Cardiac Radiation Dose and Predicted Cardiac Mortality in the UK RAPID Trial in Early Stage Hodgkin Lymphoma

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Background

The initial management of early stage Hodgkin lymphoma (HL) involves optimising the balance between maximising cure and minimising late effects of treatment including second cancers and cardiovascular disease. Results of the RAPID trial showed that patients who were PET scan "negative" after 3 cycles ABVD had a very good 3 year progression-free survival (PFS) without further treatment. Involved field radiotherapy (IFRT) improved 3 year PFS but this gain was obtained at the expense of irradiating all patients, many of whom were already cured. In the current study cardiac doses of radiation received by individual patients taking part in RAPID were calculated and the absolute excess risk (AER) of cardiac death resulting from this was predicted.

Methods

Using original treatment data, individualised cardiac dosimetry was performed for patients who had received IFRT within the RAPID trial. Cardiac doses were used to predict excess 15 year cardiac mortality using two different prediction methods; the relative seriality model and a recently derived dose-response relationship of the percentage increase in cardiac mortality per Gy mean whole heart dose (MWHD), adjusted for age at irradiation and utilising population-based cardiac mortality rates individualised for age and gender.

Results

Dosimetry was completed for the majority of patients (n=247, 79%). The average MWHD was 4.2 Gy, range 0.01 to 24.00 Gy (Table 1). Most individuals (68%) received a MWHD of <5 Gy (Figure 1).

For more than half of those who received IFRT (58% and 62%) the predicted 15-year AER of cardiac death was <0.1% and for more than three-quarters (76% and 95%) it was <1%, regardless of the prediction model used (Table 2). A minority of individuals (13% and 2%) had an estimated excess cardiac mortality of >2% at 15 years. The extent of mediastinal involvement was the main determinant of MWHD and hence the predicted AER of cardiac death (Figure 2).

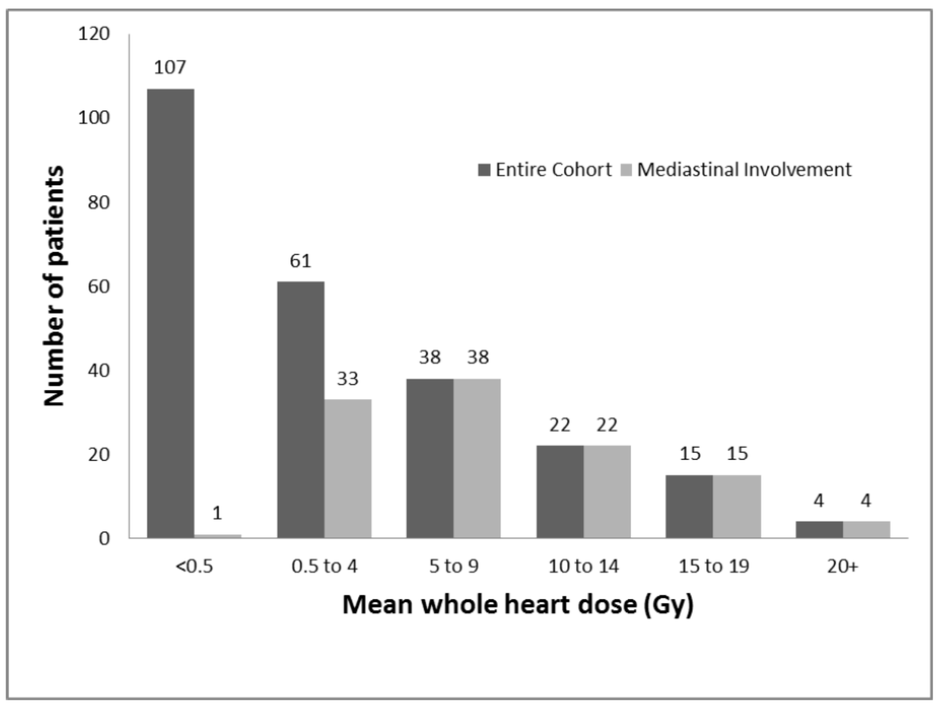

Figure 1 – Distribution of mean whole heart dose (Gy) for the entire cohort (n=247) and for those with mediastinal involvement (n=113).

