Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Dose-response relationships for radiation-related heart disease: Impact of uncertainties in cardiac dose reconstruction

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ARTICLE INFO

Article history:
Received 16 April 2020
Received in revised form 26 August 2020
Accepted 26 August 2020
Available online xxxx

Keywords:
Radiation-related heart disease
Radiation dose-response relationships
Hodgkin lymphoma
Childhood cancer
Late-effects
Cardiac dose reconstruction

ABSTRACT

Background and purpose: Radiation-related heart disease (RRHD) can occur many decades after thoracic radiotherapy for Hodgkin lymphoma (HL) or childhood cancer (CC). To quantify the likely risk of RRHD for patients treated today, dose–response relationships derived from patients treated in previous decades are used. Publications presenting these dose–response relationships usually include estimates of uncertainties in the risks but ignore the effect of uncertainties in the reconstructed cardiac doses.

Materials/methods: We assessed the systematic and random uncertainties in the reconstructed doses for published dose–response relationships for RRHD risk in survivors of HL or CC. Using the same reconstruction methods as were used in the original publications, we reconstructed mean heart doses and, wherever possible, mean left-ventricular doses for an independent case-series of test patients. These patients had known, CT-based, cardiac doses which were compared with the reconstructed doses to estimate the magnitude of the uncertainties and their effect on the dose–response relationships.

Results: For all five reconstruction methods the relationship between reconstructed and CT-based doses was linear. For all but the simplest reconstruction method, the dose uncertainties were moderate, the effect of the systematic uncertainty on the dose–response relationships was less than 10%, and the effects of random uncertainty were small except at the highest doses.

Conclusions: These results increase confidence in the published dose–response relationships for the risk of RRHD in HL and CC survivors. This may encourage doctors to use these dose–response relationships when estimating individualised risks for patients—an important aspect of personalising radiotherapy treatments today.

Patients treated in the past with thoracic radiotherapy (RT) for cancers such as Hodgkin lymphoma (HL) and childhood cancer (CC) have been at risk from radiation-related heart disease (RRHD), often manifesting decades later, due to incidental cardiac radiation during RT [1,2]. Consequently, for patients being considered for thoracic RT today, dose–response relationships between the radiation dose to the heart and the risk of RRHD help RT professionals when balancing the risks associated with RT with the likely benefits.

Several dose–response relationships for RRHD in populations of survivors of HL and CC have been published using cardiac dose-reconstruction methods [3–10]. These dose–response relationships are not easy to derive, as they depend on retrospectively estimating individual cardiac doses for large groups of survivors who were treated before the era of CT-based RT. The cardiac dose estimates in these publications were derived with retrospective dose-reconstruction methods that used limited information such as written treatment records and/or two-dimensional simulation films. The reconstructed dose estimates are estimates of the typical dose delivered given the information available regarding a patient and his or her treatment. They are subject to uncertainty in the sense that they are likely to differ from the typical dose that would have been estimated if more detailed information, such as that from the patient's own CT-scan, had been available.

In the publications presenting the dose–response relationships, the uncertainty in the risk is usually given by a standard error or confidence interval. In contrast, little attention is paid to

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https://doi.org/10.1016/j.radonc.2020.08.022
0167-8140/

uncertainty in the reconstructed doses. Systematic uncertainties in the reconstructed doses can bias the estimated risk per unit dose either upwards or downwards, while random uncertainties lead to underestimation of the risk [11,12]. If these uncertainties are small, they will have little effect on the dose–response relationship. However, if they are large, the relationship will be distorted [11–14]. The accuracy of the reconstructed doses and its potential effect on the dose–response relationships has often been questioned, but has not previously been investigated. Doing so is important, as these dose–response relationships are increasingly being used to estimate risk of RRHD in the literature and in clinical practice.

In this study we investigate the systematic and random uncertainties in the reconstructed doses for five cardiac dose reconstruction methods that have been used in the literature to derive dose–response relationships for risk of RRHD in survivors of HL and CC [3,4,7,9,10]. We then evaluate the effect of the uncertainties on these dose–response relationships [7,15–18]. Lastly, we provide information on the necessary data and resources needed to use each reconstruction method.

Materials and methods

Dose reconstruction

To evaluate the uncertainties in the five methods of dose reconstruction, we made use of information from 15 HL patients who received parallel-opposed (AP-PA) mediastinal RT planned using a 3D CT-based treatment planning system (TPS) (Pinnacle, version 7.6; Philips Radiation Oncology Systems, WI) between 1999 and 2008 [9]. These patients provide a representative range of anatomies, prescribed doses and field sizes. The whole heart and left ventricle were retrospectively delineated using the heart atlas by Feng et al. [19] For 14 of the 15 patients, the CT-based mean heart dose (MHD) was in the range 5.5–23.9 Gy. One further patient had almost no mediastinal involvement and a CT-based MHD < 1 Gy. If this outlying dose had been included in the statistical analyses described below, it would have had much more influence than any of the other doses and it was therefore excluded. We refer to the CT-based doses for the remaining 14 patients as 'reference' doses and we evaluated the differences between the reconstructed doses and the reference doses. Use of the anonymised CT-plans was approved by the University of Toronto Research Ethics Board.

