity but the risks for congestive heart failure and valvular dysfunction remained significantly increased (HR 2.7 and 3.2, respectively). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (HR = 3.04).

In concert, these studies suggest that radiotherapy for left-sided breast cancer has the potential to increase the risk of cardiac morbidity and mortality, but that these risks are markedly reduced with newer radiation therapy techniques. However, since radiotherapy-induced heart disease is generally believed to not be clinically manifest until >10–15 years post radiotherapy, and since the follow-up duration is shorter in the studies using more modern techniques (vs. the older techniques), additional follow-up is needed to be confident that the more modern techniques are indeed "safe". The interaction between the duration of follow-up, the 'era of the radiotherapy' (taken as a surrogate for the 'modern-ness' of the radiotherapy techniques), and the RR of a cardiac event associated with radiotherapy, is shown in Fig. 7. Nevertheless, we are reassured that the more modern approaches markedly reduce the volume of heart exposed to radiotherapy, and that the available data suggest modern radiotherapy for breast cancer is not associated with a marked increase in cardiac events (albeit with modest follow-up time).

Many factors appear to influence the risk of CVDs. Table 1 summarizes the association between various risk factors and the different cardiac events. The highest relative risks are reported for those treated at young age (Aleman et al. 2007; Mulrooney et al. 2009; Hooning et al. 2007; Chen et al. 2008; Swerdlow et al. 2007; Myrehaug et al. 2008) and only slightly increased risks or no increased risks are reported in patients treated at 65 years or older (Swerdlow et al. 2007).

4.1.1.2 Radiation-Associated Heart Disease: Damage to Coronary Arteries

Although radiation damage to the coronary arteries may be immediate, clinical manifestation of damage does not usually appear until 10 or more years after radiation exposure.

Radiation may cause damage to the vascular endothelium of large arteries and therefore lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism.

Because of reduction of the arterial lumen to variable degrees, a spectrum of clinical manifestations of ischemic heart disease may be observed such as stable angina pectoris, unstable angina, myocardial infarction, and chronic ischemic heart disease.

An American study including 961 stage I-II breast cancer patients treated from 1977 to 1995 treated with conventional tangential beam radiation treatment (RT) showed that a statistically significant higher prevalence of stress test abnormalities was found among left (27 of 46; 59 %) versus right-side irradiated patients (3 of 36; 8 %; $P < 0.001$) at a median follow-up of 12 years. Furthermore, 19 of 27 of left-sided abnormalities were in the left anterior descending artery territory. Thirteen left-side irradiated patients also underwent cardiac catheterization revealing 12 of 13 with coronary stenoses (92 %) and 8 of 13 with coronary stenoses (62 %) solely in the left anterior descending artery (Correa et al. 2007; Tsibiribi et al. 2006a, b; Shapiro et al. 1998).

Furthermore, an increased risk of restenosis after coronary artery stenting has been reported in patients treated with thoracic radiation for lymphoma (Schomig et al. 2007; Manojlovic et al. 2008; Halyard et al. 2009).

4.1.1.3 Radiation-Associated Heart Disease: Damage to the Valves

Increased risks of valvular problems (valvular regurgitation in the aortic or mitral valve, and sometimes aortic stenosis) with or without clinical symptoms have been reported following radiotherapy for Hodgkin lymphoma (Aleman et al. 2007; Chen et al. 2011; Adams et al. 2004; Glanzmann et al. 1998; Lund et al. 1996; Heidenreich et al. 2003; Jones et al. 2007).

There are conflicting data following treatment for breast cancer (Hooning et al. 2007; Harris et al. 2006). Progressive valvular dysfunction has also been shown during long-term follow-up after treatment for Hodgkin lymphoma with mediastinal radiotherapy and/or anthracyclines (Wethal et al. 2009). Hodgkin lymphoma patients also have a significantly higher risk (SIR 8.4) of requiring valve surgery 15–20 years after radiotherapy (Hull et al. 2003).

4.1.1.4 Radiation-Associated Heart Disease: Damage to the Pericardium

Acute pericarditis is nowadays uncommon because of improved radiation techniques and lower radiation doses to smaller cardiac volumes. Patients may present with pleuritic chest pain, fever, tachycardia, a pericardial rub, and characteristic electrocardiographic abnormalities. These symptoms and pericardial effusions may resolve spontaneously. Symptomatic treatment analgesic and anti-inflammatory drugs are usually applied to relieve the pain. Constrictive pericarditis does however develop in a minority of patients. Medical treatment may temporarily alleviate symptoms of heart failure, but patients may need a pericardiectomy (Cosset et al. 1991; Bertog et al. 2004; Galper et al. 2010).

In the past, when generally larger radiation fields were used, for instance, in Hodgkin lymphoma treatment pericarditis was seen relatively frequently. In the early Stanford study, the risk of (a) symptomatic pericarditis was 20 % following whole-heart irradiation to 30 Gy, versus 7 % with the placement of a left-ventricular block at 15 Gy, and 2.5 % with a subcarinal block at 25–35 Gy (Carmel and Kaplan 1976).

Another European study including patients treated several decades ago has estimated that 4.8 % of Hodgkin lymphoma patients treated enveloped pericarditis approximately 18 years post-radiation therapy; the cumulative incidence for pericardial disease requiring surgery in these patients rose from only 0.1 % at 5 years post- radiation therapy to 1.3 % at 25 years from treatment (Galper et al. 2010).

More recently, a variety of dose-volume-histogram-based parameters were reported to be related to pericardial effusion for patients treated for esophageal cancer (Wei et al. 2008; Martel et al. 1998). Martel et al. (1998) implicated fraction size, mean, and maximum dose as a predictors for pericarditis. Wei et al. (2008) reported that a variety of DVH-based parameters (e.g., V3 to V50 and mean dose) predicted for pericardial effusions. The dosimetric parameters were highly correlated with each other, making comparisons of their predictive abilities difficult. See for detailed information Table 5.

4.1.2 Effects of chemotherapy on the heart

Several systemic cancer therapies have been associated with the development of left ventricular dysfunction and heart failure.

4.1.2.1 Anthracyclines

Anthracyclines are used to treat a wide range of cancers including breast, uterine, ovarian and lung cancers, leukemias, and lymphomas. The incidence of anthracycline cardiotoxicity depends on the medication and the cumulative dose. For doxorubicin the reported incidence of heart failure is 3–5 % with doses of 400 mg/m^2, 7–26 % with doses of 550 mg/m^2, and 18–48 % with doses of 700 mg/m^2 (Wouters et al. 2005; Swain et al. 1997; Von Hoff et al. 1979). A 5 % risk of cardiomyopathy is seen with a cumulative dose of doxorubicin of 450 mg/m^2, of daunorubicin of 900 mg/m^2, of epirubicin of 935 mg/m^2, and of idarubicin of 223 mg/m^2 (Wouters et al. 2005; Keefe 2001), and these doses are generally regarded as the maximum lifetime cumulative dose allowed. However, no threshold dose exists below which no left ventricular dysfunction is seen. Liposomal doxorubicin, epirubicin, and idarubicin seem to have a lower incidence of heart failure. However, the longer the follow-up, the higher the incidence of cardiac dysfunction is reported to be. A higher risk is reported with intravenous high single doses, drug infusion lasting <30 min, prior radiotherapy involving the heart, use of other concomitant agents such as cyclophosphamide, trastuzumab or paclitaxel, female gender, young and old age, and underlying cardiovascular disease (Aleman et al. 2007; Myrehaug et al. 2008; Leonard et al. 2009; Lipshultz et al. 1995, 2008; Moser et al. 2006; Stickeler et al. 2009; Trudeau et al. 2009).

Acute anthracycline cardiotoxicity occurs in <1 % of patients, and manifests immediately after infusion as a reversible depression of myocardial function (Giantris et al. 1998; Wouters et al. 2005). Discontinuation of the anthracycline often leads to improvement in the cardiac function.

Early onset chronic progressive anthracycline cardiotoxicity, usually presenting within 1 year of anthracycline treatment, occurs in 1–3 % of patients. Late onset chronic anthracycline cardiotoxicity occurs at least 1 year after anthracycline treatment in 1.6–5 %, and even higher incidence figures are reported for children, depending on what severity of symptoms are required for the diagnosis. However, it may not become clinically evident until 10–20 or

Table 5 Pericarditis/pericardial effusion: Dose-volume predictors and NTCP parameters

Authors, year, reference	Diagnosis, No. of patients, years of treatment	OAR	Fractionation schedule, dose data	Predictive parameters	NTCP parameters
Carmel and Kaplan[a] (1976)	Hodgkin lymphoma 377 Patients 1964–1972	Pericardium		At $D_{pericardium}$ >30 Gy: 50 % rate of pericarditis, 36 % requiring treatment	
Cosset et al. (1991)	Hodgkin lymphoma 499 Patients 1971–1984		35–43 Gy/ 2.5–3.3 Gy/ fraction pre-3D dose data	$D_{Mediastinum}$ ≥41 Gy, d/fraction ≥ 3 Gy (marginal significance)	
Burman et al. (1991)	Historical data				LKB[b] *TD50* = 48 Gy, *m* = 0.10 *n* = 0.35
Martel et al. (1998)	Esophagus 57 Patients 1985–1991	Pericardium	37.5–49 Gy/ 1.5–3.5 Gy/ fraction 3D data	D_{mean} > 27.1 Gy[c], D_{max} > 47 Gy[c], d/fraction 3.5 Gy	LKB (95 % CI) *TD50* = 50.6 Gy (−9; 23.1), *m* = 0.13 (−0.07; 0.13), *n* = 0.64 (−0.58; 3)
Wei et al. (2008)	Esophagus 101 Patients 2000–2003	Pericardium	45–50.4 Gy/ 1.8–2.0 Gy/ fraction 3D data	D_{mean} pericardium > 26.1 Gy, V_{30} < 46 %[d]	

CI confidence interval; *LKB* Lyman–Kutcher–Burman (model); *OAR* organs at risk; *NTCP* normal tissue complication probabilities

[a] Patients were grouped according to the estimated pericardium doses. Incidence of pericarditis was distributed as follows: 14/198 (7 %): ≤ 6 Gy; 5/42 (12 %): 6–15 Gy; 23/123 (19 %): 15–30 Gy; 7/14 (50 %): >30 Gy. For pericarditis requiring treatment the corresponding distribution was: 3/198 (1.5 %), 4/42 (9.5 %), 8/123 (6.5 %), and 5/14 (36 %)

[b] In the LKB model (Kutcher and Burman 1989; Lyman 1985) the parameters meaning is *TD50:* dose to the whole organ which will lead to complication in 50 % of the population; *m* is related to the steepness of the dose–response curve, *n* represents the volume effect (large volume effect for *n* close to unity; small volume effect for *n* close to zero)

[c] Corrected to 2 Gy per fraction, $\alpha/\beta = 2.5$ Gy

[d] Wei et al.: the risk of effusion was 13 % with a V30 < 46 Gy (or mean pericardial dose <26 Gy) versus 73 % in patients with a V30 > 46 Gy (or mean dose >26 Gy)

even 30 years after treatment. Chronic progressive cardiotoxicity typically presents as dilated cardiomyopathy (Lipshultz et al. 2008).