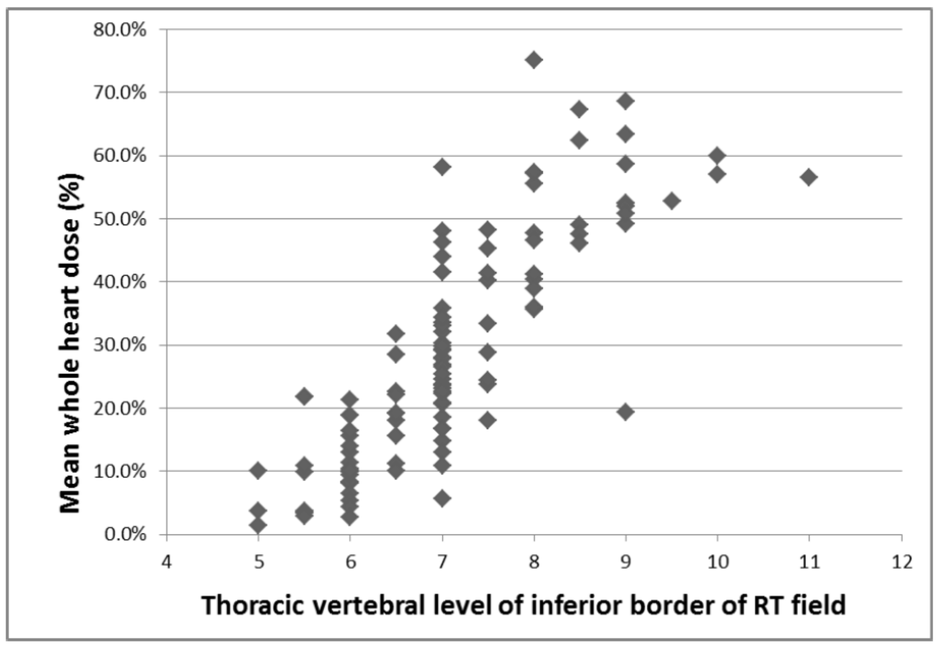

Figure 2 – Variation in mean whole heart dose (as a % of prescribed dose) by the thoracic vertebral level of the inferior border of the radiotherapy (RT) field.

Structure	Average mean dose in Gy (range), standard deviation	
	Entire Cohort (n=247)	Mediastinal Involvement (n=113)
Whole heart	4.2 (0.0 to 24.0), 5.7	8.8 (0.5 to 24.0), 5.6
Left coronary artery	4.5 (0.0 to 23.9), 6.0	9.4 (0.5 to 23.9), 5.9
Right coronary artery	4.2 (0.0 to 31.5), 6.8	8.8 (0.4 to 31.5), 7.7
Circumflex coronary artery	6.5 (0.0 to 32.5), 8.9	13.6 (0.7 to 32.5), 8.9
Aortic valve	8.6 (0.0 to 34.2), 11.5	18.2 (0.8 to 34.2), 10.9
Mitral valve	4.9 (0.0 to 32.7), 8.1	10.1 (0.5 to 32.7), 9.6
Tricuspid valve	3.7 (0.0 to 32.5), 7.3	7.8 (0.3 to 32.5), 9.3
Pulmonary valve	11.2 (0.1 to 37.7), 12.8	23.4 (1.1 to 37.7), 9.0
Left ventricle	1.9 (0.0 to 20.5), 3.2	3.8 (0.3 to 20.5), 4.0
Right ventricle	2.9 (0.0 to 26.9), 5.2	6.0 (0.3 to 26.9), 6.4
Left atrium	8.2 (0.0 to 32.8), 10.2	17.3 (0.9 to 32.8), 8.7
Right atrium	5.4 (0.0 to 33.8), 8.1	11.4 (0.5 to 33.8), 8.8
Sino-atrial node	10.8 (0.1 to 37.7), 12.8	22.8 (1.0 to 37.7), 9.6
Atrio-ventricular node	5.0 (0.00 to 32.1), 8.9	10.5 (0.5 to 32.1), 10.9

Table 1 - Average mean doses in Gy to the heart and individual cardiac structures for all patients for whom dosimetry was completed (n=247) and just for those with initial mediastinal involvement who received involved field radiotherapy including at least part of the mediastinum (n=113).

	Relative seriality model			Dose-response per Gy MWHD		
Predicted Cardiac AER	Patients (%)	Average MWHD, Gy	Average AER (%)	Patients (%)	Average MWHD, Gy	Average AER (%)
<0.1%	144 (58)	0.4	0.01	152 (62)	0.8	0.03
0.1-1%	44 (18)	4.9	0.48	82 (33)	8.8	0.28
>1-2%	28 (11)	9.4	1.35	9 (4)	14.4	1.53
>2-3%	24 (10)	14.9	2.44	3 (1)	13.9	2.56
>3%	7 (3)	20.5	4.02	1 (<1)	22.8	3.87
All	247	4.2	0.60	247	4.2	0.21

Table 2 – Predicted 15-year absolute excess risk (AER) of cardiac death according to the relative seriality model and the dose-response relationship of the percentage increase in cardiac mortality rate per Gy mean whole heart dose (MWHD)

Conclusions

A wide range of cardiac radiation doses were received by patients allocated to IFRT in the RAPID trial. In most cases the MWHD was small and the predicted absolute excess risk of cardiac mortality low, but for a minority with extensive mediastinal disease the MWHD was high and the predicted absolute excess 15-year mortality >2%. These risks are likely to be higher if the impact of anthracycline toxicity and co-existing cardiac risk factors are taken into account, and with longer follow-up.

The results of this study show that an individualised approach to treatment of early stage HL can be used to avoid the excess cardiac mortality associated with high cardiac doses of radiation. Assessment of this risk at diagnosis, combined with consideration of the risk of other late effects (particularly second cancers), will allow individualisation of the decision as to whether radiotherapy should be part of initial management, whether advanced radiotherapy techniques should be considered, or whether a chemotherapy-only approach recommended for those achieving PET negativity.

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