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RADIATION DOSE–VOLUME EFFECTS IN THE HEART

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The literature is reviewed to identify the main clinical and dose–volume predictors for acute and late radiation-induced heart disease. A clear quantitative dose and/or volume dependence for most cardiac toxicity has not yet been shown, primarily because of the scarcity of the data. Several clinical factors, such as age, comorbidities and doxorubicin use, appear to increase the risk of injury. The existing dose-volume data is presented, as well as suggestions for future investigations to better define radiation-induced cardiac injury. © 2010 Elsevier Inc.

Radiation heart disease, Dose–volume predictors, NTCP, Breast cancer, Lymphoma, Esophagus cancer.

1. CLINICAL SIGINIFICANCE

Radiation-associated cardiac disease is seen in patients treated for lymphoma, breast cancer, seminoma, peptic ulcer disease, and lung cancer, as well as in atomic bomb survivors. Acute injury, often manifest as pericarditis, is usually transient but can be chronic. Late injury, often manifest as congestive heart failure (CHF), ischemia, coronary artery disease (CAD), or myocardial infarction (MI) several months to years post-radiation treatment (RT), is more clinically significant. In some disease settings, RT-induced heart disease has offset the improvements in cancer-specific survival provided by adjuvant RT (1). For example, the leading cause of noncancer mortality among long-term RT-treated survivors of Hodgkin's lymphoma is cardiovascular death (2).

2. ENDPOINTS

Both clinical and subclinical endpoints describe the spectrum of RT-induced heart disease (Table 1). The latency of RT-associated cardiac effects ranges from months (pericarditis) to decades (CAD, MI). The most clinically significant endpoints analyzed are morbidity (*e.g.,* CHF and ischemic events such as MI) and cardiac deaths. Since these events occur at a relatively high rate in patients who have not undergone irradiation, the best data are derived from randomised clinical trials, or population-based studies with or without RT. Overall, the relative risks (RR) of these clinically significant cardiac events are within a range of 1.2 to 3.5 after RT. Subclinical abnormalities are more common, and are noted in up to 50% of patients, depending on the sensitivity of the endpoint considered and the associated comorbidities.

Pericardial disease

Acute pericarditis during RT is uncommon and usually associated with pericardiac mediastinal tumours. Delayed pericardial disease can occur from months to years after RT; it includes pericarditis and chronic pericardial effusion (usually asymptomatic). Although most cases resolve spontaneously, approximately 20% develop into chronic and/or constrictive pericarditis that may necessitate pericardectomy (3).

Ischemic heart disease

Evidence that ischemic heart disease correlates with RT comes from the Early Breast Cancer Trialists' Collaborative Group meta-analyses of randomized clinical trials. The most recent update showed an increased RR of mortality from heart disease among women treated with RT vs. no RT ([RR] = 1.27) (1).

Long-term cardiac outcomes from randomized clinical trials of postmastectomy RT (4, 5) usually reveal an

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Table 1. Endpoints related to radiation-induced heart disease

	Regional endpoints	Global endpoints
Subclinical	Localized imaging abnormality (*e.g.,* perfusion defect or regional wall motion abnormality) Myocardial fibrosis	Global imaging abnormality (*e.g.,* diffuse hypocontractility) Asymptomatic decline in ejection fraction
Clinical	Coronary artery disease Myocardial infarction Valvular disease	Congestive heart failure Pericarditis/pericardial effusion Arrhythmia Autonomic dysfunction (monotonous heart beat responding to changes in hemodynamic requirements)

increased cardiac mortality risk (RR = ∼2.5) associated with left-sided and internal mammary nodal (IMN) RT. Retrospective population-based investigations have compared mortality endpoints by laterality of RT vs. surgical controls (6–8). Some investigations have shown an increased risk of cardiac mortality (hazard ratio [HR] = ∼ 1.5) for left-sided vs. right-sided cancers treated with RT in the 1970s, but not with more modern RT techniques (7, 9, 12).