4.1.2.2 Alkylating Agents

Cyclophosphamide is an alkylating agent commonly used in the treatment for a variety of nonmalignant and malignant conditions including breast cancer, leukemia, lymphoma, multiple myeloma, mycosis fungoides, neuroblastoma, ovarian cancer, and retinoblastoma (Floyd et al. 2005). Cyclophosphamide has been associated with heart failure in 7–28 % of patients (Goldberg et al. 1986; Gottdiener et al. 1981; Pai and Nahata 2000; Braverman et al. 1991). The risk is dose related, occurring mainly in patients receiving >150 mg/kg and >1.5 g/m^2/day. It occurs within 1–10 days after the administration (Pai and Nahata 2000), and the clinical manifestations range from asymptomatic pericardial effusions to overt heart failure and myopericarditis (Gottdiener et al. 1981; Braverman et al. 1991). Cardiac failure following cyclophosphamide usually resolves over 3–4 weeks and is treated with supportive care (Floyd et al. 2005). Risk factors include previous anthracycline treatment and mediastinal radiotherapy (Goldberg et al. 1986; Pai and Nahata 2000).

Ifosfamide has been associated with cardiotoxicity in 17 % of patients (Pai and Nahata 2000; Quezado et al. 1993), occurring mainly in patients receiving doses >12.5 g/m^2 (Pai and Nahata 2000). Heart failure occurred within 6–23 days after treatment.

4.1.2.3 Antimetabolites

Fluorouracil is mainly used in the treatment for patients with cancer of the digestive tract especially colorectal cancer and head and neck cancer. Fluorouracil has been associated with symptoms of cardiotoxicity in 1–18 % of patients, most commonly as angina-like chest pain, but ischemic ECG changes may be seen in up to 68 % (Yeh and Bickford 2009; de Forni et al. 1992; Wacker et al. 2003; Jensen and Sorensen 2006; Keefe et al. 1993; Labianca et al. 1982; Tsavaris et al. 2002). In rare cases myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and sudden death have been reported (Meyer et al. 1997; Van Cutsem et al. 2002). The overall mortality of symptomatic fluorouracil cardiotoxicity has been estimated at 2.2–13 %

(de Forni et al. 1992; Wacker et al. 2003; Keefe et al. 1993; Labianca et al. 1982; Tsavaris et al. 2002; Robben et al. 1993). Cardiac events generally occur within 5 days after administration. The risk of cardiotoxicity is associated with high doses (>800 mg/m^2), continuous infusion, prior cardiovascular disease or mediastinal radiotherapy, and concurrent chemotherapy (de Forni et al. 1992; Kosmas et al. 2008; Jensen and Sorensen 2006; Labianca et al. 1982; Tsavaris et al. 2002; Meyer et al. 1997; Van Cutsem et al. 2002; Cardinale et al. 2006a, b; Rezkalla et al. 1989).

Capecitabine, an oral prodrug of fluorouracil, has been associated with cardiotoxicity with an incidence of 3–9 % (Kosmas et al. 2008; Van Cutsem et al. 2002; Ng et al. 2005; Saif et al. 2008; Walko and Lindley 2005). Typically, angina symptoms occurred 4–5 days after therapy (Jensen and Sorensen 2006) with ischemic ECG changes present in many cases (Cardinale et al. 2006a; Frickhofen et al. 2002; Schnetzler et al. 2001), but without echocardiography or coronary angiogram abnormalities (Yeh and Bickford 2009; Cardinale et al. 2006a; Schnetzler et al. 2001). Prior fluorouracil cardiotoxicity and possibly prior symptoms of coronary artery disease were risk factors (Labianca et al. 1982; Saif et al. 2008; Frickhofen et al. 2002; Schober et al. 1993).

4.1.2.4 Antimicrotubule Agents

Docetaxel is employed in the treatment of breast cancer and prostate cancer. It has been reported to be associated with heart failure in 2.3–8 % of patients (Martin et al. 2005; Marty et al. 2005). Myocardial ischemia has been reported to occur in 1.7 % of patients (Yeh and Bickford 2009; Vermorken et al. 2007).

Paclitaxel is used in patients with lung cancer, ovarian cancer, and breast cancer. It has been reported to be associated with ischemia in 5 % of patients (Rowinsky et al. 1991) and with myocardial infarction in 0.5 % (Arbuck et al. 1993). The cardiac events occurred up to 14 days after paclitaxel administration (Arbuck et al. 1993), and risk factors were previous cardiac disease including hypertension and coronary artery disease. Paclitaxel has also been associated with bradycardia, which is usually without clinical significance, but may in rare cases have clinically significant hemodynamic effects. Hypersensitivity reactions with histamine release have been implicated, and premedication to prevent hypersensitivity reactions may prevent bradycardia as well.

Vinca alkaloids, used in the treatment of lymphomas, nonsmall cell lung cancer, breast cancer, and testicular cancer, have also been incriminated. Significantly (2 fold or more) increased risks of death from myocardial infarction (Swerdlow et al. 2007) or more general cardiovascular diseases (Tukenova et al. 2010) have been reported.

4.1.2.5 Monoclonal Antibodies

Bevacizumab is a monoclonal antibody that inhibits the activity of human VEGF. It is approved for use in the setting of first-line metastatic colon cancer in combination with intravenous FU-based chemotherapy. It is also used in the treatment of nonsmall cell lung cancer and brain tumors. Bevacizumab has been associated with heart failure in 1.7–3 % of patients (Miller et al. 2005, 2007). Moreover, arterial thrombotic events have been reported in 3.8 % of patients with myocardial infarctions in 0.6 % (Scappaticci et al. 2007). Arterial thrombotic events could occur at any time during therapy, and they did not seem to be related to dose or cumulative exposure. Risk factors were older age and prior arterial thrombotic events (Scappaticci et al. 2007). The most common cardiotoxicity with bevacizumab treatment is, however, hypertension, which is reported to occur in 4–35 % of patients (Miller et al. 2005, 2007; Cobleigh et al. 2003; Hurwitz et al. 2004; Johnson et al. 2004; Kabbinavar et al. 2005; Pande et al. 2007; Yang et al. 2003). Hypertension might develop at any time during therapy, and higher dose has been suggested as a risk factor (Kabbinavar et al. 2005). Most patients can continue bevacizumab in combination with antihypertensive drugs.

Trastuzumab, used in patients with breast cancer, is associated with cardiomyopathy in 2–7 % of patients when the drug is used alone. However, when trastuzumab is used with paclitaxel the incidence is 2–13 %, and when used with an anthracycline it is up to 27 % (Ewer and O'Shaughnessy 2007; Suter et al. 2007; Gianni et al. 2007; Guarneri et al. 2006; Perez et al. 2008a; Romond et al. 2005; Seidman et al. 2002; Slamon et al. 2001; Tripathy et al. 2004; Vogel et al. 2002). Risk factors are age >50, pretreatment borderline left ventricular ejection fraction, prior cardiovascular disease, and prior treatment with anthracyclines to higher cumulative doses (287 mg/m^2 vs. 257 mg/m^2 for doxorubicin, 480 mg/m^2 vs. 422 mg/m^2 for epirubicin) (Suter et al. 2007; Guglin et al. 2008; Gianni et al. 2007; Guarneri et al. 2006; Perez et al. 2008a, b; Seidman et al. 2002; Tan-Chiu et al. 2005). Hence, increased cardiac stress seems to increase the risk of trastuzumab associated cardiac side effects, which may explain why it appears to be more frequent in clinical practice than in controlled trials (McArthur and Chia 2007). Trastuzumab cardiotoxicity is not dose related, and it is frequently reversible. However, if combined with anthracyclines, the frequency and risk of anthracycline induced myocyte death might increase (Zuppinger et al. 2007).

4.1.2.6 Small Molecule Tyrosine Kinase Inhibitors

Lapatinib is used in the treatment of disseminated breast cancer. It has been reported to be associated with

symptomatic (grade 3 or 4 heart failure) cardiotoxicity in 0.2 % of patients and with asymptomatic events (>20 % decrease in left ventricular ejection fraction without symptoms) in 1.4 % of patients (Perez et al. 2008b). The risk was increased in patients with prior anthracycline treatment (2.2 %) or prior trastuzumab treatment (1.7 %). The mean time to onset of symptoms was 13 weeks. Lapatinib has also been reported to cause QT prolongation in 16 % of patients treated with varying doses (Yeh and Bickford 2009). Lapatinib thus seems to be less cardiotoxic than trastuzumab. This may partly be due to selection bias in the trials of patients receiving lapatinib, but recent data indicate an underlying molecular mechanism for the apparent difference in cardiotoxicity, as lapatinib, but not trastuzumab protects against TNF-alpha-induced cardiomyocyte death (Spector et al. 2007).