For each of the 14 patients, 2D digitally reconstructed radiographs (DRRs) were produced from the CT images at a resolution of 512 × 512 pixels and a step size of 0.05 cm. The 2D-heart contours as seen on the DRRs (Fig. A1) were generated from the manual contours from the patient's axial CT slices to mimic the process on the simulation films in the original publications. The superior border of the heart was contoured the same way as in the historical simulation films (i.e. as a straight cranial border below the pulmonary trunk). Treatment information, similar to that usually available in historical cohorts, such as prescribed dose, beam energy, field size and source-to-skin distance were used to perform the reconstruction (Table 1).

We list the dose reconstruction methods in increasing order of time needed to perform the reconstruction per patient. The first ("%Prescribed") is based on superposition of several individual 3D-reconstructed fields to create an overall estimate of organs at risk (OAR) as a percentage of prescribed dose [3]. The DRRs were used to identify which field superposition to use and the corresponding %prescribed mean heart dose (MHD) (details in Supplementary Appendix A1). The second ("%Heart") is a simple patient-specific approach, where MHD is estimated from the percentage cardiac area exposed within the 2D-simulation film [4]. In this study the

Table 1
Patient-specific information required to perform the dose reconstructions and other parameters for each method.

	Reconstruction method				
Patient-specific information for reconstruction	%Prescribed [3]	%Heart [4]	Phantom [10]	RepCT [7]	Navigator [8]
Prescribed dose/fractions	✓	✓	✓	✓	✓
Beam energy	X	✓	✓	✓	✓
Site involved	✓	✓	✓	✓	✓
Simulation films	+	✓	+	+	✓
Surface-to-source distance	X	X	+	+	✓
Field size/borders	X	X	+	+	✓
Field Shielding	X	X	+	+	✓
Field weighting	X	X	+	+	✓
	✓=Essential, + =Non-essential but improves the reconstruction accuracy if available, X = Cannot be used				
Other parameters					
Calculation method	2D method % prescribed dose based on sites involved	2D method % of heart area in the field* xprescribed dose	3D method dose calculated on anthropomorphic phantom	3D method dose calculated on representative CT	3D method dose calculated on deformed CT based on information from simulation films
Dose calculation algorithm	n/a	n/a	In-house algorithm	AAA (Eclipse TPS¶)	CCC (Pinnacle TPS)
Average time spent per patient (minutes)*	20–30	30–40	40–60	60–120	60–120
Ability to estimate dose to other organs at risk	Yes	No	Yes	Yes	Yes
Requires proprietary software	No	No	Yes	No	Yes
Institution in which the reconstruction method was developed	Copenhagen University Hospital	The Netherlands Cancer Institute & University of Oxford	MD Anderson Cancer Center	University of Oxford	Princess Margaret Cancer Centre
Institution and researcher that performed the reconstruction in this study	University of Oxford (GN)	University of Oxford (GN)	MD Anderson Cancer Center (RMH)	University of Oxford (GN)	Princess Margaret Cancer Centre (AN&DH)

* Estimate for comparison purposes, time spent includes field reconstruction time, contouring, data preparation and collection. It does not include time for initial coding and setting up of methodology.
¶ The algorithm can vary depending on the treatment planning system (TPS) used.

ImageJ software package [20] was used to delineate and calculate the percentage cardiac area within the radiation field on the DRRs to estimate MHD. The third ("Phantom") estimates absorbed dose for a series of OAR inside and outside the treatment field, based on a combination of measurements in an anthropomorphic phantom and analytical dose calculations [10]. The fourth ("RepCT"), is a representative CT technique based on one male and one female anatomical data set in which the OAR doses are reconstructed on the representative CT using a TPS [6,7]. The fifth ("Navigator"), uses an advanced deformable image registration and navigator channels adaptation technique to reconstruct 3D organ volumes and doses on a male and a female population model [9]. All methods were used to estimate MHD and two (RepCT and Navigator) to estimate mean left ventricular dose (MLVD) for the 14 patients described above. Patient-specific information used for each reconstruction method and details of complexity and resources needed are described in Table 1.