For cardiac morbidity endpoints there is an increase in CAD and/or non-fatal MI with left-sided RT compared with either right-sided RT or no RT (6, 9–13). In two prospective studies and one retrospective study subclinical endpoints of perfusion defects have been assessed, but their clinical significance is still uncertain (11, 14, 15). At Stanford, children and adolescents with Hodgkin's lymphoma (HL) who underwent mediastinal RT had an increased RR for death from heart disease (RR = 28–37) (16). In the extended analysis including 2,232 patients of all age groups, the RR for death from acute MI was 3.2 (17). The elevated risk, already significant in the first 5 years, remained elevated throughout the follow-up period (>20 years); the average interval to MI was 10.3 years. In a recent study with 7,033 patients, the RR for lethal MI was 2.5 (18). In another analysis, mediastinal RT for HL had a greater likelihood of causing right coronary or left main or left anterior descending coronary artery lesions compared with circumflex lesions, possibly because of the location of the former (19). These studies generally included patients treated with doses ≥30 Gy. In the Stanford data, CAD risk was much reduced at doses ≤30 Gy.

Congestive heart failure

Two retrospective studies evaluating CHF among irradiated breast cancer patients yielded conflicting results (10, 12). In the Stanford data on 2,232 HL patients, the RR of death from cardiac causes other than MI decreased with use of subcarinal blocking from 5.3 to 1.4 (17). Adams *et al.* reported findings suggesting a greater impact on diastolic than systolic dysfunction in their investigation of 48 long-term survivors of childhood HL treated with mantle irradiation (median, 40 Gy) (20).

Valvular disease

For breast cancer patients, data are conflicting regarding the association of RT with valvular dysfunction. In a large study in the Netherlands the risk of valvular dysfunction was higher in the group receiving IMN RT vs. the group with no RT (HR = 3.17) (12), but this was not demonstrated in a smaller study (10).

In HL patients, valvular abnormalities include both insufficiency and stenosis, the former being more common and less clinically relevant. Incidence of left-sided valvular regurgitation ranges from 16% to 40% (vs. 2% in controls) (21, 22). Data from Stanford on 294 asymptomatic HL survivors treated with a mantle technique at a mean dose of 43 Gy showed a 34-fold increased risk of aortic regurgitation (absolute incidence, 26.1%) (23).

3. CHALLENGES IN DEFINING VOLUMES

Delineation of the clinically relevant subregions of the heart is challenging because their structural definition through the current devices used in treatment planning (*e.g.,* computed tomography [CT]) is imprecise. No imaging modality clearly shows these structures. The heart border may be difficult to differentiate from liver and diaphragm, but the segmenting of the superior border with the large vessels can be more challenging. The heart moves with the respiratory and cardiac cycles: the degree of motion, mainly in the superior–inferior direction, is modest with free breathing (24). Furthermore, the anatomy of the great vessels as they intersect the heart is complex. Newer imaging tools, such as magnetic resonance imaging, may be able to better identify cardiac subregions, but their application to RT planning is still limited.

Cardiac structures can be defined anatomically and/or based on functionality; this can be problematic because of the anatomic/functional complexities, the interactions of the various structures such as the ventricles, valves, vasculature and their overlying anatomy. Uncertainties remain regarding which region of the heart is functionally most important for RT-induced toxicities.

Three main clinical endpoints have been considered in the study of specific dose–volume response relationships: mortality from ischemic heart disease, pericarditis, and decreased myocardial perfusion. For these analyses, the volumes considered were either the entire heart (25), pericardium (26, 27), or the left ventricle alone (28) (Tables 2–4). Because coronary/ischemic events are a major concern, several investigators have calculated doses to potentially relevant

Table 2. 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* 1976 (3)	Hodgkin's 377 Patients 1964–1972	Pericardium		$D_{pericardium} > 30$ Gy 50% pericarditis, 36% requiring treatment	
Cosset *et al.* 1991 (65)	Hodgkin's 499 Patients 1971–1984		35–43 Gy/ 2.5–3.3 Gy/fraction pre-3D dose data	$D_{Mediastinum} \geq 41$ Gy d/ fraction ≥ 3 Gy (marginal significance)	
Burman *et al.* 1991 (66)	Historical data				LKB† *TD50* = 48 Gy $m = 0.10$ $n = 0.35$
Martel *et al.* 1998 (26)	Esophagus 57 Patients 1985–1991	Pericardium	37.5–49 Gy/ 1.5–3.5 Gy / fraction 3D data	$D_{mean} > 27.1$ Gy‡ $D_{max} > 47$ Gy‡ 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 (27)	Esophagus 101 Patients 2000–2003	Pericardium	45–50.4 Gy 1.8–2.0 Gy/fraction 3D data	D_{mean}pericardium > 26.1 Gy $V_{30} < 46\%$	

Abbreviations: CI = confidence interval; LKB = Lyman-Kutcher-Burman (model); OAR = organs at risk; NTCP = normal tissue complication probabilities.