Imatinib, used in the treatment of chronic myeloid leukemia and in gastro-intestinal stromal tumors, has been associated with rare heart failure (Kerkela et al. 2006). The incidence of clinical heart failure in patients treated with imatinib has been reported as 0.5–1.7 % (Atallah et al. 2007; Hatfield et al. 2007). Whether the imatinib-associated cardiotoxicity is reversible or not is still unknown.

Dasatinib, also used in the treatment of chronic myeloid leukemia, has been reported to be associated with heart failure in 2–4 % of patients, and QT prolongation has been reported to occur in 2–3 % of patients treated with dasatinib (Yeh and Bickford 2009).

Sunitinib, simultaneously approved for the treatment of renal cell carcinoma, and gastrointestinal stroma tumor, has been associated with left ventricular dysfunction in 4–11 % of patients, with symptomatic heart failure in 2.7–8 % (Chu et al. 2007; Khakoo et al. 2008). The mean time to the development of heart failure varied between 22 days and 27 weeks, and the only risk factor was prior coronary artery disease. Although heart failure responded to medical therapy, it did not seem to be fully reversible (Khakoo et al. 2008). Moreover, sunitinib has been associated with hypertension in 5 to 47 % (Chu et al. 2007), in different clinical trials, with grade 3 occurring in 2–8 % (Chu et al. 2007; Burstein et al. 2008; Demetri et al. 2006; Motzer et al. 2006a, b, 2007; Azizi et al. 2008).

Sorafenib, approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma, causes hypertension in a significant number of patients. The overall incidence in a recent meta analysis was 23.4 %, with grade 3 and 4 reported in 2.1–30.7 % in different studies (Wu et al. 2008). Sorafenib has also been associated with myocardial ischemia in 3 % of patients in clinical trials, which is significantly higher than in patients treated with placebo (Yeh and Bickford 2009; Escudier et al. 2007).

Kinase Inhibition Determines TKI-induced Toxicity to Normal Tissue:

- Cardiotoxicity is NOT a class effect for TKIs.
- Cardiotoxicity determined by the specific kinases that a TKI inhibits (whether on-target or off-target).
- Small molecule TKIs inherently inhibit many different kinases than monoclonal antibodies.
- Multi-targeted TKIs inhibit more kinases (i.e., sunitinib > imatinib).
- Certain inhibited kinases are essential to tumor cell killing and also turn out to be necessary for cardiomyocyte survival.
- Constant balance between enhanced tumor cell killing versus potential increased risk of cardiotoxicity.

4.1.2.7 Vorinostat

Vorinostat is approved for the treatment of cutaneous T cell lymphomas. Vorinostat had been reported to be associated with QT prolongation in 3.5–6 % of patients (Yeh and Bickford 2009; Olsen et al. 2007). Risk factors are female gender, older age, previous myocardial ischemia, heart failure, electrolyte imbalances, bradycardia, and medication with QT prolonging drugs (Yeh and Bickford 2009; Vorchheimer 2005).

4.1.2.8 Thalidomide

Thalidomide is used in the treatment of multiple myeloma. Bradycardia has been associated with thalidomide treatment in 2–55 % of patients. Most patients are asymptomatic, but some patients may experience fatigue, syncope, or dizziness. Patients developing third-degree atrioventricular block need a permanent pacemaker.

4.1.2.9 Arsenic Trioxide

Arsenic trioxide is used in the treatment of certain leukemias. QT prolongation has been reported in patients treated with arsenic trioxide in 26–93 % of patients (Barbey et al. 2003; Huang et al. 1998; Ohnishi et al. 2002; Shigeno et al. 2005; Singer 2001; Unnikrishnan et al. 2004; Westervelt et al. 2001). The QT interval has been reported to be prolonged from 1 to 5 weeks after treatment and then returned to baseline (Soignet et al. 2001).

4.1.2.10 Toxic Effect of Systemic Therapy on Coronary Arteries

Direct effects of chemotherapy on coronary arteries are rare.

Fluoropyrimidines (i.v. 5 fluoro-uracil (5FU) or oral capecitabine), may cause myocardial ischemia and decreased contractility of the heart (Kosmas et al. 2008; Tsibiribi et al. 2006a, b; Manojlovic et al. 2008). A spasm

of the coronary arteries is often considered to be the most important cause. The underlying mechanism is not fully elucidated yet. Experimental studies in rabbits indicate that a spasm of the coronary arteries is not the only mechanism of 5FU cardiotoxicity, and that apoptosis of myocardial and endothelial cells can result in inflammatory lesions mimicking toxic myocarditis (Tsibiribi et al. 2006a, b).

4.1.3 Effects of Combined Modality Treatment on the Heart

Whether toxicity following chemotherapy and radiotherapy are additive or synergistic is still unclear. Several clinical studies in lymphoma patients showed that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders by 2- to 3-fold compared to radiotherapy alone (Aleman et al. 2007; Moser et al. 2006). A Dutch study including 5-year survivors of Hodgkin lymphoma treated before age 41 showed that the 25-year actuarial risks of heart failure after mediastinal radiotherapy alone versus anthracycline-based chemotherapy in combination with mediastinal radiotherapy were 7.5 versus 10.7 % respectively (Aleman et al. 2007).

Myrehaug et al. 2008 evaluated the risk of hospital admission for cardiac disease in Hodgkin lymphoma patients, adjusting for age, sex, treatment, cardiac risk factors, and competing causes of death. They showed that for females and males treated with doxorubicin plus mediastinal radiotherapy at age 40, the estimated 15-year incidence rate of cardiac hospitalization was 7.3 and 16.5 %, respectively, rates 5–15 % higher than expected. They also showed that the cardiotoxic effects of radiotherapy and chemotherapy may be more than additive.

A prospective study in breast cancer patients compared 10 versus 5 cycles of doxorubicin (A) (45 mg/m2) and cyclophosphamide (C) (500 mg/m^2) chemotherapy. In retrospective subgroup analysis of patients treated with radiotherapy, an increased rate of cardiac events was found among patients receiving 10 cycles of chemotherapy and radiotherapy (Shapiro et al. 1998), with a 6-year median follow-up.

Trastuzumab and other systemic agents (e.g., taxanes and biologicals) will be used more commonly along with thoracic radiotherapy in patients. There is only limited data on possible interactions between these agents and radiation with respect to cardiotoxicity. In a recent multicenter, prospective trial assessing the utility of trastuzumab in breast cancer, the concurrent use of trastuzumab along with left-sided RT appeared to be safe, albeit with a follow-up of only 3.7 years (Halyard et al. 2009) Dose-volume data regarding the degree of heart irradiation were not reported; though purposeful irradiation of the internal mammary nodes was not permitted.

4.2 Toxic Effects on Other Blood Vessels

Arteries may be damaged by radiation. Veins seem to be less vulnerable to radiation effects. The clinically most important arterial radiation-related problems are mentioned below.

4.2.1 Carotid Arteries

Damage to the carotid arteries is of special importance. Significantly, increased risks of stroke have also been described in patients treated with radiotherapy for head-and-neck cancer (60–70 Gy; RR 2.1–9.0, depending on follow-up) (Dorresteijn et al. 2002; Haynes et al. 2002; Scott et al. 2009), Hodgkin lymphoma (median dose approximately 40 Gy; RR 2-to 4-fold increased) (Bowers et al. 2005; De Bruin and Dorresteijn 2009) and in long-term survivors of childhood leukemia and brain tumors treated with >30 Gy cranial radiotherapy (RR 5.9 and 38, respectively) (Bowers et al. 2006). The latter study also demonstrated a relationship between radiation dose and RR stroke, with significantly higher risks for cranial doses of >50 Gy compared with 30–50 Gy.

In a Dutch retrospective cohort study of 2,201 5-year survivors of Hodgkin lymphoma treated before age 51 between 1965 and 1995, there was a substantially increased risk of stroke and TIA, associated with radiation to the neck and mediastinum (De Bruin and Dorresteijn 2009). Most ischemic events were from large artery atherosclerosis (36 %) or cardioembolisms (24 %). The standardized incidence ratio for stroke was 2.2 (95 % confidence interval [CI] = 1.7–2.8), and for TIA, it was 3.1 (95 % CI = 2.2–4.2). The risks remained elevated, compared with those in the general population, after prolonged follow-up. Treatment with chemotherapy was not associated with an increased risk. Hypertension, diabetes mellitus, and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease, whereas smoking and overweight were not.

4.2.2 Aorta

Increased risks of atherosclerosis following radiation exposure of other arteries have been reported, leading to stenosis of the subclavian artery, (Hull et al. 2003) of the aorta (Piedbois et al. 1990), and of arteries supplying the small bowel (Patel et al. 2006). Described numbers of patients are however small.

In a recent small case–control study, treatment with anthracyclines has been shown to increase aortic stiffness significantly within 4 months of treatment compared with controls (Chaosuwannakit et al. 2010). Stiffening of the aorta increases left ventricular afterload, and it is an independent predictor of adverse cardiovascular events. Stiffening of the aorta was correlated with the cumulative anthracycline dose. The addition of trastuzumab or cyclophosphamide did not increase the risk of stiffening.