Effects of systematic and random uncertainty

The systematic uncertainty in the reconstructed doses was assessed by performing a regression of the reconstructed doses (y_i) on the reference (i.e. CT-based) doses (x_i). The regression model considered was:

$$y = \alpha + \beta x + \varepsilon$$

where the intercept (α) and the slope (β) are unknown parameters representing the systematic uncertainty in the reconstructed doses while ε represents the random uncertainty. If the variance of the random uncertainty appeared constant over all values of x then a simple regression model was fitted but, if necessary, a weighted regression model was used in which the standard error increased with the square of the reference dose. Significance tests, using 5% as the critical level, were conducted to determine whether the inclusion of a quadratic term in x, or an additive term indicating the patient's gender improved the fit of the model. The significance of the departure of $\widehat{\alpha}$ from 0 and of $\widehat{\beta}$ from 1 were then considered to select the final model. Where possible, the effect of the random uncertainty was assessed by comparing its variance with the variance of the doses in the original dose–response relationship using the method of regression calibration (details in Supplementary Appendix B). All statistical analyses were performed using Stata statistical software version 14.2 (StataCorp, College Station, TX).

Results

The relationship between the reconstructed and reference doses was well summarised by a linear model for all five methods (Figs. 1,2; Tables 2,3). In no case did a quadratic term in dose or a term representing the patient's gender significantly improve the fit of the regression model. Details are given below for each method.

The %Prescribed method was the quickest to use (20–30 minutes per patient) and required only basic software and computing resources. The random variability did not increase with increasing dose and the fitted regression line was y = 12.65 + 0.40x (Table 2, Fig. 1). Therefore, doses reconstructed using the %Prescribed method can be corrected using the relationship x = (y–12.65)/0.40 provided they lie within the range of reconstructed MHDs included in the present study (i.e. 13.0–22.8 Gy). However,

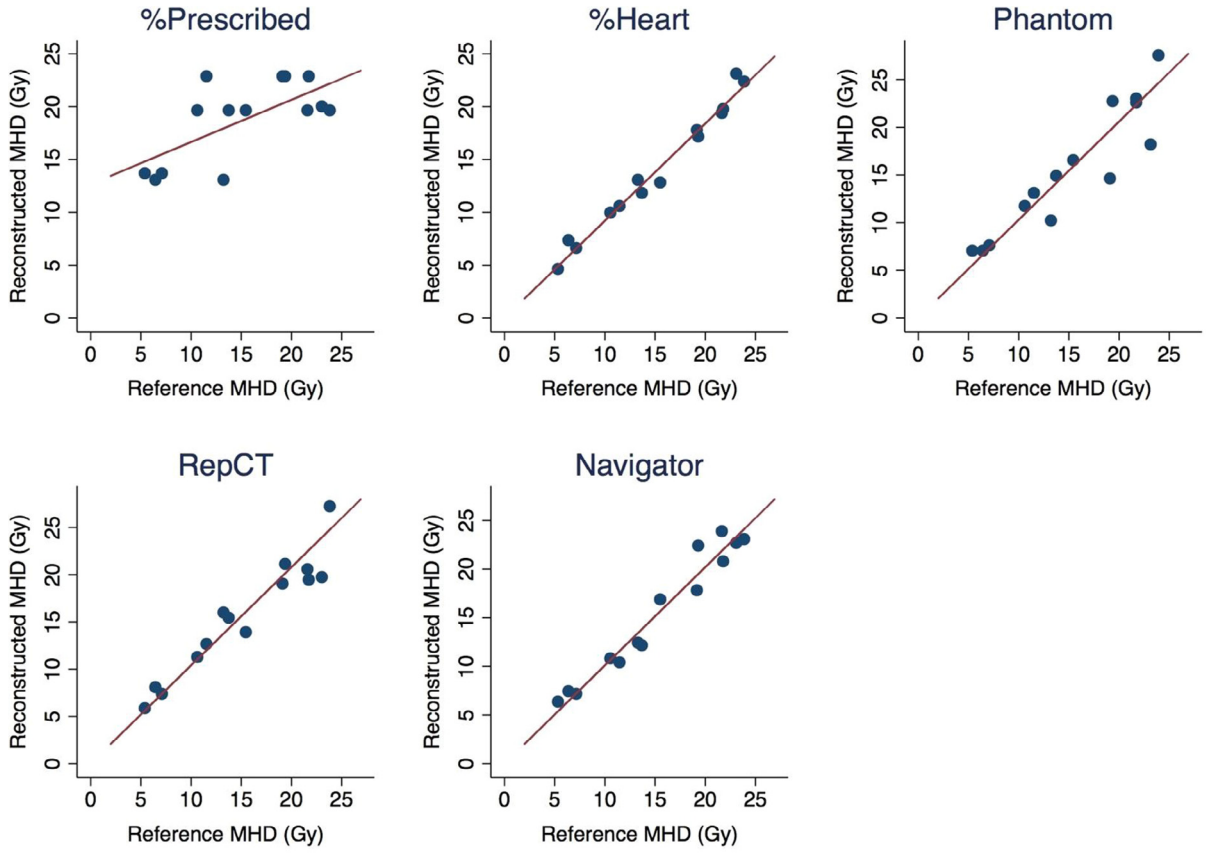

Fig. 1. Reconstructed versus CT-based 'reference' mean heart dose (MHD) and fitted regression lines for each reconstruction method. See Table 1 for details of fitted regression lines.