* 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%).

† In the LKB model (47, 66) 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).

‡ Corrected to 2 Gy per fraction, $\alpha/\beta = 2.5$ Gy.

substructures such as coronary arteries or the left ventricle (29–31).

4. REVIEW OF DOSE/VOLUME FACTORS

The risk of cardiac events is probably related to both dose and irradiated volume. For example, as breast cancer treatment techniques have evolved to reduce cardiac exposure, there has been a steady decline in the RR for RT-associated events (32). In the Stanford HL series, the RR of death from cardiac causes (other than MI) was decreased with use of subcarinal blocking from 5.3 to 1.4 (17). In the large study in the Netherlands, the risk of valvular dysfunction was higher in the group receiving IMN RT vs. the group with no RT (HR = 3.17) (12). Furthermore, whole pericardial irradiation can lead to a high rate of pericarditis that is reduced with shielding of the left ventricular and subcarinal areas (3).

Dose is similarly important. In the Stanford series of children and adolescents with Hodgkin's disease (HD), all of the excess deaths from heart disease were in the patients receiving 42 to 45 Gy (16). Boivin *et al.* noted that the anteriorly placed coronary arteries were more often affected by RT (compared with the circumflex artery) (19). In HL, the frequency of both aortic and mitral stenosis and regurgitation is increased, with a threshold RT dose of ~30 Gy (20). In this report, 42.6% of patients had at least one significant valve abnormality. Additional dose/volume data are reviewed later in the text.

5. FACTORS AFFECTING RISK

Evidence suggests that the risk of RT-associated heart disease may be affected by baseline patient cardiac risk factors and cardiotoxic chemotherapy. All of these investigations are retrospective in design.

Patient risk factors

Large population studies have identified factors associated with cardiac disease. Well-validated models such as the Framingham and Reynolds risk models can estimate the risk of future cardiac events based on the presence, number, and severity of baseline cardiac risk factors (33–35) such as age, gender, diabetes mellitus (and hemoglobin A_{1c}), smoking, hypertension, total cholesterol, low- and high-density lipoprotein cholesterols, high-sensitivity C-reactive protein, and parental history of early MI at age <60 years.

In patients with breast cancer, a multi-institutional study of ≥10-year survivors noted that smoking and RT synergistically increased the rate of fatal MI (HR = 3.04 vs. no smoking/no RT) (12). Similarly, synergy was noted between hypertension and left-sided RT for causing CAD

Table 3. Cardiac mortality from ischemic heart disease/myocardial infarction: Dose–volume predictors and NTCP parameters

Authors, Year, Reference	Diagnosis, No. of patients, Years of treatment	OAR	Dose data	Predictive parameters	NTCP parameters
Hancock *et al*. 1993 (17)	Hodgkin's 2232 patients 1960–1990	Heart	Dose up to 44 Gy Pre-3D dose data	$D_{mediastinum} > 30$ Gy	
Gagliardi *et al*. 1996 (25)	Breast 809 patients 1964–1976	Heart*	45–50 Gy† 1.8–2.5 Gy/fraction treatments reconstructed in 3D on average patients		RS‡ (*CI 68%*) *D50* = 52.3 Gy (49;57) γ = 1.28 (1.04;1.64) *s* = 1 (0.63; at limit)
Eriksson *et al*. 2000§ (51)	Hodgkin's 157 patients 1972–1985	Heart	~40 Gy‖ 2 Gy/fraction Individual treatments reconstructed in 3D on phantom	$D_{35} > 38$ Gy	RS: Hodgkin's *D50* = 70.3 Gy γ = 0.96 *s* = 1 RS: Hodgkin's + breast *D50* = 63 Gy γ = 0.94 *s* = 1
Carr *et al*. 2005 (52)	Peptic ulcer, 1,859 patients, 1936–1965	Heart (Alderson Phantom)	1.5 Gy /fraction 250-kVp X-rays Treatment simulated on phantom	D_{mean} to 5% >12 Gy heart volume within the beam $D_{mean} > 2.5$ Gy whole heart volume	
Paszat *et al* 2007 (6)	Breast, 619 patients, 1982–1988	Heart	40–50 Gy 2–2.67 Gy/fraction to breast¶ Pre-3D dose data	RT to Internal Mammary Chain	

Abbreviations: CI = confidence interval; NTCP = normal tissue complication probabilities; OAR = organs at risk; RS = relative seriality (model).