4.2.3 Microcirculation

Damage to the peripheral circulation can impair circulation and predispose to thrombosis. The impact of antineoplastic therapies on the peripheral circulation can be ascribed to damage to the intima of vessels. Damage to the vessel can involve injury to the intimal layer or disruption of endothelial cell-to-cell communication. In either case, the loss of integrity of the vessel lining activates the coagulation cascade. Hemorrhage and arterial thromboembolism have been observed in patients treated with angiogenesis inhibitors such as thalidomide and lenalidomide (van Heeckeren et al. 2007). Venous thromboembolism has been associated with different chemotherapeutic agents such as alkylating agents (in particular cisplatin), angiogenesis inhibitors, histone deacetylase inhibitors, and tyrosine kinase inhibitors (Czaykowski et al. 1998; Rodeghiero and Elice 2003; Zangari et al. 2007).

Drugs that modify the expression pattern of adhesion molecules such as integrins and cadherins on endothelial cells alter cell to cell and cell to matrix connections and interrupt endothelium integrity. This leads to an increased risk of hemorrhage and thromboembolism. This is the case for some drugs such as doxycycline and lenalidomide (Fainaru et al. 2008; Lu et al. 2009; Matsumura et al. 1997).

4.2.4 Possible Interaction Between Macrovascular and Microvascular Injury for the Myocardium

Radiation appears to cause both microvascular injury to the myocardium as well as macrovascular injury to the coronary arteries. How these two types of injury interact to cause clinical dysfunction is uncertain. A reasonable hypothesis is as follows. Radiotherapy causes microvascular injury in the relatively short-term interval post radiotherapy (months to years). This usually remains asymptomatic perhaps since the myocardium has an extensive network of collateral flow. In addition, radiotherapy also causes damage to the coronary arteries, but typically on a longer time scale (years to decades). When an obstructive coronary lesion develops, it might be more likely to cause a clinical event due to the relative loss of collateral flow (from the microvascular injury) (see Fig. 8; from Darby et al. 2010).

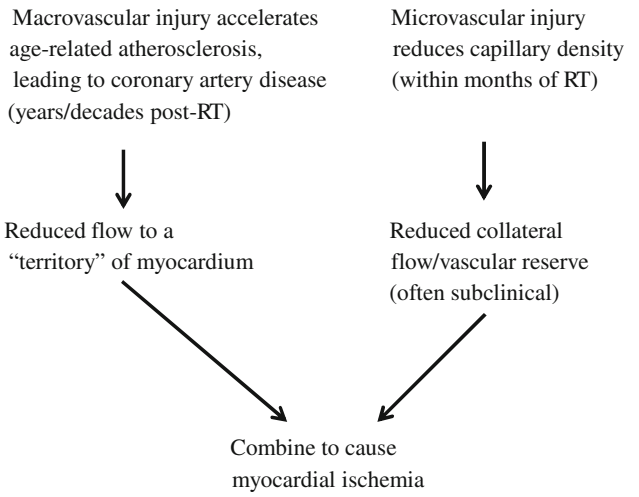

Fig. 8 Schematic illustration of how microvascular and macrovascular radiation-related cardiac injury could theoretically combine to cause myocardial ischemia after RT (From Darby IJROBP 2010)

5 Radiation Tolerance

5.1 Radiation dose- volume effects of the heart

Data on relationships between cardiovascular toxicity in relation to radiation dose, radiation volume, and irradiated structure are still scarce, and thus much uncertainty remains.

Mortality data from the life span study (LSS) of the Japanese atomic bomb survivors and from occupational and environmental studies provide some evidence of a dose response for mortality from heart diseases and stroke (Shimizu et al. 1999; Preston et al. 2003; Little 2009, 2010) (Fig. 9).

A recent report (AGIR 2010), calculating aggregate risks from many studies, estimated an excess relative risk per Gy (ERR/Gy) of 0.10 (95 % CI 0.07, 0.13) for morbidity and 0.08 (95 % CI 0.04, 0.12) for mortality from circulatory disease taken as a whole (Subgroup on Circulatory Disease Risk of the Advisory Group on Ionizing Radiation 2010; ICRP Report 2012).

There are indications that cardiotoxicity from therapeutic radiation is related to total radiation dose and dose per fraction to the heart (Hancock et al. 1993a; Heidenreich et al. 2007; Darby et al. 2010; Gagliardi et al. 2010). Large doses per fraction are expected to be relatively more damaging to the heart than low doses per fraction, and indeed increased complication rates were reported for Hodgkin lymphoma patients treated with 3×3.3 Gy per week, compared with patients treated with 4×2.5 Gy per week to the same total dose (Cosset et al. 1988).

Furthermore, the volume of the heart included in the irradiation field influences the risk of cardiotoxicity (Schultz-Hector and Trott 2007; Moser et al. 2006; Tukenova et al. 2010). For pericarditis, TD 5/5 values (total dose for 5 % incidence at 5 years) of 60, 45, and 40 Gy have been estimated when 1/3, 2/3, and the whole heart is irradiated using 2 Gy per fraction (Emami et al. 1991). A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction has been reported in Hodgkin lymphoma patients treated after partial

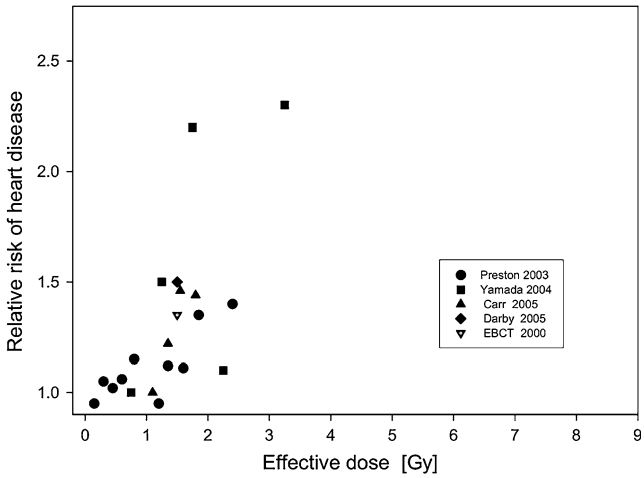

Fig. 9 Relative risk of death from heart disease increases with radiation dose: Preston et al. (Preston 2003) and Yamada et al (Yamada 2005) reported on cardiac mortality in atomic bomb survivors (life span study [LSS]); Carr et al. (Carr 2005) reported on mortality from coronary heart disease at >10 years after radiation therapy of peptic ulcers; Darby et al. (Darby 2005) and the Early Breast Cancer Trialists group (EBCTCG 2000) analyzed mortality from heart disease after radiotherapy for breast cancer. Figure adapted from Schultz-Hector and Trott (Schultz-Hector 2007)

shielding of the heart and restriction of the total, fractionated, mediastinal dose to <30 Gy (Hancock et al. 1993, b). Radiotherapy techniques have greatly improved over the past 20 years, leading to more homogeneous dose distributions and reduced risks of toxicity (Lee et al. 1995, b). In two more recent reports on cardiotoxicity in childhood cancer survivors dose- and volume effects have been studied in detail. Tukenova et al. (Tukenova et al. 2010) report a linear relationship between the average radiation dose to the heart and the risk of cardiac mortality (with an estimated relative risk at 1 Gy of 1.6; i.e., a 60 % increase). Mulrooney et al. 2009 also find indications for a relationship between the risk of cardiovascular disease and mean radiation dose to the heart (Mulrooney et al. 2009) (see Fig. 10). Compared with siblings, survivors of childhood cancer were significantly more likely to report CHF (hazard ratio [HR] = 5.9), MI (HR = 5.0), pericardial disease (HR = 6.3), or valvular abnormalities (HR = 4.8). Cardiac radiation exposure of 15 Gy or more increased the risk of CHF, MI, pericardial disease, and valvular abnormalities by 2- to 6-fold compared with nonirradiated survivors. There was no evidence for increased risk following doses less than 5 Gy, and slight elevations in risk were not statistically

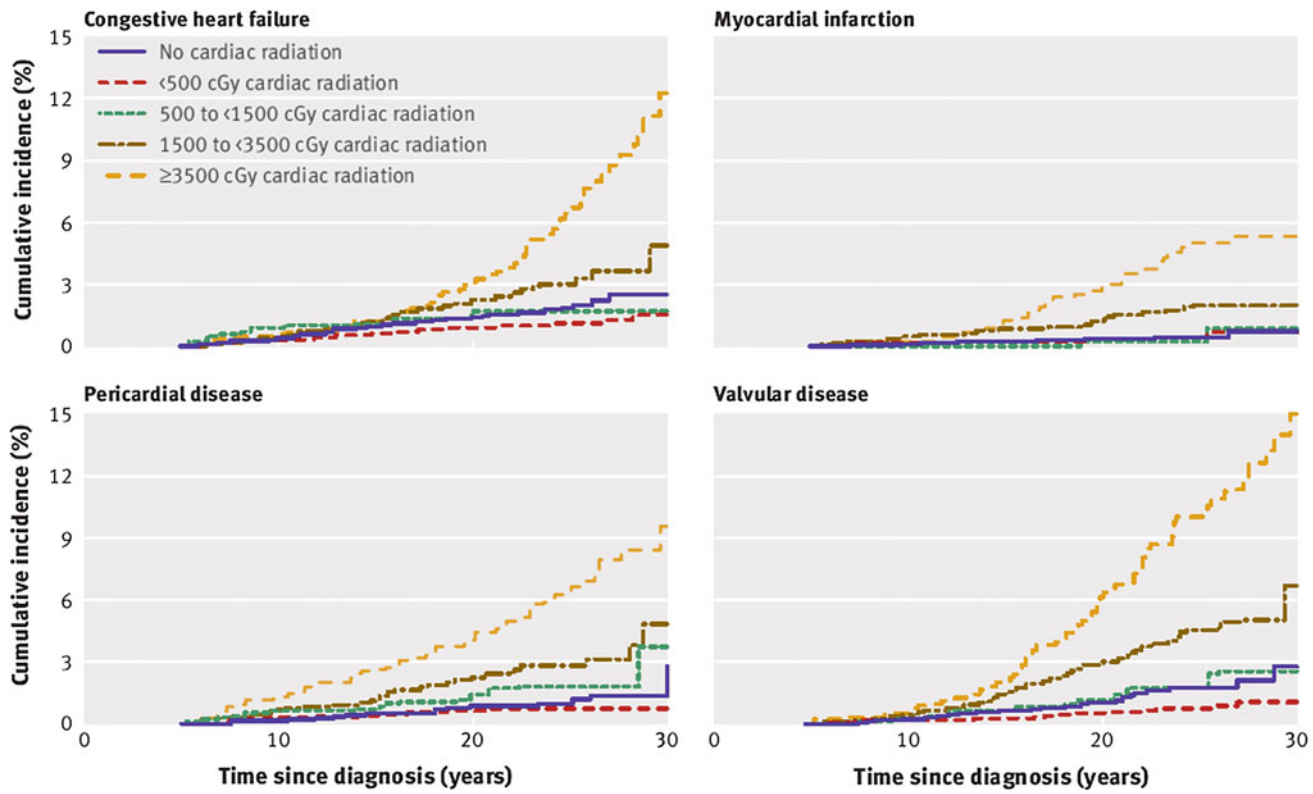

Fig. 10 Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose from Mulrooney (Mulrooney 2009)