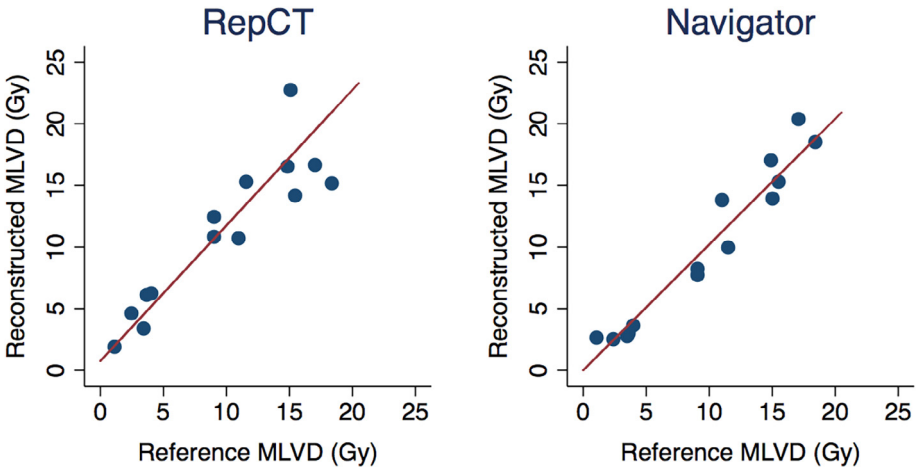

Fig. 2. Reconstructed versus CT-based 'reference' mean left ventricular dose (MLVD) and final fitted regression lines for each reconstruction method. See Table 2 for details of fitted regression lines.

Table 2
Reconstructed mean heart doses derived by each reconstruction method and compared with the CT-based 'reference' doses.

Subject	Prescribed dose in fractions	Reconstructed MHD (Gy)					'Reference' MHD (Gy)†
		%Prescribed [3]	%Heart [4]	Phantom [5,10]	RepCT [7]	Navigator [8]	
Patient 1	21 Gy in 14	13.7	4.6	7.0	5.8	6.3	5.5
Patient 2	20 Gy in 10	13.0	7.3	7.0	8.0	7.4	6.5
Patient 3	21 Gy in 12	13.7	6.6	7.6	7.3	7.0	7.2
Patient 4	30 Gy in 20	19.5	9.9	11.6	11.2	10.7	10.7
Patient 5	35 Gy in 20	22.8	10.6	13.0	12.6	10.4	11.6
Patient 6	20 Gy in 10	13.0	13.1	10.2	15.9	12.4	13.3
Patient 7	30 Gy in 20	19.5	11.7	14.8	15.4	12.1	13.8
Patient 8	30 Gy in 20	19.5	12.8	16.5	13.8	16.7	15.5
Patient 9	35 Gy in 20	22.8	17.8	14.5	18.9	17.8	19.2
Patient 10	35 Gy in 20	22.8	17.0	22.7	21.1	22.4	19.4
Patient 11	30 Gy in 20	19.5	19.3	23.0	20.4	23.8	21.7
Patient 12	35 Gy in 20	22.8	19.7	22.5	19.4	20.7	21.8
Patient 13	30.6 Gy in 17	19.9	23.0	18.1	19.7	22.6	23.2
Patient 14	30 Gy in 20	19.5	22.3	27.5	27.2	23.0	23.9
Mean (Gy)		18.7	14.0	15.4	15.5	15.2	15.2
Mean absolute difference (Gy)		4.9	1.4	2.0	1.6	1.1	-
		Regression modelling					
Simple or weighted regression	simple	simple	weights:$\frac{1}{x^2}$	weights:$\frac{1}{x^2}$	weights:$\frac{1}{x^2}$	–	
Fitted regression line	$y = 12.65+0.40x$	$y = 0.92x$	$y = 1.03x$	$y = 1.04x$	$y = 1.01x$	–	
95% confidence interval for slope	0.12–0.67	0.89–0.95	0.94–1.13	0.97–1.11	0.95–1.06	–	
Standard error of slope	0.13	0.01	0.04	0.03	0.03	–	
*p-value for test of slope = 1	<0.001	<0.001	0.42	0.21	0.76	–	
Standard deviation of random uncertainty	6.21	0.88	0.16x	0.12x	0.10x	–	