* Heart was contoured from infundibulum of right ventricle, right atrium and right atrium auricle, and excluded the pulmonary trunk, ascending aorta, and superior vena cava down to the most caudal slices. Analysis was also performed on the myocardium, providing similar results.

† DVH corrected to 2 Gy per fraction, $\alpha/\beta = 3$ Gy.

‡ In the RS model, parameter meanings are, respectively: *D50* is the dose to the whole organ that will lead to complications in 50% of the population; γ is the normalized dose–response gradient; *s* reflects the degree to which the organ architecture is considered to be serial (*s* = 1) or parallel (*s* = 0) (49).

§ In this study, NTCP analysis was performed also jointly with breast cancer data. It should be emphasized that the use of the steeper dose–volume response curve, *i.e.,* only breast (25), represents a more conservative and thus safer approach.

‖ Note that the prescribed dose here ranged between 7 and 45 Gy but that 43% of patients were treated to 40 Gy and 37% to 42 Gy. Dose–volume histograms were corrected to 2 Gy/fraction, $\alpha/\beta = 3$ Gy.

¶ Treatment also involved an anterior boost of 5–20 Gy in 2–3 Gy to breast; photon, or electron anterior Internal Mammary Chain field with total dose of 40–55 Gy in 1.8- to 3.7-Gy fractions.

(HR = 11.4 vs. right-sided RT without hypertension) (10). The impact of age is unclear, but some studies implicate age >60 years (8), vs. age <50 or 60 years (36), to be associated with MI post-RT.

Adult HL survivors with adverse cardiac risk factors (older age, obesity, hypertension, family history of cardiac disease, abnormal lipoprotein levels, and smoking) have an increased risk for cardiac morbidity (37).

Treatment risk factors

Anthracycline-containing chemotherapy regimens for treatment of breast cancer and Hodgkin's lymphoma are used routinely. Without RT, anthracyclines are known to have a cumulative dose-dependent risk of dilated cardiomyopathy and CHF, with a 1% to 5% risk with doses <550 mg/m^2 for doxorubicin and 900 mg/m^2 for epirubicin, and a sharp increase in risk thereafter (38, 39). In fact, lower doses appear to be associated with cardiac injury in children. Congestive heart failure may be wholly or partially reversible with medications such as angiotensin-converting enzyme inhibitors or β-blockers (40). The long-term risk of CHF, especially in patients also treated with paclitaxel and among elderly women, may be higher (41, 42).

Few prospective studies have addressed potential synergistic effects of RT and cardiotoxic chemotherapy among breast cancer patients. A single institution randomized trial designed to evaluate cardiotoxicity with 10 vs. five cycles of doxorubicin (A) (45 mg/m^2) and cyclophosphamide (C) (500 mg/m^2) chemotherapy reported results from a retrospective subgroup analysis among patients treated with RT (43). With a 6-year median follow-up, a significant increase in cardiac events was found among patients receiving 10 cycles of chemotherapy and RT

Table 4. Cardiac perfusion defects: Dose–volume predictors and NTCP parameteters

Authors, Year, Reference	Diagnosis, No. of patients, Years of treatment	OAR	Fractionation schedule, Dose data	Predictive parameters	NTCP parameters
Das *et al.* 2005 (28)	Breast 73 Patients, 1998 (started)	Left ventricle contoured on SPECT	45–60 Gy/ 1.8–2.0 Gy/fr Individual 3D data	Left ventricular volume V_{23}, V_{33}	RS (95% CI) *D50* = 12 Gy (8;24) γ = 0.6 (0.4;4.6) s = 1 (0.6;1) LKB* (95% CI): TD50 = 29 Gy (18;44) σ (dose var) = 12 Gy (8;35) a = 6.3 (2.5;9.8)

Abbreviations: 3D = three-dimensional; CI = confidence interval; LKB = Lyman-Kutcher-Burman (model); NTCP = normal tissue complication probabilities; OAR = organs at risk; RS = relative seriality (model).

* Conventionally the parameters m and n are used in the LKB model. In this case $\sigma = m$ x TD50 and $a = 1/n$.

as compared with estimated baseline cardiovascular risk. In three doxorubicin-based trials (mean dose, 294 mg/m^2), the rate of CHF was four in 116 vs. two in 521 in patients with vs. without left-sided RT, respectively ($p = 0.012$). With median follow-up of only 1.5 years, no increased frequency of cardiac events has been identified with the use of trastuzumab with doxorubicin and RT vs. no RT (44).