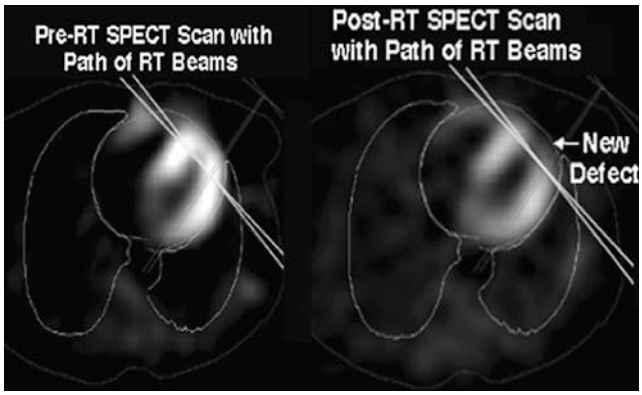

Fig. 11 Representative axial images pre-RT (*left panel*) and post-RT (*right panel*) cardiac SPECT perfusion scans. The deep borders of the tangential RT beams are shown as *solid lines*. A new perfusion defect in the anterior left ventricle after radiation is seen (From Darby IJROBP 2010)

significant following doses between 5 to 15 Gy. Exposure to 250 mg/m^2 or more of anthracyclines also increased the risk of CHF, pericardial disease, and valvular abnormalities by 2 to 5 times compared with survivors who had not been exposed to anthracyclines.

Clinically, significant cardiovascular abnormalities, like reduced left ventricular dimensions, valvular, and conduction defects, are very common, even in asymptomatic cancer survivors (Adams et al. 2004; Heidenreich et al. 2003).

Several studies have considered subclinical endpoints to assess radiotherapy-induced injury (Girinsky et al. 2000; Marks et al. 2005). For example, in a prospective study of 114 women with breast cancer, left-sided tangential photon fields appear to cause reductions in regional myocardial perfusion at relatively short times post-radiotherapy (e.g. 0.5–2 years) (Marks et al. 2005) (Fig. 11). The perfusion defects are associated with the irradiated area, and not with the territory of a coronary artery (Lind et al. 2003), thus suggesting that the radiation-induced injury is at the microvascular level. These perfusion abnormalities are associated with corresponding abnormalities in wall motion, but not reductions in ejection fraction (Marks et al. 2005) and are largely persistent up to 6 years post-radiotherapy. Such perfusion abnormalities are seen in $\approx$20, $\approx$30 and >50 % of patients with <1, 1–5, and >5–10 % of their left ventricle within the planned tangential fields (suggesting a strong volume dependence) (Evans et al. 2006). The clinical relevance of these perfusion abnormalities is unknown. These results are largely consistent with the findings from several other studies. Several studies have assessed for perfusion abnormalities post-radiotherapy for breast cancer (See Table 6). Most detect perfusion abnormalities, and these defects can be associated with wall motion abnormalities (Seddon et al. 2002). Similarly, in patients irradiated for Hodgkin lymphoma or other intrathoracic tumors, perfusion defects are also often seen (See Table 6), but these are usually not associated with any clinical events. The follow-up in these studies, however, may be too short to detect clinically meaningful events.

Recently, pre-existing heart disease was shown to be associated with an increased risk of cardiac hospitalization following treatment for Hodgkin lymphoma, particularly mediastinal radiotherapy with or without anthracyclin-containing chemotherapy (Myrehaug et al. 2010).

5.2 Summary and Recommendations Concerning Radiation Tolerance of the Heart

Overall, these observations demonstrate that incidental irradiation of the heart can cause dose- and volume-dependent cardiotoxicity. For example, there is a clear risk of Coronary Artery Disease (CAD) after radiotherapy, typically manifest >10–15 years post-RT, as well as pericardial injury occurring sooner post-RT. More sensitive tests (e.g., imaging) can detect more subtle changes (often relatively soon post-RT), but the clinical relevance of these findings is unclear. Given the paucity of good dose-volume-outcome data (especially for the more meaningful long-term risks), it is challenging to formulate strict dose-volume guidelines. One is left perhaps to conclude that there are no particular 'safe' doses/volumes, and that one should minimize all exposures to the degree possible. Indeed, the recent Quantec review (Gagliardi et al. 2010) similarly was unable to recommend strict guidelines. They concluded saying, "Radiation-induced cardiac complications have different significance and implications depending on the clinical scenario". As such, constraints/NTCP values can be used only for guidance; they must always be considered in relation to probability of tumor control and the specific patient. Nevertheless, the following broad dose-volume guidelines are suggested. In patients with breast cancer, it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising the target coverage. In many cases, conformal blocking and breath-hold techniques can essentially eliminate the heart from the primary beams. If NTCP models for cardiac mortality are used, it should be considered that an NTCP value 5 % could jeopardize the beneficial effect on survival of radiotherapy. So as not to underestimate this risk, the most conservative approach is provided by the use of the [steepest available] dose–response curve, that is, the one from the breast data (Gagliardi et al. 1996).

Although currently, there is no direct evidence that successful treatment of traditional cardiac risk factors will alter the natural history of radiation-associated cardiac disease, it is prudent to optimize patient cardiovascular risk

Table 6 Studies assessing for perfusion defects following radiotherapy for breast cancer. Adapted from Prosnitz RG, Marks LB: Radiation-induced heart disease: vigilance is still required. J Clin Oncol 23:7391–4, 2005

Author	Years post-RT	Patient subset	Rate of perfusion defects
Gyenes (Gyenes 1994)	≈18	Left-sided, photon/electron-treated	5/20
	19	Right-sided,photon/electron-treated	0/17
Hojris (Hojris 2000)	8	Left-sided, electrons	4/9
		No RT	4/7
Cowen (Cowen 1998)	≈8	Left-sided, photons	0/17
Seddon (Seddon 2002)	≈7	Left-sided, photons	7/24
		Right-sided, photons	2/12
Gyenes (Gyenes 1996)	≈1	Left-sided, photons	4/4
		Left-sided, electrons	2/8
Marks (Marks 2005)	0.5–2	Left-sided, photons: % of Left ventricle estimated to be in the tangents:	
		<1	≈20 %
		1–5	≈30 %
		>5 %	≈ >50 %

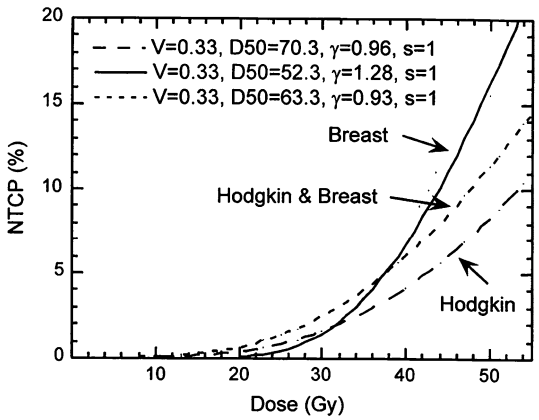

Fig. 12 Dose–response curves for long-term cardiac mortality based on Hodgkin's disease and breast cancer datasets (from Eriksson 2000)

profiles (Executive Summary of the Third Report of the National cholesterol Education Program (NCEP) 2001; Mosca et al. 2007; Jones et al. 2007) (Fig. 12).

6 Prevention and Management

6.1 Prevention

6.1.1 Prevention radiation-related cardiovascular toxicity

With respect to radiation, it is important to use conventionally fractionated radiation, and to limit both radiation dose and volume as is clinically possible/practical. Modern radiation techniques such as intensity modified radiotherapy may facilitate a reduction in heart exposure without compromising the radiation dose in the target volume. Inspiratory breathholding techniques during delivery of radiation therapy for left-sided breast cancer can reduce incidental cardiac exposure, while maintaining radiation dose to the target (Chen et al. 1997, 2002; Lu et al. 2000). The diaphragm is pulled downwards, displacing the heart caudally and often medially. Inspiration increases the anterior–posterior diameter of the chest and displaces the left breast away from the heart. These anatomic changes result in decreased cardiac irradiation, with complete displacement of the heart outside the field in 21 % of patients (Crone et al. 2002; Chen et al. 1997). Clinical introduction of these and other novel simulation techniques has shown initial promise (Korreman et al. 2006). Ongoing research is expected to give more information concerning which cardiac structures are most critical and whether it is less harmful to include a slightly larger volume to a low dose or a smaller volume to a slightly higher dose.

Optimization of treatment choice is still an important subject of study. In the future, we hope to be able to identify survivor groups at high risk of late adverse effects (based on treatment and/or genotype) for which screening should be recommended and/or intervention trials could be designed.