Gy: Gray, MHD: Mean heart dose, Mean absolute difference: arithmetic mean of absolute differences between reconstructed and 'Reference' MHD.
† CT-based MHD. * Where the fitted regression line did not include an intercept and the slope did not differ significantly from 1 (i.e. $p \geq 0.05$), the final model selected assumed the slope to be 1.

for individuals with no cardiac exposure, reconstructed and reference doses must both be 0 Gy. Therefore, the large intercept in the fitted regression line (estimate 12.65 with standard error 2.07) indicates that the fitted regression line does not hold for doses much below 13 Gy. The %Prescribed method has been used to estimate that the hazard ratio for cardiovascular disease increases by 1.5% per Gy MHD in survivors of HL [15] (Table 4). However, 25% of the 6039 individuals on which this dose–response relationship was based had reconstructed doses lower than 8 Gy. Hence our fitted regression line does not describe the relationship between reference and reconstructed doses throughout the range of doses used to estimate the dose–response relationship. Nor can it be used to assess the impact of either systematic or random uncertainty on this dose–response relationship.

The %Heart method was also fast (30–40 minutes per patient) and simple to use, requiring only DRRs and freely available software (ImageJ) to calculate the % Heart area. The random variability did not increase with increasing dose (Fig. 1). No intercept was needed in the regression modelling and the fitted line was $y = 0.92x$ (Table 2). The fitted line can therefore be used to estimate the effects of uncertainty in the published dose–response relationship, which suggests the coronary heart disease rate increases by 7.4% per Gy (95% CI 3.3–14.8) in HL survivors [16]. The estimated effect of systematic uncertainty is overestimation of 9% (i.e. $100 \times ((1.00/0.92)-1.00)$) while random uncertainty would have led to under-estimation of 3% (i.e.$100 \times (0.8/(0.8 + 28.9))$) if no zero doses had been included in the derivation of the dose–response relationship (Table 4). However, as 13% of the study

Table 3
Reconstructed mean left ventricular doses derived by each reconstruction method and compared with the CT-based 'reference' doses.

Subject	Prescribed dose in fractions	Reconstructed MLVD (Gy)		'Reference' MLVD (Gy)†
		RepCT [7]	Navigator [8]	
Patient 1	21 Gy in 14	1.8	2.6	1.2
Patient 2	20 Gy in 10	4.5	2.4	2.5
Patient 3	21 Gy in 12	3.3	2.7	3.5
Patient 4	30 Gy in 20	6.1	2.9	3.7
Patient 5	35 Gy in 20	6.2	3.5	4.1
Patient 6	20 Gy in 10	12.3	8.1	9.1
Patient 7	30 Gy in 20	10.8	7.6	9.1
Patient 8	30 Gy in 20	10.6	13.7	11.0
Patient 9	35 Gy in 20	15.2	9.8	11.6
Patient 10	35 Gy in 20	16.4	17.0	14.9
Patient 11	30 Gy in 20	22.7	13.8	15.1
Patient 12	35 Gy in 20	14.1	15.2	15.6
Patient 13	30.6 Gy in 17	16.6	20.3	17.1
Patient 14	30 Gy in 20	15.1	18.5	18.5
Mean (Gy)		11.1	9.9	9.8
Mean absolute difference (Gy)	2.2	1.3	–	
	Regression modelling			
Simple or weighted regression	weights: $\frac{1}{x^2}$	simple	–	
Fitted regression line	$y = 0.75 + 1.10x$	$y = 1.02x$	–	
95% confidence interval for slope	0.88–1.33	0.94–1.10		
Standard error of slope	0.10	0.04		
*p-value for test of slope = 1	0.32	0.57	–	
Standard deviation of random uncertainty	$0.28x$	1.61	–	

Gy: Gray, MLVD: Mean left ventricular dose, SD: Standard deviation, Mean absolute difference: arithmetic mean of absolute differences between reconstructed and 'Reference' MLVD, † CT-based MLVD.
* Where the slope of the fitted regression line did not differ significantly from 1 (i.e. $p \geq 0.05$), the final model selected assumed the slope to be 1.

population had zero doses, the effect of random uncertainty will be less than this. The overall effect of uncertainty was therefore between 6% (i.e. 1.09/1.03, assuming 3% underestimation due to random uncertainty) and 9% (i.e. assuming no effect of random uncertainty). The dose–response relationship would therefore change to between 6.8% (95% 2.9–12.9) and 7.0% per Gy MHD (95% CI 3.1–14.0) when both types of uncertainty are taken into account.