A report on 1,474 HL survivors ≤41 years of age at the time of treatment and followed for a median of 18.7 years provided data of the combined effects of anthracyclines and RT (45). The risks of MI and CHF were increased with standardized incidence ratios of 3.6 and 4.9 respectively, resulting in 35.7 excess cases of MI and 25.6 of CHF per 10,000 patient/year. Mediastinal RT increased the risks of MI, angina pectoris, CHF and valvular disorders (2- to 7-fold), anthracyclines significantly added to the elevated risks of CHF and valvular disorders from mediastinal RT, with HRs of 2.81 and 2.10, respectively. The 25-year cumulative incidence of CHF and combined RT and anthracyclines was 7.9%.

6. MATHEMATICAL/BIOLOGICAL MODELS

Tables 2 to 4 summarize dose–volume constraints and normal tissue complication probability (NTCP) parameter values for pericarditis, cardiac mortality, and perfusion defects, respectively.

Pericarditis/pericardial effusion

Several studies conducted over a long period of time, including pre–three-dimensional (3D) and modern 3D data, note correlation between dose–volume parameters and the pericarditis risk (Table 2). Stewart and Fajardo (46) compiled data from several institutions: in patients with HL in whom the RT field was estimated to include ≥50% of the external heart contour, the overall pericarditis rate was 6%. There appeared to be a steep dose response, with an incidence ≤5% for low nominal standard doses (NSD; ≤ 1,300 rets computed using the NSD formalism), vs. a 5% to 10% rate for ~1,400 to 1,600 rets and a rate of ≥30% for ≥1,600 rets. A similar steep dose response was seen in patients with breast cancer in whom the irradiated volumes were smaller, with a 0%, ~4%, and ≥20% incidence of pericarditis for <1,800, ~1,900, and >2,000 rets, respectively (46). In Carmel and Kaplan's classic report, in HL, the high rate of pericarditis seen with whole pericardial irradiation was reduced to 7% with left ventricle (LV) shielding and to 2.5% with more extended shielding after 30 Gy (3).

Two studies on esophageal cancer considered 3D-derived data (26, 27). Martel *et al.* (26) implicated fraction size as a predictor for pericarditis (*e.g.,* no cases occurring in patients receiving <3.5 Gy/fraction). The mean and maximum doses of 27.1 and 47.0 Gy (corrected for fractionation with α/β = 2.5 Gy) were predictors of pericarditis ($p = 0.014$) (Table 2). Parameter values were fit to the Lyman-Kutcher-Burman (LKB) model (47). Wei *et al.* reported that a variety of DVH-based parameters (*e.g.,* V_3 to V_{50} and mean dose) predicted for pericardial effusions. The dosimetric parameters were highly correlated with each other, making comparisons of their predictive abilities difficult. Nevertheless, V_{30} < 46% was found to be a discriminator: the risk of effusion was 13% with a $V_{30} < 46$ Gy (or mean pericardial dose < 26 Gy) vs. 73% in patients with a $V_{30} > 46$ Gy (or mean dose >26 Gy) (27) (Table 2).

Long-term cardiac mortality

Data for this endpoint are derived from retrospective studies of patients treated with outdated techniques and target definitions. The dose–volume constraints and NTCP parameters reported are therefore affected by the intrinsic inaccuracies of the dosimetric data. Some results are reported in Table 3.

Patients with HL have an increased rate of cardiac mortality with whole heart doses >30 Gy, in agreement with results from pathological studies (17).

A few studies, based on model estimates of 3D dose/volumes, suggest that dose and, to a lesser degree the irradiated volume, are important parameters. A dose–response curve for cardiac mortality has been derived (25) based on the data from two breast cancer randomized trials of surgery with or without RT, which showed an increased cardiac mortality in the RT group (5, 48). The data were fit to an NTCP model (49) (Table 3). The value of $s = 1$ (s being the parameter related to tissue architecture) suggests a limited volume

dependence. A joint analysis of the breast cancer and Hodgkin's material (50, 51) yielded higher *D50* (*i.e.*, dose giving 50% of complication probability) and a lower γ (steepness) values than in the breast analysis (Fig. 1); note that different parts of heart are irradiated in the two situations.