Although the design of mediastinal fields for some cancers may not allow for the effective use of respiratory maneuvers, it is worth exploring every possible means to decrease cardiac and valvular exposure when designing radiation portals.

6.1.2 Prevention chemotherapy-related cardiovascular toxicity

The evidence about the effectiveness of technologies to reduce or prevent cardiotoxicity from anthracyclines is limited in quantity and quality (van Dalen et al. 2008; 2009). The available evidence mainly comes from treatment of children. Optimization of chemotherapy dosage schedules, for instance anthracycline dosage schedules (i.e., avoiding peak doses), has been studied. However, so far results have been disappointing (van Dalen et al. 2009).

Anthracyclines release free radicals that damage the cardiac myocytes, which are especially susceptible to free radical damage because of their highly oxidative metabolism and poor antioxidant defenses. The free-radical scavenging cardioprotectant, dexrazoxane has been shown to reduce anthracycline-associated myocardial injury in rats (Herman et al. 2001) and in selected studies in humans (Swain et al. 1997). Lipshultz demonstrated that in children with acute lymphoblastic leukemia treated with anthracycline, the concomitant use of dexrazoxane resulted in less troponin T release during therapy (Lipshultz and Adams 2010). Eight years later, these patients also had higher LVEFs as compared to the control group that received no dexrazoxane (Chen et al. 2011; Lipshultz et al. 2004). Greater use of this compound has been limited by concern about its possible interference with anthracycline's anticancer activity (Yeh and Bickford 2009). This delicate balance between cancer cure and cardioprotection is an ongoing area of investigation and research.

Furthermore, there are some indications of a possible beneficial effect of angiotensin-converting enzyme inhibitors (ACEI) and of beta blockers (Noori et al. 2000) after cardiotoxic chemotherapy (Cardinale et al. 2006b), especially with initiation within 6 months of diagnosis of cardiotoxicity (Cardinale et al. 2010) Cardinale has shown that early initiation of ACEI and beta blockers is cardioprotective (Cardinale et al. 2010). These treatments not only help prevent late cardiac events; they also improve LVEF in those who show an early decrease in LVEF during anthracycline therapy (Cardinale et al. 2010). These results are pertinent because another study had initially shown no permanent improvement in LVEF in children with anthracycline-associated cardiomyopathy who were started on ACEI 6–7 years after treatment (Lipshultz et al. 2002). The difference may reflect the differing population of adults and pediatrics and also the different time course in initiation of ACEI.

6.1.3 Prevention of cardiovascular toxicity related to novel targeted therapy

We are just beginning to understand the potential cardiovascular effects of the multitude of new targeted agents that are being approved. However, there is some data already that suggest aggressive management of hypertension both prior to initiation of targeted therapy with VEGF inhibitors and also during therapy, may reduce the risk of heart failure associated with certain agents. Patients in Phase III trials of sunitinib that excluded hypertensive patients had lower incidence of heart failure on sunitinib, a multi-targeted tyrsoine kinase inhibitor that also inhibits VEGFR (Chen et al. 2008; Chu et al. 2007; Maitland et al. 2010). In this age of personalized medicine, anti-cancer regimens would eventually be optimized for each individual with improved understanding of an individual's particular likelihood of response and a risk of cardiotoxicity. Collaboration between oncologists and cardiologists in the management of patients with cancer would optimize the chance for a "cure" while minimizing potential cardiovascular issues in the years to come (Albini et al. 2010; Hampton 2010).

6.2 Management

Diagnosis and management of treatment-related cardiotoxicity in cancer survivors are complex endeavors. One reason why the diagnosis is so difficult is because radiation-associated and chemotherapy-associated effects often emerge decades after exposure. Another difficulty of diagnosis is that as cancer survivors age, like their healthy counterparts, they accrue additional co-morbidities for cardiovascular disease. Thus, it can be difficult to definitively attribute late cardiovascular effects to cancer therapy versus other age-related comorbidities.

Ultimately, the best way to ameliorate late-onset effects is through increased awareness and vigilance. To that end, we discuss five common cardiovascular effects associated with cancer treatment, in order to guide clinicians when referring these patients for further cardiac screening. In addition, we will give an overview of their cardiac work-up and propose some recommendations for how physicians can help these patients manage and minimize cardiovascular risks and events.

6.2.1 Heart Failure

Heart failure is one of the most serious complications of anti-cancer therapy. It is the end stage of several types of cardiovascular disease that impairs either ventricular filling or ventricular ejection. Heart failure ensues when the compensatory mechanisms of the heart are overwhelmed, and cardiac output falls with resulting fluid overload. However, no single test is diagnostic for heart failure; therefore the diagnosis of heart failure is complex, and can be made only after detailed evaluation and assessment. The patient's history, physical examination, noninvasive testing and imaging, and serum biomarkers must all be integrated

to determine the diagnosis of heart failure, along with its etiology and severity (Hunt et al. 2009).

Heart failure symptoms include dyspnea, fatigue, and exercise intolerance. The nonspecific nature of these symptoms means that diagnoses other than heart failure also must be considered. For example, dyspnea may result from pulmonary disease or as an equivalent for angina in patients with occult coronary artery disease. In addition to heart failure, fatigue in cancer survivors may result from depression and/or medical deconditioning.

On physical examination, signs of volume overload include jugular venous distention, ascites, and peripheral edema. Symptoms of heart failure in conjunction with signs of edema on physical examination strengthen the likelihood of heart failure. However, peripheral edema can be caused by noncardiac diseases, e.g., liver failure and renal dysfunction, both of which may also be a result of anti-cancer therapy.

EKG can aid in establishing whether coronary disease or arrhythmias are likely causes of heart failure. Chest X-ray may be useful, if there is demonstration of cephalization of pulmonary vasculature, peribronchial cuffing, or edema. Echocardiography also should be considered as a diagnostic tool in patients with suspected heart failure, since echocardiography can potentially elucidate differentials such as dilated cardiomyopathy, diastolic dysfunction, coronary artery disease, valvular heart disease, and/or pericardial disease. Furthermore, pulse and tissue doppler imaging performed during echocardiography allows assessment of cardiac hemodynamics that may suggest low output states or elevations in atrial or ventricular chamber pressures.

In addition to traditional imaging methods, serum biomarkers can also be useful in helping diagnose heart failure in patients whose diagnosis is unclear. The serum biomarkers brain natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP) are most commonly used. BNP is a natriuretic hormone, produced predominantly by the heart, and released into the circulation after it is cleaved from the C-terminal of its pro-hormone pro-BNP. The N-terminal fragment (NT-proBNP) that also results from the cleavage of pro-BNP, is released into the blood circulation along with BNP. In heart failure patients, elevations of both BNP and NT-proBNP levels are seen (Palazzuoli et al. 2010). However, there are limitations to BNP or NT-proBNP measurements, since other diseases such as sepsis may also cause abnormal BNP levels. Furthermore, some heart failure patients may not exhibit any significant elevation in BNP or NT-proBNP. Therefore, BNP and NT-proBNP levels should be considered in context of the entire clinical picture, and levels in isolation are not diagnostic of heart failure.

Troponin is a sensitive and specific marker for cardiomyocyte injury; it is now routinely and widely used in the general population to assess myocardial damage from coronary artery disease. Recently, there has been significant interest in using troponin levels to assess myocardial damage from anti-cancer therapy in particular, to guide initiation of cardioprotective therapy, and also to prognosticate future cardiac events from anti-cancer therapy. Cardinale et al. 2000 and 2010 have published a significant body of work that elucidates the utility of biomarkers in patients who have received high-dose chemotherapy, anthracycline therapy, and now also trastuzumab therapy. Cardinale found that early release of troponin I after high-dose chemotherapy was correlated with increased risk of LV systolic dysfunction 9–10 months later. Furthermore, there is evidence that troponin I levels may also be useful in predicting late cardiotoxicity in patients receiving new targeted agents such as trastuzumab (Cardinale et al. 2010).

Since heart failure from anthracycline and radiation therapy is a progressive process that worsens with time, proper treatment is crucial. Thus, the goal of chronic heart failure management is symptom management, and slowing the progression of the disease, with the hope of decreasing mortality. In a patient with established heart failure from anti-cancer therapy, the medical management focuses on both life-style modification and pharmacological therapy as needed. Co-morbidities that result in additional stress to the heart should be tightly managed, i.e., thyroid dysfunction, smoking cessation, hypertension management, reduction of alcohol consumption, avoidance of recreational drug use, and maintenance of ideal body weight (Lejemtel et al. 2004). Salt and fluid restriction, along with daily weights is integral to minimizing fluid overload. Medical management of any co-occurring valvular heart disease, ischemic heart disease, cardiac arrhythmias, and renovascular disease that may worsen heart failure is also warranted.

The goals of pharmacologic management of heart failure are to improve symptoms of volume overload and improve cardiac performance. Diuretics, beta blockers, digoxin, ACE-inhibitors, and angiotensin receptor blockers are the mainstay of heart failure therapy and have been shown to prolong survival in the general population with heart failure (McCray et al. 2009). However, among cancer survivors who develop heart failure from anthracyclines or radiation therapy, it is currently unknown whether heart failure medications initiated at the time of onset of heart failure, will similarly improve long-term cardiac outcomes. Therefore, oncologists should be aware of the possible signs of heart failure or cardiac dysfunction in their patients, especially those who have received cardiotoxic anti-cancer therapy. Early referral to cardiology consultants for assessment and management may improve both the quality of life and survival for patients with heart failure.