The Phantom method is more complex and labour-intensive and requires proprietary in-house software and trained staff and thus the reconstruction would have to be outsourced. Depending on the plan complexity, the reconstruction can take between 40 and 60 minutes per patient. In the final fitted regression model no intercept was needed and the slope did not differ significantly from one, indicating no significant effect of systematic uncertainty in the reconstructed doses (Fig. 1, Table 2). The overall effect of both types of uncertainty is therefore just that of random uncertainty which increased with increasing dose. Rate ratios for ischaemic heart disease in survivors of CC were estimated in the original study [17] for categories of MHD (Table 4). Random uncertainty in the doses does not change these rate ratios, but rather changes the doses and the boundaries of the dose categories (see section B2 in Supplementary Appendix B). Doses at the boundaries of the lowest two dose categories (5 and 15 Gy) changed by less than 1%, and doses at the highest boundary of 35 Gy reduced by 3%, to 34 Gy.

The RepCT method is also labour-intensive. It can, however, be developed in any centre with a commercial TPS available and a library of patient CT scans. Once the methodology is established, the time spent for each patient will vary between 1 and 2 h based on plan complexity and the researcher's level of experience. The slope of the final fitted regression line for MHD did not differ significantly from one (Table 2), providing no evidence of systematic uncertainty in the reconstructed doses, while the random uncertainty increased with increasing dose. Rate ratios for heart failure in survivors of HL were estimated in the original study in categories of MHD [7] (Table 4). Hence, the overall effect of both types of uncertainty on the reconstructed MHDs is just that of random uncertainty, changing the boundaries of the dose categories. A dose of 21 Gy increased by 2%, while a dose of 26 Gy reduced by 5% to 25 Gy and a dose of 31 Gy reduced by 12% to 27 Gy.

MLVDs were also reconstructed using the RepCT method and for these the fitted regression line was $y = 0.75 + 1.10x$, and the random error increased with increasing dose (Table 3). The slope of 1.10 did not differ significantly from one and the intercept did not differ significantly from zero ($p = 0.06$). Therefore, it was concluded that there would be no effect of systematic error, leaving just the effect of random uncertainty. Rate ratios for heart failure in survivors of HL were estimated in the original study in categories of MVLD [7] (Supplementary Appendix C). Doses of 16 Gy reduced by 1%, while doses of 21 Gy reduced by 14% to 18 Gy and doses of 26 Gy reduced by 25% to 19 Gy.

The Navigator method is also labour intensive, requiring proprietary in-house software in addition to a TPS. The time spent for each patient will vary between 1 and 2 h based on plan complexity and the researcher's level of experience. For MHD, the slope of the final fitted regression line did not differ significantly from one, indicating that there was no significant effect of systematic uncertainty in the reconstructed doses (Table 2), while the random uncertainty in the reconstructed doses led to an underestimation of 19% (i.e. $100 \times (5.3/(5.3 + 22.2))$). Therefore, the dose–response relationship for any cardiac event after correcting for uncertainty is 11.2% per Gy MHD (95% CI 2.5–19.8), slightly steeper than the original 9.0% per Gy (95% CI 2.0–16.0) [18] (Table 4).

MLVDs have also been reconstructed using the Navigator method and for these the slope of the fitted regression line did not differ significantly from one and the intercept did not differ significantly from zero, indicating that there was no significant effect of systematic uncertainty in the reconstructed doses (Table 3). No dose–response relationships based on the Navigator method and MLVD have been published to date, therefore, the effect of the random uncertainty could not be assessed.

Table 4
Effect of systematic and random uncertainties in reconstructed mean heart doses on the dose–response relationships derived using each reconstruction method.