Carr *et al*. examined the long-term outcomes of patients treated for peptic ulcer disease between 1937 and 1965 using (typically) orthovoltage RT, with the field including a portion of the cardiac apex (estimated 5% of heart volume) but only a small part of the coronary vessels (52). The RR of coronary artery disease was increased in patients in whom the (in-field) cardiac apex dose exceeded ~12 Gy, corresponding to an estimated mean heart dose >2.6 Gy. Similarly, in 4,414 breast cancer survivors with a minimum of 10 years of follow-up treated between 1970 and 1986, the risk of cardiovascular disease was found to increase with mean cardiac doses (12). The maximum heart distance (MHD), that is, the maximum distance from the posterior edge of the tangent field to the heart contour, has been proposed as a surrogate for the irradiated heart volume in the high-dose region in patients treated with tangential fields (53). However, in 1,601 breast patients with 0 to 24 years (median, 16 years) of follow-up, there was no clear association between the MHD and cardiovascular disease risk; the potential role of low heart doses was discussed (13).

Cardiac perfusion defects

Extensive analysis of perfusion defects induced by radiotherapy in the left ventricle have been prospectively carried out in a group of 73 breast cancer patients (Table 4). Subclinical injury, inferred from abnormalities on regional myocardial perfusion imaging tests, occurred in a volume-dependent manner: an incidence of <20% was found for tangential fields including <5% of the LV vs. >50% with >5% LV volume (54). Two NTCP models (LKB and relative seriality[RS]) were fitted to the data (28). A serial behavior of the LV is suggested by the fit with the RS model; however, the D50 values obtained from the two fits were mutually inconsistent. The clinical siginificance of these perfusion defects has not been clearly established (54).

7. SPECIAL SITUATIONS

Several aspects, both general and heart specific, have to be considered when applying NTCP models and dose–volume constraints to clinical treatment planning.

First, there are anatomical and functional considerations in defining the organ or parts of the organ at risk, e.g., heart vs. pericardium vs. coronary vessels. For example, applying pericarditis NTCP parameters obtained from the pericardium dose distribution to the whole heart is more acceptable in a calculation and/or comparison exercise than in clinical situations. The recent study by Wei *et al*. suggests that clinical data on pericardial effusions are better correlated with parameters derived from the dose–volume histograms (DVHs) of the pericardium than with those of the whole heart (27).

Second, the irradiated heart in patients with breast cancer is at or beyond the field edges. In these volumes, the accuracy of the dose calculations varies between different treatment planning systems (TPS) (55) and influences NTCP modelling, due to the differences in heart dose calculated; even small differences might be relevant if NTCP should be kept low.

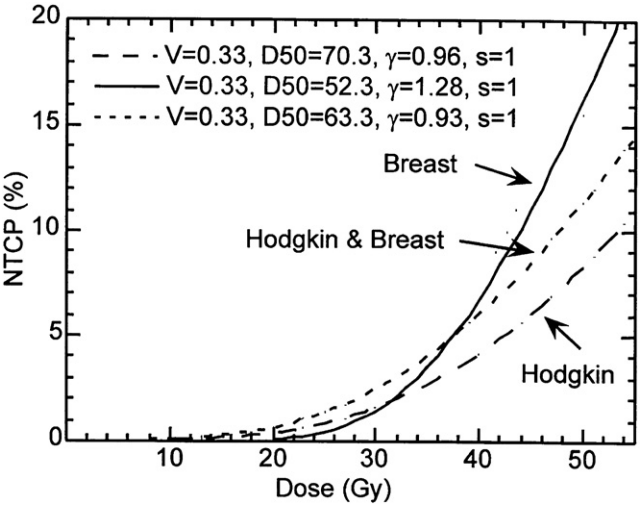

Fig. 1. Dose–response curves for long-term cardiac mortality based on Hodgkin's disease (HD) and breast cancer data sets. From Eriksson *et al*. (51), with permission. Curves were obtained by fitting, respectively, Stockholm and Oslo breast cancer trials data (25) (denoted "Breast" in the figure); data from a patient cohort treated for HD (denoted "Hodgkin"), the joint material (denoted "Hodgkin + Breast"). Plotted curve corresponds to a uniform irradiation of one third of the heart volume, in the interval of the clinical data. Parameter values are also reported. Note that in the interval of the clinical and dosimetric data of interest, the curve from breast data only is much steeper than the other curves.