6.2.2 Coronary Artery Disease

Severe obstructive coronary artery disease may result in acute myocardial infarction, unstable angina, or sudden death. It frequently may present with minimal or no prior symptoms, and can be rapidly fatal (Chen et al. 2011). Screening for coronary artery disease in high-risk populations is undertaken to detect subclinical disease prior to cardiac events, so that cardioprotective strategies can be implemented, and/or invasive interventions can be performed in those patients with severe obstructive disease involving the left main coronary artery. Importantly, the decision to screen asymptomatic individuals must be carefully considered after understanding the pretest probability of coronary artery disease in any specific population being screened. The probability of true coronary artery disease following a stress test is directly related to the pretest probability of cardiac risk and the results of the exercise test.

Abnormal resting ECG in asymptomatic individuals has been demonstrated to be correlated with an increased risk for cardiovascular disease as compared to those with normal ECG. However, utility of ECG screening is limited because one-half to one-third of individuals with normal coronary arteriogram have abnormal ECG, while 30 % of those with angiographically proven coronary artery disease have a normal resting ECG (Coronary Artery Surgery Study (CASS) 1983; Rose et al. 1978). Importantly, most coronary events occur in individuals who have ECG free of abnormalities.

Exercise ECG test is an important modality used to detect ischemia, as determined by ST segment depressions on ECG. However, in patients who have LBBB, and pre-existing ST changes >= 1 mm exercise testing with imaging should be considered (Klocke et al. 2003).

Stress testing with imaging can be performed with the use of echocardiography, nuclear imaging, or MRI. The choice of imaging modality to use depends on the availability, expertise at the different centers, cost, radiation exposure, and portability. In general, stress echocardiography with its portability, its wide availability and also its lack of radiation exposure, is frequently used. Computed tomography either conventional or electron beam computed tomography can measure coronary artery calcification (CAC). A high score may be indicative of heart disease in asymptomatic individuals (Haberl et al. 2001; Andersen et al. 2010). However, the additional radiation exposure to the patient that CT entails, and the lack of diagnostic cardiac data that CT provides in a known high-risk population, must be considered before ordering this test.

Angiography (or cardiac catheterization) is considered the gold standard for detecting CAD, but predictive validity is low since arteriography does not assess implications of dysfunction (e.g., detected lesions).

Coronary artery disease can be managed medically, surgically, or by some combination of both. Medical versus surgical/percutaneous management of patients with coronary artery disease is in part determined by whether patients are at low versus high risk for cardiac events. Stress testing can help risk-stratify patients. Low/intermediate risk cardiac patients are usually treated medically. Coronary angiography with percutaneous coronary intervention (PCI) or coronary artery bypass surgery is usually reserved for high-risk patients.

Medical management of CAD typically involves several simultaneous approaches: (1) ASA each day, (2) modification of cardiac risk factors, (3) reduction of other co-morbidities that increase myocardial demand, and (4) control of stable angina.

Management of cardiac risk factor is an important strategy in decreasing risk of CAD. As previously discussed, many long-term cancer survivors are at increased risk for coronary artery disease because of their anti-cancer therapy. Although cancer survivors' treatment history is an immutable cardiac risk factor, as are their age, gender, and family history of cardiac disease, the majority of cardiac risk factors can be reduced. In fact, in the general population, nine modifiable cardiac risk factors are associated with 90 % of the attributable risk of an initial myocardial infarction (Yusuf et al. 2004). Aggressive cardiac risk factor reduction including smoking cessation, lipid lowering, weight reduction, and blood pressure and glycemic control have been demonstrated to lead to improved patient outcomes. Therefore, prevention and amelioration of cardiac late effects in long-term cancer survivors, who are at risk of premature CAD, should focus on aggressive cardiac risk factor modification through diet, lifestyle modification, and medical therapy.

Another important tactic in ameliorating CAD in survivors of (childhood) cancer is to control comorbidities. Survivors who develop cardiovascular events frequently have multiple medical comorbidities such as hypertension (Aleman et al. 2007). Comorbidities that generally lead to increased myocardial demand (i.e., thyroid function, hypertension, or valvular heart disease) should be aggressively managed.

Finally, medical management of angina, if any, is generally accomplished with one or more types of anti-ischemic medications, including nitrates, beta blockers and calcium channel blockers.

6.2.3 Valve Disease

With the advent of echocardiography, valvular heart disease has become one of the more straightforward cardiovascular diagnoses. In patients who have developed cardiomyopathy and also for those that have received radiation therapy, valvular heart disease is a frequent occurrence. In patients

who have received cancer therapy, echocardiography is a Class I recommendation for screening (Cheitlin et al. 2003). Clinically, significant disease involves regurgitation or stenosis that is at least moderate in severity.

Valvular disease is known to be progressive in many patients. When the degree is severe, valve repair or replacement should be considered. Furthermore, any precipitating causes that may worsen valvular dysfunction should be corrected, if possible. The optimal timing and type of valve surgery to undertake are decisions that require integration of pathophysiology, the anatomy involved, patient preference for anti-coagulants, the patient's surgical risk, the surgeon's expertise, and valve type.

6.2.4 Conduction Block

While there is some degree of knowledge about the screening and management of heart failure and constrictive pericarditis, conduction block is a late cardiovascular effect of cancer treatment that is somewhat less well understood. Radiation fibrosis of the heart's conduction system results in electrical changes on the electrocardiogram that may be clinically silent or result in symptoms. Depending on the degree of heart block, the type, and the severity, a pacemaker may be warranted. Complete heart block may occur suddenly in long-term survivors who have received chest radiation and who develop syncope. Referral to cardiology for assessment is prudent when there is evidence of second-degree heart block on EKG, since advanced second-degree or third-degree heart block is a class I indication for a permanent pacemaker.

6.2.5 Constrictive Pericarditis

Constrictive pericarditis may be caused by radiation therapy (see above) and is an important cause of diastolic heart failure. The pericardium becomes fibrous and scarred by chronic inflammation, encasing the heart in an inflexible shell. As a result of pericardial constriction, diastolic filling of the atria and ventricle is impaired. While early diastolic filling is rapid or even normal, the pericardium constricts filling at mid-and end-diastole. Given the pericardium's rigidity, there is marked interdependence between the right and left ventricle, which can result in equalization of diastolic pressures between the left and right ventricles. Importantly, systolic function is usually preserved, until constrictive pericarditis becomes very severe. At that point, stroke volume may start to fall as the heart no longer can adequately fill.

Symptomatically, the patient may insidiously develop fatigue, dyspnea, and volume overload. Physical examination may reveal pedal edema, ascites, pleural effusions, and hepatomegaly. Since these symptoms are nonspecific, unless the suspicion for constrictive pericarditis is high, they may be misattributed to cirrhosis or liver disease (Francis et al. 2004).

Imaging studies are helpful in establishing the diagnosis of constrictive pericarditis. Echocardiography is a class I recommendation for screening in patients suspected of constriction (Cheitlin et al. 2003). Both calcification of the pericardium and pericardial thickening can frequently be seen on echocardiography. However, the gold standard for pericardial imaging is cardiac magnetic resonance (MR) imaging. Classic features on MR include increased pericardial thickening and dilation of the inferior vena cava, although the data suggest that up to 20 % of patients with constrictive pericarditis may have normal pericardial thickness (Talreja et al. 2003).

Direct measurement of intracardiac pressures on cardiac catheterization frequently is needed to make a more definitive diagnosis of constrictive pericarditis. During assessment of cardiac hemodynamics, the dip and plateau or "square root" sign in the RV and LV diastolic pressure tracings are classically seen in patients with constriction. In patients with suspected constrictive pericarditis, it is important to exclude restrictive cardiomyopathy and end-stage liver disease in the differential. In certain situations, biopsy of the endomyocardium and the pericardium is used to distinguish the constriction versus restrictive cardiomyopathy. Furthermore, noninvasive imaging, i.e., echocardiography with tissue doppler imaging, may provide some evidence of constrictive versus restrictive physiology. To complicate matters, however, most patients who have received chest radiation may develop both constrictive and restrictive physiology.

With regard to treatment, it is important to accurately distinguish constrictive pericarditis and restrictive cardiomyopathy, since the former is amenable to surgery. Constriction can be treated by surgical stripping of the pericardium, although there are risks.

Pericardiectomy is associated with significant operative mortality; current mortality rates are about 6 % in patients operated on between 1977 and 2000 at the Mayo and Cleveland clinic (Chowdhury et al. 2006; Tirilomis et al. 1994). In addition to increased mortality, patients who undergo pericardiectomy following chest radiation may also face decreased long-term survival. Seven-year survival after pericardiectomy for radiation-induced constrictive pericarditis is especially poor, reaching 27 %, as compared with other etiologies (Bertog et al. 2004). Decreased survival in this population is secondary to many other late effects of chest radiation, including restrictive cardiomyopathy, interstitial pulmonary disease, sepsis, and/or secondary neoplasms that all reduce survival (Ling et al. 1999).

7 Historic Perspective and Summary

7.1 Radiation-Associated Cardiovascular Toxicity

In the past, the heart was considered to be a relatively radioresistant organ. Since the 1960s there is, however, growing evidence of increased risks of cardiovascular diseases following exposure of (parts of) the heart to therapeutic radiation doses (Cohn et al. 1967; Brosius et al. 1981; Hancock et al. 1993a; Schultz-Hector and Trott 2007), largely in patients with Hodgkin lymphoma and left-sided breast cancer. In particular, the development of coronary pathology in young individuals following radiation who lack risk factors for atherosclerosis has raised awareness of a possible cause-and-effect relationship.

During the last decades there is also emerging evidence, especially from the Japanese LSS cohort, that radiation exposure of the heart to low doses can lead to increased risks of cardiovascular morbidity and mortality. For example, an increased risk of cardiovascular disease risk has been described in the Japanese atomic bomb survivors, who received single whole-body exposure to a range of doses less than 5 Gy (Wong et al. 1993; Shimizu et al. 1999; Preston et al. 2003; Little 2009; Little et al. 2010).