	Reconstruction method				
Original study	%Prescribed Maraldo et al. [15]	%Heart van Nimwegen et al. [16]	Phantom Chow et al. [17]	Rep CT van Nimwegen et al. [7]	Navigator Hahn et al. [18]
Type of cancer	Hodgkin lymphoma	Hodgkin lymphoma	Childhood cancer	Hodgkin lymphoma	Hodgkin lymphoma
Relationship reported in original study	Increase in hazard ratio per Gy of MHD for cardiovascular disease	Excess relative risk of coronary heart disease per Gy of MHD	Rate ratios for ischaemic heart disease for radiation versus no radiation	Rate ratios for heart failure for radiation versus no radiation	Increase in hazard ratio per Gy of MHD for any cardiac event
Dose-response reported in original study	1.5% per Gy [95% CI 0.6–2.4]	7.4% per Gy [95% CI 3.0 to 13.6]	<5 Gy RR: 0.8 [0.3–1.8] 5–14 Gy RR: 2.4 [1.4–4.2] 15–34 Gy RR: 3.7 [2.5–5.4] ≥35 Gy RR: 7.8 [5.4–11.2]	1–20 Gy RR: 1.4 [0.8–2.5] 21–25 Gy RR: 1.0 [0.6–1.7] 26–30 Gy RR: 2.8 [1.7–4.6] ≥31 RR: 4.2 [2.1–8.1]	9.0% per Gy [95% CI 2.0% – 16%]
Effect of systematic uncertainty*	–¶	9% overestimation	No significant effect	No significant effect	No significant effect
Dose-response after correction for systematic uncertainty	–¶	6.8% per Gy [95% CI 2.9–12.9]	As in original study	As in original study	As in original study
Estimated variance of random uncertainty in reconstructed doses§	–¶	0.8 Gy^2	11.3 Gy^2	6.1 Gy^2	5.3 Gy^2
Estimated variance of 'reference' doses in study population#	–¶	28.9 Gy^2	365.7 Gy^2	93.5 Gy^2	22.2 Gy^2
Effect of random uncertainty†	–¶	<3% underestimation	5 Gy increased by < 1% 15 Gy increased by < 1% 35 Gy reduced by 3%	21 Gy increased by 2% 26 Gy reduced by 5% 31 Gy reduced by 12%	19% underestimation
Overall effect of uncertainty in doses	–¶	6–9% overestimation	As for effect of random uncertainty	As for effect of random uncertainty	As for effect of random uncertainty
Dose-response after correction for systematic and random uncertainty	–¶	6.8% per Gy [95% CI 2.9–12.9]to 7.0% per Gy [95% CI 3.1–14.0]	<5 Gy RR: 0.8 [0.3–1.8] 5–14 Gy RR: 2.4 [1.4–4.2] 15–33 Gy RR: 3.7 [2.5–5.4] ≥34 Gy RR: 7.8 [5.4–11.2]	1–20 Gy RR: 1.4 [0.8–2.5] 21–24 Gy RR: 1.0 [0.6–1.7] 25–26 Gy RR: 2.8 [1.7–4.6] ≥27 RR: 4.2 [2.1–8.1]	11.2% per Gy [95% CI 2.5% – 19.8%]

MHD: Mean heart dose, Gy: Gray, CI: Confidence interval.
* i.e. $100\ x|1-1/\beta|$ where β is slope of fitted regression model in Table 1. Values of β below 1 indicate overestimation of the dose–response relationship and values above 1 indicate underestimation.
¶ Cannot be assessed formally. See text for details.
§ i.e. the square of the standard deviation of the random uncertainty from Table 1. See Supplementary Appendix for details. For Phantom and RepCT methods, estimated at mean dose in study population, after exclusion of unexposed individuals, i.e. at 20.8 and 22.4 Gy respectively. For Navigator method, estimated at mean dose i.e. 23.7 Gy.
# i.e. σ_x^2 where $\sigma_x^2 + \sigma_\varepsilon^2$ is the estimated variance of the doses in the original study population. See Supplementary Appendix B for details.
† i.e. $\sigma_\varepsilon^2/(\sigma_x^2 + \sigma_\varepsilon^2)$.

Discussion

This study is the first to evaluate the effect that uncertainties in the reconstructed cardiac doses have on the published dose–response relationships for the risk of RRHD. We demonstrate that there is a linear relationship between reconstructed and reference doses for all five reconstruction methods for the range of doses studied. We also show that uncertainties in the reconstructed MHDs did not have a substantial effect on most of the published dose–response relationships for the risk of RRHD in HL and CC survivors. This is an important finding, as a common criticism of such studies is that the retrospective dosimetry methods employed may not be sufficiently accurate to give confidence in using the results to inform clinical practice. The present study addresses this issue directly. Lastly, this study provides clarity on the type of data and resources required to use each reconstruction method.

Comparison of the different methods

For the %Prescribed method there was a linear relationship between the reconstructed and reference CT-based MHDs. This method was developed to estimate MHDs for patients receiving RT to the entire mediastinum and, consequently, the lowest reconstructed MHD is high, at 65% of the prescribed dose, i.e. 13.0 Gy [3]. Therefore, whilst reconstructed doses above about 13.0 Gy can be corrected using our linear relationship, it is not appropriate for doses below this. The %Prescribed method is, however, the only method that can provide MHDs when no original patient imaging data are available. This can be particularly useful for observational studies in HL cohorts for which only the RT field arrangement and prescribed dose information are known, or when an estimate of MHD is needed for a patient treated decades ago and who requires re-irradiation.