Third, if inhomogeneity corrections for the low density of lung tissue are not made in the treatment plan, the heart dose is underestimated, thus affecting the evaluation of the dosimetric predictors (56).

Fourth, because of differences in setup accuracy, the planned and actual cardiac exposures can vary, with implications for the estimated NTCP (57).

Fifth, the parameters derived for the various models are based on limited clinical data in a reduced number of diseases and which generally do not involve a wide range of fraction sizes. Therefore, these models may not be applicable in the evolving era of hypofractionation and in a broader range of diseases.

Finally, concerning the applicability of the results obtained, the main criterion remains diagnosis. Dosimetric modeling data may be most applicable in the disease setting from which they were derived. For example it may be questionable to apply results based on Hodgkin's disease studies to breast cancer cases, considering the different irradiated volumes.

8. RECOMMENDED DOSE/VOLUME LIMITS

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

situation. 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 jeopardise the beneficial effect on survival of RT (1). So as not to underestimate this risk, the most conservative approach is provided by the use of the steeper dose–response curve (Fig. 1), that is, the one from the breast data (25). For partial irradiation, conservative (NTCP) model-based estimates predict that a V_{25Gy} < 10% (in 2 Gy per fraction) will be associated with a <1% probability of cardiac mortality ∼15 years after RT. For this a conservative (*i.e.,* overly safe) model was used that may overestimate the risk. Conversely, as the time horizon (*i.e.,* follow-up interval) used is modest, this may underestimate the risk. In general, when applying NTCP models, it is recommended that the user be aware of the assumptions involved in the parametrisations, for example, organ at risk definition, corrections for fractionation, dose calculation algorithms, and confidence intervals.

It is rare in the modern era to treat lymphoma with radiation but without chemotherapy. Historically, whole heart doses up to 30 Gy were reasonably well tolerated (17). For the vast majority of lymphoma patients who receive chemotherapy (particularly doxorubicin) and RT, it seems prudent to limit whole heart doses to ∼15 Gy, with field reductions, as appropriate in the given clinical situation, to areas of persistent (post-chemotherapy) residual tumor or to areas of previous bulky involvement.

For pericarditis, according to the Wei *et al.* study, the risk increases with a variety of dose parameters, such as mean pericardium dose >26 Gy, and V_{30} > 46% (27). NTCP parameters as in Table 2 can be considered for clinical studies (26). Care should be taken to differentiate between the DVHs for the heart vs. the pericardium.

Even though the relevance of perfusion defects as a clinical endpoint is questionable, evidence of subclinical myocardial injury has been demonstrated and might be relatively common. The irradiated volume of the left ventricle has been shown to be the most important predictor of a perfusion defect.

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 profiles (58–60).

9. FUTURE TOXICITY STUDIES

Improved toxicity prediction requires prospective clinical trials based on 3D dosimetric data and careful long-term follow-up of patients who have received potentially cardiotoxic chemotherapy and RT. Prospective cardiac mortality studies are unlikely to be numerous. Hopefully, the few existing dose–volume predictors for cardiac mortality will be modified by new retrospective analyses based on larger data sets, in which dose to the left descending artery will also be considered. Future longitudinal studies on pericarditis and on perfusion defects are to be expected.

The following points should be kept in mind:

a) Additional work is needed to better evaluate whether the modern radiotherapy treatment approaches for patients with breast cancer are associated with significant cardiac toxicity. The clinical relevance of the perfusion abnormalities, observed despite modern techniques, needs clarification.
b) Additional study is needed to relate doses to subvolumes of the heart (*e.g.,* coronary arteries) to clinical outcomes. Computed tomography contrast could be useful for defining the heart borders. Additional studies are indeed needed in radiation-treated patients with other thoracic tumors (*e.g.,* lung cancer), in whom an increased rate of heart disease has been noted (61 ,62) but dose–volume data are lacking.
c) Future studies should incorporate baseline cardiovascular risk factors, such as the Framingham or Reynolds score (33–35). This will allow consideration of potential interactive effects between RT and traditional cardiac risk factors.
d) Additional work is needed to understand the impact of hypofractionated radiation regimens on the heart.
e) A deeper understanding of the global physiological effects of thoracic RT is needed (*e.g.,* interactions between the heart and lung irradiation, as suggested in some animal studies) (63).

10. TOXICITY SCORING

We recommend that the LENT-SOMA system (64) be considered to describe cardiac effects, as it explicitely addresses clinical, radiological, and functional assessments of cardiac dysfunction.

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