Radiation-associated heart disease includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities (Adams et al. 2003; Aleman et al. 2007; Mulrooney et al. 2009). Radiation-associated heart diseases, except for pericarditis, usually present 10–15 years after exposure, although nonsymptomatic abnormalities may develop much earlier. The long delay before expression of serious damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

The risk for cardiovascular diseases might also be increased through indirect effects of radiotherapy; irradiation of the left kidney during paraaortic and spleen radiotherapy, for example, might lead to hypertension (Verheij et al. 1994).

Radiation causes both increased mortality (mainly fatal myocardial infarction) and increased morbidity from cardiovascular disease. Data on morbidity are more difficult to acquire, and therefore still more scarce than data on mortality.

7.2 Chemotherapy-Induced Cardiovascular Toxicity

Cardiotoxicity associated with anticancer drugs, including not only classical cytotoxic drugs but also newer targeted therapies, is becoming one of the most important complications of cancer treatment (Albini et al. 2010; Sereno et al. 2008). The progress in the treatment of cancer leads to large numbers of long-term survivors who are at risk for long-term cardiotoxicity.

Cardiomyopathy from anthracyclines has been recognized for many years (Lipshultz et al. 1991, 1999; Singal and Iliskovic 1998). However, cardiotoxicity from anticancer drugs can manifest itself as left ventricular dysfunction and/or heart failure, myocardial ischemia, hypertension, and interference with the cardiac conduction system causing bradycardia and heart block or QT prolongation and ventricular arrhythmias (Yeh and Bickford 2009).

The occurrence of cardiotoxicity from chemotherapeutic agents depends on a number of factors related to the oncological treatment: the type of drug, the dose administered during each cycle of treatment, the cumulative dose of the drug, the schedule of administration, the route of administration, the combination with other cardiotoxic drugs, and the combination with radiotherapy (Bovelli et al. 2010). It is also dependent on patient-related factors such as the age of the patient, the presence of cardiovascular risk factors, previous cardiovascular disease, and prior irradiation including the heart.

Heart failure has been associated with several different classes of agents, including anthracyclines, alkylating agents, antimetabolites, antimicrotubule agents, monoclonal antibodies, proteasome inhibitors, and small molecule tyrosine kinase inhibitors. Myocardial ischemia and infarction is seen after treatment with antimetabolites, antimicrotubule agents, monoclonal antibodies, and small molecule tyrosine kinase inhibitors.

Hypertension is common in the general population,and therefore occurs frequently in cancer patients. New anticancer treatments targeting angiogenesis are associated with an increased risk of hypertension, which may lead to serious complications such as hypertensive encephalopathy and cerebral hemorrhage.

Bradycardia and heart block have been associated with angiogenesis inhibitors and with antimicrotubule agents. QT prolongation has been associated with histone deacetylase inhibitors and small molecule tyrosine kinase inhibitors. Moreover, QT prolongation may also be caused by concomitant medication often used in cancer patients, such as antiemetics and certain antibiotics, and the risk may increase due to electrolyte disturbances caused by vomiting and diarrhea. QT prolongation is not symptomatic in itself. However, it is an abnormality of the electrical activity of the heart which may increase the risk for ventricular arrhythmias.

Vascular toxicity caused by anticancer drugs is primarily a local phenomenon at or near the site of infusion. However,

antineoplastic therapies may also damage the intima of the blood vessels in general, thereby activating the coagulation cascade and predisposing to thrombosis (Albini et al. 2010). In this way, peripheral circulation may be impaired.

Apart from the direct cardiovascular damage caused by cancer treatment, cardiovascular disease in cancer survivors may also result from accelerated atherosclerosis due to treatment-related cardiovascular risk factors (de Haas et al. 2010). These risk factors cluster into the so-called metabolic syndrome, whose core components are dyslipidemia, hypertension, central obesity, and insulin resistance (Alberti et al. 2006, 2009; Einhorn et al. 2003; Grundy et al. 2005). The metabolic syndrome is associated with certain cancers, e.g., colon and breast cancer, and hence patients with such malignancies have a higher risk of these risk factors even at the time of diagnosis. In survivors of adult cancer, the metabolic syndrome has been assessed in testicular cancer and after stem-cell transplantation for hematological diseases (Annaloro et al. 2008; Haugnes et al. 2007; Majhail et al. 2009; Nuver et al. 2005; Wethal et al. 2007). The reported prevalence varied between 26 and 55 %, which is significantly higher than expected in the healthy reference populations. Both local treatments (surgery and radiotherapy) and systemic treatments (chemotherapy, biologicals, and hormone therapy) can cause changes in endocrine and metabolic functions which may contribute to the development of the metabolic syndrome (de Haas et al. 2010).

7.3 Other Risk Factors for Treatment-Associated Cardiac Toxicity

General risk factors for cardiovascular diseases, such as hypertension, diabetes, hypercholesterolemia, overweight, and smoking (Miura et al. 2001; Chobanian et al. 2003; Haider et al. 2003; Kannel 1996; Bakx et al. 2001), probably also contribute to the risk for cardiovascular diseases in patients treated for malignancies (Glanzmann et al. 1994; Bowers et al. 2005; Hooning et al. 2007). The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity, like congestive heart failure, remains to be elucidated. In this regard, only a few studies in humans provide evidence that genetic susceptibility may play an important role in the risk of anthracycline-associated cardiotoxicity (Wojnowski et al. 2005; Deng and Wojnowski 2007; Blanco et al. 2008).

8 Future Directions and Research

8.1 Future Directions and Research Regarding Radiotherapy

Cardiotoxicity from radiotherapy is likely to remain an important issue. Although radiation techniques have improved over time leading to less toxicity, in general the number of people treated with radiation gradually grows, in several diseases higher radiation doses are used and radiation is combined frequently with (cardiotoxic) chemotherapy. Modern radiation techniques such as intensity-modulated radiotherapy and inspiratory breathholding techniques during delivery of radiation therapy that are currently not used for many patients because of costs and lack of technical capacity to do this.

Research must focus on the following points:

- Quantifying dose- and volume effects of radiation-associated cardiotoxicity for specific cardiac sub structures.
- Evaluate possible interaction of radiation and chemotherapy with respect to cardiotoxicity.
- Evaluate whether cardiac risk may be modified by other factors such as preexisting cardiovascular disease or diabetes, lifestyle factors including smoking.
- Investigation possibilities to prevent radiation toxicity through interventions.
- Further improvement of radiation techniques minimizing radiation exposure of the heart and its particular ‘critical’ substructures.

8.2 Future Directions and Research Regarding Chemotherapy

Cardiotoxicity from systemic anti-cancer treatment is likely to become an increasing problem for a number of reasons. The number of long-term survivors increases, and hence the number of patients at risk for this complication will increase. Patients are treated with more and more systemic treatment, because they survive longer and because new drugs are being developed. These new drugs have new mechanisms of action, and hence new risks for cardiac complications.

The challenge will be to develop drugs and combinations of drugs that are more and more effective with regard to tumor response, without at the same time increasing the risk of cardiovascular complications. Research must focus on the following points:

- Elucidating the mechanisms of action on the cardiac structures of existing and new anti-cancer drugs, and if possible finding different mechanisms than the ones responsible for the anti-cancer effects, thus enabling selective blocking of cardiotoxicity without decreasing the desired effects on the tumor.
- Investigating new technologies for delivering systemic anti-cancer therapy, e.g., in nanoparticles, which may decrease cardiotoxicity of the drugs.
- Analyzing the dose and schedule dependence of the drugs, with the aim of finding the least cardiotoxic schedule with full anti-tumor effect.
- Development of new and effective drugs and classes of drugs with less or no cardiotoxicity.

8.3 Future Directions and Research Regarding Treatment and Prevention

Preventative strategies for cardiovascular health will focus on a better understanding of the temporal role of risk factors in onset of cardiovascular disease. Furthermore, there will be greater importance placed on the treatment of subclinical disease. Although novel technologies may be applied in the detection of disease, the focus should be on management rather than on detection alone. Testing that further exposes a patient to radiation should be carefully considered, and alternatives sought if possible. Given the rising cost of healthcare in all nations, the cost of tests will be greater scrutinized. Therefore, studies assessing the most cost-effective strategies to employ will be of greater import. Work and research are already underway in many groups to use electronic medical records and the Internet to enhance the interaction between patient and their healthcare providers.

Further research is also necessary to determine whether high-risk patients who undergone anti-cancer therapy should be started immediately on cardioprotective agents such as beta blockers and ACE inhibitors. Collaboration between radiation oncologists and cardiologists will allow for development of early intervention for cardiotoxicity that may arise from life-saving anti-cancer therapy.

9 Landmark Studies

Classic reports in this area include the following:

i. Carmel and Kaplan (1976): Demonstrate the strong volume dependence of pericardial injury in patients irradiated for Hodgkin lymphoma.
ii. Cuzick: Convincingly demonstrates that post-mastectomy radiation for left-sided breast cancer increases the rate of subsequent mortality (Cuzick et al. 1988), due primarily to an excess risk of cardiac events (Cuzick et al. 1994).
iii. Fajardo and colleagues: Describe the radiotherapy-induced pathologic findings (Cohn et al. 1967; Stewart et al. 1995; Fajardo et al. 2001).
iv. Sarah Darby and colleagues: Conducts a series of population studies further documenting the risk of RT-associated heart disease in patients irradiated for breast cancer (Darby et al. 2003, 2005).
v. Fiona Stewart and colleagues: Further determines the molecular mechanisms that underly RT-associated heart disease (Stewart et al. 2006).
vi. Hancock and others note increased rates of IHD in patients irradiated for Hodgkin lymphoma (Hancock et al. 1993a, b; Hancock and Hoppe 1996).
vii. van Luijk: Conducts elegant studies in animals suggesting and interaction between cardiac and pulmonary injury from radiotherapy (van Luijk et al. 2007).

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