Where simulation films are available for most patients and MHD is the required dosimetric parameter, the %Heart method offers a good solution as it is the quickest way of estimating the MHD with a minimum of resources and its performance is close to that of the more sophisticated techniques. The best overall performance was that of the Phantom method, with no significant systematic uncertainty and only a small effect of random uncertainty (Table 4). It is arguably the most practical option for accurate MHD estimates in large patient cohorts. However, it requires access to proprietary software, substantial resources and trained staff. If simulation films are not available to individualise the reconstruction for each patient, the Phantom method can still be used but its accuracy may be compromised compared to its performance in this study. It is the most widely used method in the literature and has been used to estimate cardiac doses for thousands of patients and for various observational studies within the Childhood Cancer Survivor Study (CCSS) [2,17,21,22].

Reconstruction methods such as RepCT and Navigator take more treatment-specific characteristics into consideration and would be expected to provide more accurate dose estimates. However, they are also the most labour and resource-intensive and, therefore, likely to be feasible only for small patient groups. For the RepCT method there was no significant evidence of systematic uncertainty in the reconstructed MHDs or MLVDs, while the random uncertainty had a negligible effect at small doses and only a moderate one at higher doses. A clinically relevant effect of the correction for the RepCT method is to increase the upward curvature of the dose–response relationships for heart failure previously reported [7], resulting in a lower 'tolerance dose' for this late effect and larger estimated increases in risk above the tolerance dose. For the Navigator method, there was no significant effect of systematic uncertainty for either MHD or MLVD. However, for MHD, the estimated dose–response relationship was based only on individuals with non-zero exposure. This has the advantage of avoiding the assumption that individuals with and without cardiac exposure differ in no other respects, but the absence of having any patients with zero reference and reconstructed doses, results in a larger effect of random uncertainty, although, this is still only moderate, at 19%.

Strengths and limitations

This study provides, for the first time, a methodology to examine the effect of dose-reconstruction uncertainties on the published dose–response relationships. The methods investigated here cover the vast majority of retrospective cardiac dosimetry methods used for thousands of survivors in epidemiological studies to derive dose–response relationships for RRHD in HL and CC. Further strengths were that all five methods were compared against the same reference doses calculated using CT-based dosimetry, the dose reconstruction was blind (i.e. the reference doses were unknown when the reconstructions were performed) and the same amount of patient information was used for all methods.

One limitation was the low number (14) of patients used in the case-series, as a balance between adequate sample size and realistic timelines and cost had to be reached. However, the 14 patients provided a wide range of field sizes, heart positions and shapes (Fig. A2) leading to a wide range of cardiac doses, similar to those seen in the patients in the historical treatments. Additionally, the standard errors of the slopes of the fitted regression lines were small enough for the hypothesis that the slope of the fitted regression line was equal to one was rejected decisively (with $p < 0.001$) for both the %Prescribed and the %Heart methods, while for the other methods in Table 2 and for both methods in Table 3 the confidence intervals for the fitted regression lines were not unduly wide. In addition, the plots in Figs. 1 and 2 show that our regression models fitted the data well and suggest that including additional individuals would have been unlikely to have had a major impact on our results.

In this study DRRs (used to mimic simulation films) were available for every patient. However, in most epidemiological studies simulation films are missing for some patients and their doses have to be imputed. In principle, this brings additional uncertainties. The impact of imputed doses for a small proportion of patients on the dose–response relationship when using the RepCT and %Heart methods has, however, been shown to be negligible [7,16].

Future perspectives

Studies to evaluate the reconstruction accuracy for other measures of cardiac dose, dose to substructures and for doses in different OARs would be helpful, as would studies on the effect of patient variation in mediastinal separation on cardiac doses. The dose–response relationships evaluated in this study consider only the typical cardiac dose received during treatment and do not consider variation in patient positioning. Following the increasing use of CT-based treatment planning since the early 2000s, cardiac doses based on a patient's individual CT scan and from more modern RT techniques will gradually become available for epidemiological studies in the next few decades. This will provide more accurate dose-estimates and may also help determine whether MHD, MLVD, mean dose to another cardiac substructure, or another volumetric dose parameter is the best predictor of RRHD.

In conclusion, this study has demonstrated that the effect of uncertainties in reconstructed MHDs did not substantially affect the overall conclusions for the majority of epidemiological studies that have published dose–response relationships for the risk of RRHD in HL and CC survivors. This may encourage doctors to make

increased use of these dose–response relationships when attempting to individualise the risks for patients in the clinic; an important aspect of personalising RT treatments today.

Funding sources

GN was supported by a DPhil studentship and an Early Career Postdoctoral Research Fellowship from the Nuffield Department of Population Health, University of Oxford. SCD, MA, and DJC were supported by Cancer Research UK (grant no C8225/A21133) and the University of Oxford. These funding bodies had no role in the collection, analysis or interpretation of the data, or in the writing of the report.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.08.022.

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